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The perceptions of lean in primary healthcare centres in Kuwait: a cross-sectional survey of primary healthcare staff

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ABSTRACT

Objective: To assess the current state of lean utilisation by exploring the knowledge of healthcare workers regarding lean within Kuwait’s primary healthcare centres (PHC)
Design: A literature search in MEDLINE, CINAHL, Embase and Cochrane Library databases focusing on lean within Kuwait’s healthcare followed by a cross-sectional semi-structured survey in Kuwait
Setting: Four PHCs in Kuwait
Subjects: Healthcare workers at different levels and departments
Intervention: The data was collected from healthcare workers in four PHCs using a cross-sectional semi-structured survey.
Main outcome measures: Lean is considered a new concept in the PHC in Kuwait. The majority of PHC staff did not have adequate knowledge regarding lean. However, they were enthusiastic and willing to participate and become involved in future improvement initiatives. They emphasised and agreed that the current system requires improvement.

Result: There were no published articles regarding lean in Kuwait’s healthcare. Out of 160 questionnaires circulated to PHC staff, 120 were eligible for analysis. Respondents included 44 physicians, 30 nurses, 23 pharmacists, 17 technicians and 6 administrative staff. The majority (92%) believed that the development of healthcare processes is important and 80% of participants were willing to be involved in any future healthcare process improvement initiative. Even though 54% were familiar with the concept of eliminating waste from processes or the principle of continuous improvement, only 11% were familiar with lean.

Conclusion: The lean approach is relatively new in the Kuwaiti healthcare system and is not commonly used by staff in Kuwait’s PHC. Although the majority of PHC staff are not familiar with lean, there is considerable interest in efforts to improve healthcare and eliminate waste, which does suggest that staff may find insights from lean interesting and useful.

KEY WORDS: Kuwait, lean, primary healthcare, Toyota production system

INTRODUCTION

Kuwait's government, represented by the Ministry of Health (MOH), has continuously remained vigilant regarding their healthcare system (HCS)\(^1\). The infrastructure expansion demonstrates how serious the MOH is about delivering better healthcare services\(^2\). The Kuwaiti HCS is facing several challenges. An aging population, increased demand, new technological advances and expensive services continue to increase the pressure on HCS. In this era, providing high quality health services and achieving patient expectation within existing resources is considered demanding. Therefore, a new method of providing healthcare services must be adopted\(^3\). Lean philosophy could be part of the solution as it promises to provide more with less\(^4\). Lawal et al described lean as 'a set of operating philosophies and methods that help create maximum value for patients by reducing waste and wait' \(^6\). Many healthcare organisations, mainly in developed countries, have explored whether lean is able to support efforts to enhance the quality of care, improve patient satisfaction and reduce costs. A

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systematic review conducted by Moraros et al concluded that lean interventions have a potentially positive, yet inconsistent, effect on process outcomes and called for more research[9]. On the other hand, despite lean having the potential for providing benefits to developing countries[8], there is a shortage of extensive research from that context, especially in primary care settings[9,10]. To help address this gap, in this paper we aim to review current literature and undertake a staff survey to determine staff perceptions about lean methodology in primary healthcare centres (PHC) in Kuwait. Our survey focuses on staff from the PHC setting because lean methodology involves input from key stakeholders such as front-line staff.

This work forms part of a wider doctoral study aimed at ‘Exploring the case for adopting lean in Kuwait to enhance the flow of patients with diabetes in Primary Healthcare Centres’.

LITERATURE REVIEW

Based on the literature review, an overview of lean philosophy was provided that relied on searching research databases including MEDLINE, CINAHL, Embase and Cochrane Library. The inclusion criteria for articles involved in this research were: to be written in English, published in peer-review journals, conducted between 2000 to April 2018 and used the previously mentioned database. The keywords include lean, Toyota production system, Kuwait, lean philosophy and primary healthcare. The search was aimed at exploring lean in healthcare in general with a focus on the studies that were undertaken or implemented in Kuwait. The initial search revealed 375 articles. After reviewing the titles and abstracts, 175 articles were deemed relevant. Furthermore, following the snowball method, another 32 articles were found. After excluding duplicates and unrelated articles, 87 studies were retained.

An overview of lean philosophy

Interest in lean began about 25 years ago as a way to improve the efficiency and productivity of various organisations or service providers. The term ‘lean’ was first mentioned by Krafcik and was popularised by the book ‘The Machine that Changed the World’[11]. Lean philosophy was first implemented in the automotive industry, but many other industries began to adopt lean including the aerospace industry, industrial production, consumer production[12] and more recently, the healthcare sector. This method was initially developed in the Toyota car manufacturer and was known as the Toyota Production System in the 1950s[4,13]. The principal notion behind lean is to eliminate waste and only provide what the customer values using minimal resources. In other words, it is about process improvement concentrating on the efficiency of providing products or services to the customers. Nevertheless, there is no agreed definition of the meaning of lean production[14]. Lean is a collective of management principles and methodology aiming for continuous process improvement[6]. In their book, ‘Banish Waste and Create Wealth in Your Corporation’ published in 1996, Womack and Jones highlight five principles that guide lean application: value, value stream, flow, pull and perfection[16]. The healthcare sector showed considerable interest in adopting lean, especially with the various challenges facing health services.

Lean in healthcare

Lean philosophy is one of the newest approaches for management adopted by the healthcare sector in the last decade[19]. The healthcare sector waited 50 years before starting to adapt and adopt lean. Interest is quickly growing, mainly in developed countries[16]. Many published articles mention encouraging experiences with the implementation of lean[17], but the transformation of the health sector into a lean system requires readiness factors and numerous changes[18]. The lean method promises to increase the service efficiency from the patient’s perspective by involving the front-line workers to redesign the system to become more efficient, reduce the chance of errors and to minimise waste and resources required[19]. Waste in healthcare is seen in several areas such as waiting times, delays, errors, repeated work, improper procedures, overproduction, transportation and fragmented services[20]. Inefficient service has the potential to compromise healthcare service quality, patient safety, patient satisfaction, staff confidence and performance, cost efficiency and organisation productivity[9]. While the interest in a lean concept application within healthcare increases, the adoption of such a management method as a holistic approach is slow[21]. As a starting point, the tools of lean were used for improvement projects usually on localised services or areas of work. The aim is to have lean HCSs although the literature mostly represents case studies on a relatively small scale, for example clinics, departments, operating theatres and hospitals.

Two further principals behind lean philosophy are continuous improvement and respect[13]. Most commonly, the literature focuses upon improving the process in order to save time and reduce queuing by following the concept of eliminating (or at least minimising) waste[19,22,23]. Moreover, many organisations were aiming for cost reductions by improving productivity[19,22], while others targeted the quality of services and enhanced patient safety by reducing the chance of errors[24]. Lean is more than a
tool box; it is a management approach that aims to create a culture of continuous improvement by empowering the front-line engagement in the processes of service improvement[16]. The leading example of adopting lean is the Virginia Mason Medical Center, located in Seattle, USA[20]. They report an improvement in both the quality and flow involving a reduction in staff walking distance by 38%, reducing both the inventory and the leading time by a half[25]. Another example of hospitals mentioned by Spear is the Western Pennsylvania Hospital aiming to save staff time, increase process speeds and reduce work-in-progress[26]. Lean appears to have the potential for providing benefits to healthcare in developing countries[8], however there is a shortage of extensive research in that context[9,10]. Most of the research has been conducted in developed countries[16,17] where the context and the level of system development are different than in developing countries.

The Kuwait healthcare environment

The Kuwait MOH is aiming to maintain and improve its population’s wellbeing by providing a high standard of healthcare services[11]. The expenditure on healthcare sectors is dramatically increasing worldwide[27]. Kuwait has a similar profile as in 2016/2017 healthcare costs were 2.8 billion KD, whereas ten years ago, this figure was only 0.447 billion KD[28], possibly because the free service system leaves it more susceptible to abuse. Furthermore, the government of Kuwait has committed to expenditure on expanding the MOH infrastructure by building clinics and hospitals with the aim to double the total MOH bed capacity within four years[2]. While the MOH has spent much effort and resources to meet the growing demand by improving their infrastructure, it continually faces pressure and challenges to establish an efficient system. Kuwait’s MOH is the main healthcare financier and provider in the state of Kuwait, while the private sector provides a small percentage of services. The Kuwait HCS consists of a total of 100 PHC (primary care), five general hospitals (secondary care) and nine subspecialty hospitals (tertiary care)[29]. These hospitals are distributed to five administrative areas, where each area consists of one general hospital, and numbers of PHC range from seven to twenty-one, while all the tertiary hospitals were located in Al-Subah specialised area. It is worth noting that some general hospitals also provide limited tertiary services.

METHODS

The developed methodology concentrated on identifying the current situation of lean implementation in Kuwait by gathering information from surveying healthcare workers (HCWs) with different roles and expertise. To gain an understanding of the existing experience of using lean tools and techniques, researchers surveyed staff from different member levels including front line workers, those in leadership and those providing direct care in Kuwait’s PHC. Using this methodological approach and collecting primary data helps to establish a baseline for future initiatives and studies.

This research aims to

- Review the published articles about lean in Kuwait’s healthcare.
- Assess the current situation of lean implementation with Kuwait PHCs.
- Determine knowledge about lean among HCWs
- Assess the employee’s beliefs about the requirement to develop and improve the current system and determining if they are willing to participate in future initiatives.

The questionnaire

To the best of the researcher’s knowledge and based on the literature review, there is no previous research about lean in the Kuwait PHC. Finland had a similar situation when they attempted to explore the use of lean in healthcare by developing a questionnaire based on the literature review[30]. The Finnish questionnaire consists of a set of 28 questions and has face-validity.

Researchers used the same questionnaire with some modifications to fit the context and the HCS where the research was to be implemented. The modified version of the questionnaire consisted of 22 questions (Appendix 1). Eight questions were removed and two questions (questions two and three) were added. The reason for the addition of question two was to gain a sense of the HCW’s tendency to participate in future improvement projects. The notion behind adding question three was that sometimes HCWs were aware of some of the principles of lean without knowing the word ‘lean’. A background information section consisting of four parts was also added. The first part asked for the participant’s gender, age and nationality. The second part was concerning the number of years the participant had worked for Kuwait’s MOH. The next section was regarding the location of work and the final section asked about their occupation. In the modified version, the questionnaire ended at three points:

1. At question five: if the participant is not familiar with lean.
2. At question nine: if the participant is familiar with lean but not aware or involved in any lean initiative/project.
3. At question twenty-two: if the participant is
familiar with lean and aware or involved in any lean initiative/project.

There was only one correct answer for each question unless mentioned otherwise. For questions 4, 8, 15 and 22, the participant was able to choose more than one answer. Two physicians working in the Kuwaiti MOH and having a direct role in service improvement within Kuwait’s PHC reviewed the questions for any problematic or confusing phrasing. The necessary changes were made according to their observations and comments. The final version was distributed to three HCWs to be piloted and ensure that all questions were clear and understandable, and any further changes were made accordingly.

Convenience sample

The sampling frame were healthcare staff in the four selected PHCs. Healthcare staff included physicians, nurses, pharmacists, medical technics and administrative staff. Staff who were considered eligible to take part in this survey worked in Kuwait’s MOH in the selected area, spoke English, were available during the data collection time period, were involved directly or indirectly with the patient flow and volunteered. Paper-based questionnaires were distributed by hand (not by email or post) to staff by the lead researcher to HCWs at various levels in different departments working in the four selected PHCs, and were collected between March and May 2019. There were two reasons for selected manual distribution instead of the email system: the return and response rate of an emailed questionnaire can be low and the email system is not well established in the MOH.

To distribute the questionnaires, the researcher met the head of each PHC. The head nominated a specific person who worked in the PHC to help the researcher in the process of distribution and collection. All participants were given the freedom when to complete and submit the questionnaire. Participants were approached in their working environment over a period of three weeks with two reminders/ encouragement or incentives to participate and complete the questionnaire.

Data analysis

The collected data was entered into a Microsoft Excel spreadsheet. The statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 22.0). Descriptive analyses involved tables with counts and percentages for each question stratified by gender, age, nationality, years worked for Kuwait MOH and occupation.

RESULTS

From examining the literature, researchers were unable to find any published articles regarding lean in Kuwait’s healthcare. In total, 160 questionnaires were circulated in four PHCs and 138 were returned for a response rate of 86%. A total of 18 incomplete questionnaires, where one question or more was not answered, were excluded from the analysis leaving us with 120. The respondents were split into physicians (n=44), nurses (n=30), pharmacists (n=23), technicians (n=17) and administrative staff (n=6). The majority of respondents (92%, 111/120) believe that the development of healthcare processes is important/
Table 1: Cross table of the first five questions against background information

<table>
<thead>
<tr>
<th>Question One</th>
<th>Question Two</th>
<th>Question Three</th>
<th>Question Four</th>
<th>Question Five</th>
</tr>
</thead>
<tbody>
<tr>
<td>How important do you consider the development of healthcare processes?</td>
<td>Are you willing to be involved in any healthcare process improvement initiative in the future?</td>
<td>Are you familiar with the concept of eliminating waste from a process or the principle of continuous improvement?</td>
<td>Are you familiar with the following methods? (choose those that you know something about)</td>
<td>Are you familiar with Lean thinking/Lean management/Lean methodology?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not Important</th>
<th>Not Important</th>
<th>Important / High Imp. / Very High Imp.</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>PDSA cycle</th>
<th>Root causes</th>
<th>Value-stream mapping</th>
<th>Kaizen</th>
<th>5S</th>
<th>Kanban</th>
<th>Visual control</th>
<th>None of the above</th>
<th>Total</th>
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<td>Total</td>
<td>7</td>
<td>(5.8%)</td>
<td>2</td>
<td>(1.7%)</td>
<td>111</td>
<td>(92.5%)</td>
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</tbody>
</table>

(80%) (20%) (54%) (46%) (11%) (89%) 120
highly important/very highly important. Of participants, 80% (96/120) were willing to be involved or participate in future healthcare process improvement initiatives. Even then, 54% (65/120) of participants were familiar with the concept of eliminating waste from processes or the principle of continuous improvement, yet only 11% (13/120) answered ‘yes’ for question five which asked if the participants have knowledge about lean (familiar with Lean thinking/Lean management/Lean methodology). Of those who knew lean, none were involved or had an ongoing lean initiative or project. The detailed results are provided below and divided into four sections according to the survey design.

Background information (Demographic)

Table 1 summarises the result of the first five questions against background information. Two-thirds of participants were Kuwaitis (n=80) and one third were non-Kuwaitis (n=40). The majority of participants were in the age group 30-39 years, representing half of the responders. The rest fell within the other categories, where the lowest percentage was for participants who were 50+ years old. For the question relating to number of years participants worked for Kuwait's MOH, the results showed that 38.3% (46/120) had less than five years of experience, 25% (30/120) had six to ten years' experience, 19.1% (23/120) had eleven to fifteen years of experience, and the last three categories of over fifteen years of experience, represent 17.6% (21/120).

All participants questions (first five)

All participants answered the first five questions and the results are shown in Table 1. The response to the first question regarding the importance of healthcare processes development in relation to occupation is shown in Figure 1.

The majority of respondents (92%, 111/120) believed that the development of healthcare processes is important/highly important/very highly important.

---

**Table 2: The awareness about different methods**

<table>
<thead>
<tr>
<th>Method</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDSA cycle</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>Root causes</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>Value-stream mapping</td>
<td>2</td>
<td>118</td>
</tr>
<tr>
<td>Kaizen</td>
<td>7</td>
<td>113</td>
</tr>
<tr>
<td>5S</td>
<td>1</td>
<td>119</td>
</tr>
<tr>
<td>Kanban</td>
<td>2</td>
<td>118</td>
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<tr>
<td>Visual control</td>
<td>23</td>
<td>97</td>
</tr>
<tr>
<td>None of the above</td>
<td>62</td>
<td>58</td>
</tr>
</tbody>
</table>

---

**Fig 2:** HCW beliefs about where in healthcare functions does lean methodology have the greatest potential
Table 3: The result from question six to nine of those participants who were familiar with lean methodology.

<table>
<thead>
<tr>
<th>Question six</th>
<th>Question seven</th>
<th>Question eight</th>
<th>Question nine</th>
</tr>
</thead>
<tbody>
<tr>
<td>In your opinion, where in healthcare functions does Lean methodology have the greatest potential?</td>
<td>Have you considered using Lean methodology in your organisation?</td>
<td>What are the enabling factors for Lean initiatives/project? (choose those that you think applicable)</td>
<td>Did you involved or have an ongoing (or have you had) a Lean initiative(s) or project(s)?</td>
</tr>
<tr>
<td>Healthcare support functions</td>
<td>Healthcare functions indirectly involved in patient processes</td>
<td>Patient processes/patient treatment processes</td>
<td>None of the above</td>
</tr>
<tr>
<td>Number</td>
<td>4 (31%)</td>
<td>2 (15%)</td>
<td>7 (54%)</td>
</tr>
</tbody>
</table>
The participants who were familiar with lean (until question nine)

Those participants who were familiar with lean (13/120) were to proceed with answering the survey until question nine (see Table 3). Results show that 61% (8/12) of participants had considered using the lean methodology in their organisation. The result of the participants opinion of ‘Where in healthcare functions does lean methodology have the greatest potential?’ can be seen in Figure 2. Similarly, 54% (7/12) believe that lean methodology has the greatest potential for improving patient processes/patient treatment processes. On the other hand, 31% (4/12) and 15% (2/12) of participants think that the benefits of lean will be best felt in healthcare support functions (accounting, transportation, general administration, etc.) and healthcare functions indirectly involved in patient processes (pharmacy, laboratory, etc.) respectively. Participants’ views about the enabling factors for lean initiatives/project are presented in Table 4. Further to the enabling factors was good financial resources (10/12), followed by enough time for project (7/12), then a good flow of information (6/12). Four participants believed that lean education, committed management and committed employees were considered as enabling factors for lean initiatives/projects.

The participants who are aware or involved in any lean initiative (until question twenty-two)

Of those who knew lean, no one was involved or had an ongoing lean initiative or project. Therefore, none of the participants completed the questionnaire (from question ten to twenty-two).

DISCUSSION

Researchers were unable to find any published articles regarding lean in Kuwaiti HCS. This study found that most of the HCWs had minimal awareness of lean. Of those who knew lean, none were involved in an ongoing lean initiative or project. However, the HCWs who were involved in this study were enthusiastic and willing to participate and were supportive for adopting an approach for the improvement of the system. The majority agreed that it is important to develop and improve the current system.

Another notable finding is that lean is considered as a relatively new concept in Kuwait. HCWs in PHCs lacked sufficient knowledge and experience in lean implementation. This concurs with the results of a systematic review which mentioned that lean tools are a relatively recent introduction into healthcare in developing countries, mostly in hospitals[32]. Even though 54% (65/120) were familiar with the concept of eliminating waste from processes and the principle of continuous improvement, only 11% (13/120) answered ‘yes’ for question five asking if the participants have knowledge about lean (familiar with lean thinking/lean management/lean methodology).

Furthermore, 80% (96/120) of participants were willing to be involved or participate in any future healthcare process improvement initiative. A total of 54% (65/120) were familiar with the concept of eliminating waste from processes or the principle of continuous improvement, where targets include cost reduction, reduction of queues or better productivity. Table 2 provides the variable response of the results of question four, asking participants on their familiarity with various lean tools and methods. Almost half of the participants were not familiar with the mentioned lean tools and methods. Some 20% of participants were familiar with the plan-do-study-act (PDSA) cycle, root causes and visual control. Kaizen was known by 5.8% of the participants, while less than 2% were aware of value-stream mapping, Kanban and 5S. Despite half of the participants being familiar with at least one lean tool or method, the awareness of lean was very low (see Table 1). Only 11% (13/120) answered ‘yes’ for question five which asked if the participants have knowledge about lean (familiar with lean thinking/lean management/lean methodology).

Table 4: The enabling factors for lean initiatives/project from HCW point of view

<table>
<thead>
<tr>
<th>Committed management</th>
<th>Committed employees</th>
<th>Good financial resources</th>
<th>Enough time for projects</th>
<th>Lean education</th>
<th>Good flow of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4</td>
<td>4</td>
<td>10</td>
<td>7</td>
<td>4</td>
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<td>6</td>
<td>9</td>
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</tbody>
</table>

Of those who knew lean, no one was involved or had an ongoing lean initiative or project. Therefore, none of the participants completed the questionnaire (from question ten to twenty-two).
initiative. Therefore, running a proper awareness campaign and training program prior to lean application is essential for reducing the resistance towards lean implementation and system design changes.

Moreover, the data analysis revealed that HCWs involved in this study emphasised and agreed that the current system needed to be developed. This same opinion is held by 97% of physicians and 93% of nurses, who believe that it is important to develop and improve the current system. The findings of this study are consistent with the results of earlier research which mentioned that 90% of respondents considered developing healthcare processes as very important[32]. The role of the frontline workers is crucial in any improvement project as they play a vital role in identifying problems, finding solutions, facilitating implementation and maintaining results as mentioned and highlighted by more than one researcher[33,34]. In our study, the results indicate that HCWs require the opportunity, support and empowerment from a higher authority to deliver healthcare services in a better and smoother manner with minimum delay and interruption. Despite the low level of awareness of lean philosophy among the respondents, 80% of participants were willing to be involved or participate in any future planned initiative. The perception of participants for future lean initiatives is encouraging as most of the respondents look forward to participating in any upcoming initiative aimed to improve the HCS once they have the opportunity. Introducing a new concept in the environment where employees are overworked and express exhaustion with a bad experience from previous quality initiatives would be a challenge for running a new future improvement project or initiative.

Unexpectedly, less than 2% of participants were aware of the value-stream map. On the other hand, 20% of participants were aware of the PDSA cycle, root causes and visual control. In the literature, the value stream mapping was found to be the most common tool mentioned and used in various lean initiatives[32]. It is highly recommended to start the lean journey with the appreciation of the current situation by involving the front-line workers. Value stream mapping is the ideal tool that allows the HCWs to work together, share knowledge and identify the whole picture of the current state. Consequently, a road map will be developed as a holistic picture with collective minds that will be the end product of this task. Participants selected the following as enabling factors: good financial resources, enough time for the project, good flow of information, lean education, committed management and committed employees. Accordingly, our results are aligned with literature, that stresses the importance of these enabling factors[35]. For example, the leadership role is essential for facilitating the processes of continuous improvement and creating a healthy environment for running a successful project[33]. Higher authorities and leadership should show full support for the HCWs to implement lean. This could be in the form of providing opportunities, resources, commitment and support for adopting lean.

Despite the literature consisting of an abundance of studies on lean implementation in western developed countries[36], Kuwait, as an example of a developing country, is still unexplored and underprivileged when it comes to adapting lean as a management philosophy. Lean is influenced by the context, the complexity and the social environment where it pretends to be applied as an intervention[36]. It is worth having a variety of experiences of lean implementation in different settings and with different methods as the philosophy considers the context, the environment and the culture where the lean pretended to be implemented. Based on the survey results, there are several recommendations to be followed in any future lean initiative implementation. Firstly, it is crucial before starting implementation for any lean initiative to conduct a training program on lean principles, concepts and tools. Furthermore, drawing the current stream map is also essential and highly recommended to be presented for the multidisciplinary teams that are responsible for improving the healthcare services, where they will appreciate the services provided from a systems perspective. Following that, the formed improving team must meet on a regular basis for three to five days to map out the future process map, where all the changes and corrective actions are considered to have an efficient system aiming to improve patient flow, reducing errors, time, and waste with minimum resources. The improvement team recommended brainstorming opportunities for waste elimination within the current process and creating a list of certain actions necessary to attain an improved future state map.

CONCLUSION

This study has explored the lean concept within the context of the Kuwaiti PHCs. It has assessed the HCWs knowledge and perception of lean. The lean approach is relatively new in the Kuwaiti HCS and is therefore not commonly used by the HCWs in Kuwait’s PHC. Most of the HCWs did not possess significant knowledge of lean. They were mainly familiar with PDSA cycle, root causes and visual control methods without realising the philosophy behind these tools. Therefore, it is vital to attain an understanding of the best way of introducing lean in Kuwait’s HCS
environment and avoid the difficulties and challenges facing the other organisations interested in lean philosophy. In order to gain successful results from the lean concept, investment, empowerment and engagement of the staff in the processes of the improvement are mandatory. This requires establishing a healthy environment where HCWs are comfortable and enthusiastic about participating in the continuous processes of improving the system. It is essential to acknowledge that lean is a long-term methodology, and not an on-and-off approach, where the ultimate goal is to reach perfection. Therefore, sustainability and the cycle of continuous improvement is required to develop a culture where the higher authority supports the implementation of such philosophy within daily work activities for all HCWs. It is worth trialling on a small scale with proper monitoring and evaluation in order to achieve this.

Study limitations

Even though the study objective was accomplished, for any future research, certain limitations should be taken into account. One of the limitations of this study was the sample size. Despite the high response rate, the distribution of respondents was limited. Many sites and sub-specialties were not covered, and some organisations did not have a representative. This could result in the over-representation of a particular group in a study where all perceptions and opinions are considered significant. The other limitation was that if the participant was not familiar with lean, the questionnaire ended at question five. This restricted the full awareness of lean among participants and failed to provide sufficient reflection on the full ramifications of this approach. Also, the survey instrument we used was not formally validated, although it had been used in a previous whole-country survey in Finland and has the merit of having face-validity. However, the extent to which the survey instrument is valid and reliable needs further study. The lack of any published studies on lean in Kuwait are consistent with the findings of the survey: lean is new in Kuwait healthcare. This research was limited to the public healthcare sector without considering the other available sectors where the context could be different. Thus, generalising the result may not reflect the existing situation accurately. Nevertheless, this study was conducted in the larger sector in Kuwait (public sector) that provided healthcare services for more than 85% of the population, and can be considered as a basis.

Implications for society and practice

Kuwait’s HCS is undergoing massive changes in its infrastructure, finances and function. The Kuwaiti government is considering a new approach to providing healthcare services, especially in regard to future challenges. They aim to develop an efficient system with the financial constraints. There is growing evidence for the potential that could be gained in improving the system’s efficiency by adopting lean philosophy as a way of system management. Lean could be the solution as it concerns providing more with less. Lean promises to provide positive results, specifically in improving efficiency and patient flow, which will be reflected in the quality of services and patient safety. The authors believe that researching Kuwait’s HCS environment to demonstrate that lean is a way of creating a culture of continuous improvement and of changing the current situation toward efficiency is paramount. Kuwait still lacks sufficient experience in adopting lean and this could give the advantage to benefit from the variety of the previous attempts of lean implementation from different organisations. To become a lean organisation is not an easy journey. However, the organisation that works on eliminating waste, encourages teamwork and creates a culture of continuous improvement shows indications of being on track to accomplish the lean principles. Kuwait may be required to provide a strong foundation and context with the systematic approach for lean adaptation. It is necessary to assess the organisational readiness to change before introducing lean initiatives. The feasibility of lean as a management system and to provide an evidence-based result with a rigorous methodology is highly recommended. At the beginning of lean implementation, it is vital that critical personnel who have higher authority and significant impact on the decision making be a part of the lean project. Their involvement will directly influence and be a drive for a successful result. The majority of the participants in the study (80%) have shown willingness and enthusiasm to be a part of any future initiative for system improvement. This could be encouraging for the attempt to introduce lean into Kuwait’s MOH. Moreover, 61% of the participants in this study who knew about lean but had not been involved in a previous initiative were considering introducing lean in their organisation. This is a positive finding for groups that are interested in lean implementation within Kuwait’s HCS, as the existing environment is ready for lean.

ACKNOWLEDGMENT

Originality/value

This research considers the first attempt for exploring and evaluating the current status of lean concepts within the Kuwaiti PHC. It explores the level of HCW awareness about lean.
Competing interests: The authors declare that they have no competing interests.

Consent for publication: Not applicable.

Ethics, consent and permissions: This study has been ethically approved by the Kuwait MOH ethics committee. Also, the approval has been granted by the Chair of the Humanities, Social and Health Sciences Research Ethics Panel at the University of Bradford on 06/08/18. All participants in this study survey were provided with an information sheet and have the choice to participate in completing the survey.

REFERENCES

2. Kelendar H. The future of Kuwait healthcare system challenges and aspirations: can lean management be the solution, in Kuwait conference on quality in healthcare. Kuwait; 2017
10. Rexhepi L, Shrestha P. Lean Service Implementation in Hospital: A case study conducted in “University Clinical Centre of Kosovo, Rheumatology department”. 2011.
Appendix 1:

Bradford University, School of Health
PhD in Health service improvement

Form 2: healthcare worker level of awareness about lean

Exploring the case for adopting lean in Kuwait to enhance the flow of patients with diabetes in Primary Healthcare Centres

Information sheet

Dear Participant,

Read the following information carefully before deciding in your mind to participate in this study.

1. Taking part in this study is only for the research reason
2. The participation in this study is voluntary.
3. If you have any questions or inquiries regarding this study, please feel free to contact the researcher (Contact details are provided at the end of this page).

There are many development initiatives going on in Kuwait healthcare system. I am writing to ask you to take part in the 2019 Kuwait Health Service (KHS) Staff Survey to identify your perceptions and level of awareness about lean. I am conducting this survey across the KHS, as it is an important way of ensuring that the views of staff working in the KHS are considered to understand the current states of lean within KHS.

Completing this questionnaire is voluntary, will not affect your career development and will take between 2 to 15 minutes of your valuable time depending on your answers. For the background information tick the appropriate box. For the rest of the questions started from question one, circle the letter of the appropriate answer to each question. There is only one correct answer for each question unless it mentions otherwise. This questionnaire is anonymous as no name or any identity information is requested. The study will produce anonymous statistics, from which no individual’s responses can be identified, for each organisation in the KHS taking part in the survey.

This questionnaire is part of a study undertaken by Dr. Hisham Kelendar, as part of his PhD study in the University of Bradford. This study has been ethically approved by the Kuwait MOH ethics committee. Also, the approval has been granted by the Chair of the Humanities, Social and Health Sciences Research Ethics Panel at the University of Bradford on 06/08/18.

I would be grateful if you could return your completed questionnaire. If you have any questions or queries about the study or the questionnaire, please feel free to contact me using the contact details below.

Many thanks for accepting to participate in this study.

Name of Investigator: Dr. Hisham Kelendar
PhD student, University of Bradford, United Kingdom
Tel Number: 00965 99542707
Email: dr.hisham81@gmail.com or h.a.y.kelendar@student.bradford.ac.uk
Circle the letter of the appropriate answer to each question. There is only one correct answer for each question unless it mentions otherwise.

1) How important do you consider the development of healthcare processes?
   a) Not important   b) low important   c) important   d) high important   e) very high important

2) Are you willing to be involved in any healthcare process improvement initiative in the future?
   a) Yes   b) No

3) Are you familiar with the concept of eliminating waste from a process or the principle of continuous improvement? Targets can be, cost reduction, reduction of queues or better productivity
   a) Yes   b) No

4) Are you familiar with the following methods?
   (choose those that you know something about)
   a) PDSA – cycle (defining and solving problems: ‘plan, do, study, act’)
   b) Root causes (finding out the root causes of a problem)
   c) Value-stream mapping (describing customer value in a process map)
   d) Kaizen (or continuous improvement: Improving and aiming for better results)
   e) 5S (tool aims for better coordination: ‘sort, set in order, shine, standardise and sustain’)
   f) Kanban (visual tool – often a card – aiming at, for example, better flow of material)
   g) Visual control (using visual codes, colours and markers, signal tapes, etc.)
   h) None of the above
5) Are you familiar with Lean thinking/Lean management/Lean methodology?
   a) Yes   b) No

6) In your opinion, where in healthcare functions does Lean methodology have the greatest potential?
   a) Healthcare support functions (accounting, transportation, general administration, etc.)
   b) Healthcare functions indirectly involved in patient processes (pharmacy, laboratory, etc.)
   c) Patient processes/patient treatment processes
   d) None of the above
   e) Other, where?........................................................................................................................

7) Have you considered using Lean methodology in your organisation?
   a) Yes   b) No

8) What are the enabling factors for Lean initiatives/project?
   (choose those that you think applicable)
   a) Committed management
   b) Committed employees
   c) Good financial resources
   d) Enough time for projects
   e) Lean education
   f) Good flow of information
   g) Other, what?..........................................................................................................................

9) Did you involved or have an ongoing (or have you had) a Lean initiative(s) or project(s)?
   a) Yes   b) No

10) When did you first launch a Lean – project/initiative?
    a) More than five years ago
    b) 3-5 years ago
    c) 1-3 years ago
    d) Less than one year ago

11) What was the initial reason for initiating Lean in your organisation?
    a) Financial saving/increasing productivity
    b) Better quality of care/fewer errors
    c) Better patient satisfaction
    d) Better patient flow
    e) Other, what?......................................................................................................................

12) Who introduced the first Lean – initiative/project in your organisation?
    a) Member of the front-line staff (nurse, physician, technician, etc.)
    b) Supervisor level (chief nurse, chief physician, etc.)
    c) Middle management (nurse manager, physician manager)
    d) Executive level/top management
    e) Somebody outside your organization

13) Do you have a Lean expert in your organisation?
    a) Yes   b) No

14) In your opinion, how has Lean been implemented in your organisation?
    a) Lean thinking is a part of our organisation’s daily operations.
    b) Lean thinking is systematic but is not included as part of daily operations/management.
    c) Lean thinking is part of process development.
    d) Lean thinking is used in our organisation but not systematically.
    e) Lean thinking has been used but is not currently in use.
15) **What Lean methods have you used in your organisation/unit?**
   (choose those that you have been using)
   a) Lean thinking as a management system
   b) PDCA cycle (defining and solving problems: ‘plan, do, study, act’)
   c) Root causes (finding out the root causes of a problem)
   d) Value-stream mapping (describing customer value in a process map)
   e) Kaizen (or continuous improvement: Improving and aiming for better results)
   f) 5S (tool aims for better coordination: ‘sort, set in order, shine, standardise and sustain’)
   g) Kanban (visual tool – often a card – aiming at, for example, better flow of material)
   h) Visual control (using visual codes, colours and markers, signal tapes, etc.)
   i) Other, what?.............................................................................................................

16) **What is the amount of money invested in your Lean initiative/project?**
   a) More than 50,000 KD
   b) 10,100 – 50,000 KD
   c) Less than 10,000 KD
   d) No money invested/done in daily work
   e) N/A

17) **What (if measured) is the amount of money saved with Lean – initiative/project?**
   a) More than 50,000 KD
   b) 10,100 – 50,000 KD
   c) Less than 10,000 KD
   d) N/A

18) **Do you or did you require specific or measurable goals when initiating a Lean project?**
   a) Yes  b) No

19) **In your opinion, have Lean initiative/project been successful in your organisation?**
   a) Yes  b) No

20) **What is the most important benefit that Lean methodology has brought to your organisation?**
   a) Economic savings/better productivity
   b) Better quality of care/fewer treatment errors
   c) Better patient satisfaction
   d) Other, what?.............................................................................................................

21) **Which professional group was the least supportive of your organisation’s Lean initiative/project?**
   a) Nurses
   b) Physicians
   c) Other personnel involved in patient/treatment processes
   d) Supervisors
   e) Middle management
   f) Executive management

22) **What are (in your opinion) the reasons for resistance to Lean initiative/project?**
   (choose those that you think applicable)
   a) Tired of development projects
   b) Lack of knowledge
   c) The will to maintain old ways to do things
   d) Discrepancies between professional groups
   e) Negative experiences from previous Lean initiatives
   f) Other, what?.............................................................................................................
Five-year laboratory-based study of *Candida albicans* versus non-*albicans* *Candida* species at a tertiary pediatric care hospital in Iran

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6Department of Medical Laboratory Science, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran

**ABSTRACT**

**Objective:** To determine the distribution of *Candida albicans* and non-*albicans* *Candida* species in various specimen types of pediatric patients

**Design:** Retrospective cross-sectional study using laboratory database

**Setting:** Children’s Medical Center, Tehran, Iran from 2012 to 2016

**Subjects:** All specimens from pediatric patients with positive culture for *Candida* species in microbiological examinations

**Intervention:** None

**Main outcome measures:** Frequency of *Candida* species in different specimen types for five years

**Results:** During the study period, 2755 out of 2,95,525 (0.93%) specimens were positive for *Candida* growth in culture. Of them, 550 (19.96%) were from normally sterile specimens or sites. *C. albicans* was the predominant species (68.9%), significantly isolated from both genders (*P*=.009), and all age groups (*P*=.011). However, in 2014 and 2015, almost 50% of isolates from normally sterile specimens or sites were non-*albicans* *Candida* species. Urine samples were the greatest source of isolation (n=1314, 47.7%), followed by throat swabs (n=472, 17.1%) and blood specimens (n=344, 12.5%). Children were the prevailing age group for *Candida* isolation (n=1435, 52.1%), followed by infants (n=1012, 36.7%) and neonates (n=308, 11.2%).

**Conclusion:** *C. albicans* was the dominant species in Children’s Medical Center. However, the proportion of non-*albicans* *Candida* species was higher in some specimen types and the frequency of *Candida* species was different in various wards. These data could be beneficial in a clinical setting.

**KEY WORDS:** *Candida*, candidemia, candidiasis, infant, Iran

**INTRODUCTION**

*Candida* species are among the most important fungi with an opportunistic nature. They can cause a variety of diseases known as candidiasis, ranging from cutaneous involvement to blood stream and systemic infections[1,2]. These fungi are the fourth most prevalent etiology of sepsis in the United States and the third most common cause of healthcare associated sepsis in children[3,4]. Invasive candidiasis is associated with a mortality rate of 10% in children and it results in prolonged hospital stay and economic burden[5].

The genus *Candida* comprises of more than 30 species with clinical importance and *Candida albicans* (*C. albicans*) has been reported as the prevailing cause of candidiasis in various patient groups including neonates and children[6,7]. However, an increasing
trend in the incidence of non-albicans Candida (NAC) species has been observed in recent decades\[1,4,8\], which is supposed to be associated with the prophylactic use of antifungal drugs\[9,10\], and it is of great clinical importance. NAC species have less susceptibility to antifungal drugs such as fluconazole in comparison to \textit{C. albicans}\[8\]. Also, intrinsic resistance to azoles and amphotericin B in some NAC species has been reported\[10\]. Furthermore, in recent years \textit{Candida auris} has emerged as a multidrug resistant NAC species which is associated with high mortality rates\[11\].

The changing role of NAC species in clinical setting implies the need for awareness of epidemiology of \textit{Candida} species\[10\]. Considering the importance of early initiation of therapy in candidiasis, treatment is usually initiated empirically without the aid of laboratory data\[12\], which increases the risk of treatment failure in the case of resistant species. Therefore, identification of causal agents as \textit{C. albicans} or NAC species (especially those with intrinsic resistance) helps in appropriate antifungal selection\[10,12,13\].

Although several studies on different patient groups are available in Iran, few reports have been published on pediatric patients\[14-20\]. To the best of our knowledge, there is no comprehensive report with large scale study population on pediatrics in Iran. Therefore, the aim of the present study was to retrospectively analyze the prevalence of \textit{C. albicans} and NAC species in a wide variety of specimen types of pediatric patients during a five-year period to provide a general view of the etiology of candidiasis in these patients.

**SUBJECTS AND METHODS**

**Data collection**

This retrospective study was carried out for five years from 2012 to 2016 at Children’s Medical Center as a tertiary care hospital for pediatrics affiliated to...
Table 1: The annual and total number of Candida albicans and non-albicans Candida species isolated from various specimen types in a pediatric tertiary care hospital in Iran

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Candida species</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Total n</th>
<th>Total n (%)</th>
<th>Chi-square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>CA</td>
<td>98</td>
<td>164</td>
<td>256</td>
<td>178</td>
<td>156</td>
<td>852</td>
<td>1314 (47.7)</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td></td>
<td>NAC</td>
<td>72</td>
<td>172</td>
<td>70</td>
<td>81</td>
<td>67</td>
<td>462</td>
<td>472 (17.1)</td>
<td>P=.496</td>
</tr>
<tr>
<td>Throat swab</td>
<td>CA</td>
<td>16</td>
<td>48</td>
<td>110</td>
<td>134</td>
<td>91</td>
<td>399</td>
<td>344 (12.5)</td>
<td>P=.561</td>
</tr>
<tr>
<td></td>
<td>NAC</td>
<td>0</td>
<td>13</td>
<td>15</td>
<td>27</td>
<td>18</td>
<td>73</td>
<td>185 (6.7)</td>
<td>P=.217</td>
</tr>
<tr>
<td>Blood</td>
<td>CA</td>
<td>36</td>
<td>30</td>
<td>43</td>
<td>22</td>
<td>56</td>
<td>187</td>
<td>97 (3.5)</td>
<td>P=.937</td>
</tr>
<tr>
<td></td>
<td>NAC</td>
<td>21</td>
<td>34</td>
<td>40</td>
<td>35</td>
<td>27</td>
<td>157</td>
<td>60 (2.1)</td>
<td>P=.873</td>
</tr>
<tr>
<td>Stool</td>
<td>CA</td>
<td>0</td>
<td>35</td>
<td>47</td>
<td>34</td>
<td>7</td>
<td>123</td>
<td>97 (3.5)</td>
<td>P=.937</td>
</tr>
<tr>
<td></td>
<td>NAC</td>
<td>0</td>
<td>13</td>
<td>22</td>
<td>24</td>
<td>3</td>
<td>62</td>
<td>185 (6.7)</td>
<td>P=.217</td>
</tr>
<tr>
<td>Sputum</td>
<td>CA</td>
<td>3</td>
<td>1</td>
<td>24</td>
<td>25</td>
<td>38</td>
<td>91</td>
<td>97 (3.5)</td>
<td>P=.937</td>
</tr>
<tr>
<td></td>
<td>NAC</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>64 (2.3)</td>
<td>P=.075</td>
</tr>
<tr>
<td>Dialysis fluid</td>
<td>CA</td>
<td>14</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>33 (1.1)</td>
<td>P=.084</td>
</tr>
<tr>
<td></td>
<td>NAC</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>15</td>
<td>48 (1.7)</td>
<td>P=.538</td>
</tr>
<tr>
<td>Wound discharge</td>
<td>CA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>11</td>
<td>32</td>
<td>46 (1.7)</td>
<td>P=.760</td>
</tr>
<tr>
<td>BALc</td>
<td>NAC</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>14</td>
<td>43 (1.6)</td>
<td>P=.359</td>
</tr>
<tr>
<td>CVCd</td>
<td>CA</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>13</td>
<td>23</td>
<td>38 (1.4)</td>
<td>P=.760</td>
</tr>
<tr>
<td>Tracheal aspirate</td>
<td>CA</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>31</td>
<td>26 (0.9)</td>
<td>P=.278</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>CA</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>8</td>
<td>21</td>
<td>22 (0.8)</td>
<td>P=.925</td>
</tr>
<tr>
<td>Ocular specimens</td>
<td>CA</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>15</td>
<td>18 (0.7)</td>
<td>P=.730</td>
</tr>
<tr>
<td>CSFc</td>
<td>CA</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>15</td>
<td>10 (0.4)</td>
<td>P=.493</td>
</tr>
<tr>
<td>Suprapubic urine</td>
<td>CA</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>4 (0.1)</td>
<td>P=.317</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>CA</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>3 (0.1)</td>
<td>P=.480</td>
</tr>
<tr>
<td>Abscess drainage</td>
<td>CA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2 (0.07)</td>
<td>-</td>
</tr>
<tr>
<td>Ear discharge</td>
<td>CA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>P=.480</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>CA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1 (0.015)</td>
<td>-</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>CA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.015)</td>
<td>-</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>NAC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>P=.317</td>
</tr>
<tr>
<td>Total</td>
<td>NAC</td>
<td>1314</td>
<td>185</td>
<td>329</td>
<td>529</td>
<td>444</td>
<td>1897</td>
<td>2755 (100)</td>
<td>P&lt;.001</td>
</tr>
</tbody>
</table>

*Candida albicans; †Non-albicans Candida species; ‡bronchoalveolar lavage; ††central venous catheter; †‡cerebrospinal fluid

Tehran University of Medical Sciences, Tehran, Iran. The protocol of this study was approved by the ethics committee of Tehran University of Medical Sciences. Medical records of 2,955,525 microbiology laboratory specimens from 2,19,486 patients were reviewed in laboratory database and all cases with Candida growth in culture were recorded. Candida isolation from specimens of blood, central venous catheter, suprapubic urine, abscess drainage, wound discharge, synovial fluid, peritoneal fluid, pleural fluid, dialysis fluid and cerebrospinal fluid were considered clinically significant.

Information including demographic data of patients, hospitalization ward, specimen type and Candida species (C. albicans / NAC species) were extracted for all the Candida isolates. In the case of age, patients were categorized as neonate (≤28 days), infant (1-12 months) and child (1-18 years).
Laboratory analysis

All specimens were examined based on the routine microbiology laboratory procedures. Culture of specimens of normally sterile body fluids was done in Bactec automated system (Bactec 9120, Becton Dickinson, USA). Culture of other specimen types and sub-culture of positive cases in Bactec were carried out on blood agar (Merck, Darmstadt, Germany), chocolate agar (Merck, Darmstadt, Germany) and MacConkey agar culture media (Merck, Darmstadt, Germany). All culture plates were incubated at 35 °C and checked daily for up to seven days. In order to distinguish between C. albicans and NAC species, germ tube test in fresh serum (incubation at 37 °C for up to three hours) was performed and all germ tube forming isolates were considered as C. albicans.

Statistical analysis

Data were analyzed using chi-square test. Mantel-Haenszel and Extended Mantel-Haenszel chi square were carried out to determine the linear trend over time. The association between time and annual incidence per 1000 laboratory admissions was studied using Kendall Tau-b. The distribution of C. albicans and NAC species in various hospital wards was studied using Pearson’s chi-squared test. All analysis was performed in SPSS version 22 and P-value less than 0.05 was considered as significance level.

RESULTS

During the five-year period of this study, 2755 out of 2,95,525 (0.93%) specimens were positive for Candida growth in culture. These isolates were recovered from 1946 out of 2,19,486 (0.89%) patients. In the case of clinical relevance, 550 out of 2755 (19.96%) Candida isolates (C. albicans, 330 isolates; NAC species, 220 isolates) were recovered from normally sterile sites or specimens (Figures 1A and 1B).

Urine samples were the greatest source of isolation (n=1314, 47.7%), followed by throat swabs (n=472, 17.1%) and blood specimens (n=344, 12.5%). A total of 181 Candida isolates were recovered from respiratory tract specimens including sputum, tracheal aspirate and bronchoalveolar lavage. The least common sources of isolation were pleural and synovial fluids (each 1 isolate). Table 1 represents the annual and total number of C. albicans and NAC species isolated from various specimen types during the study period.

According to the statistical analysis, the ratio of C. albicans / NAC species was significantly increased over time for urine samples (P<.001). Although the same trend was not observed for other specimen types (Table 1), for pooled data of all the specimens, the ratio was changed significantly as well (P<.001). The incidence of Candida isolation per 1000 microbiology laboratory specimens was changed over time from 4.59 in 2012 to 10.04 in 2016 with a peak at 12.57 in 2014.
However, a statistically significant increasing trend was not observed ($P=0.327$) (Table 1). *Candida* species were significantly more isolated from males than females (60.9% vs. 39.1%; $P=0.009$). Furthermore, *C. albicans* was more frequently isolated than NAC species in general (68.9% vs. 31.1%) and in both genders (female: 72.6% vs. 27.4%; male: 66.4% vs. 33.6%) which was statistically significant (female: $P=0.008$; male: $P<0.001$). The median age of patients was 1 year (range: 1 day to 18 years). Children were the prevailing age group for *Candida* isolation (n=1435, 52.1%), followed by infants (n=1012, 36.7%) and neonates (n=308, 11.2%) (Figure 1C). The total number of isolates in children and infants in comparison to neonates had a significant increasing trend over time ($P=0.011$). Furthermore, in children and infants the ratio of *C. albicans* / NAC species was significantly increased from 2012 to 2016 (children: $P<0.001$; infant: $P=0.036$). The same trend was not observed in neonates ($P=0.511$).

Outpatients constituted the main source of *Candida* isolation (n=454, 16.48%) followed by patients in cardiac intensive care unit (ICU) (n=298, 10.82%). The least number of isolates were recovered from bone marrow transplantation ward, with only one isolate during the study period (Figure 2). The frequency of *C. albicans* isolation compared to NAC species was higher throughout the study and the ratio of *C. albicans* / NAC species was significantly different in various hospital wards ($P<0.001$). Furthermore, the distribution of *C. albicans* and NAC species in various specimen types of different age groups was not similar (Figure 3).

**DISCUSSION**

*Candida* species are among normal commensals of many parts of the body including the skin, mucous membranes, respiratory system, gastrointestinal and genital tracts$^{[21]}$. Nevertheless, colonization of this organism in any site of the body can cause infection in that area$^{[22,23]}$. The isolation of *Candida* species from surveillance cultures during hospitalization has been defined as colonization$^{[22,23]}$. It is evident that colonization is a main marker for potential invasive infection, therefore recovery of *Candida* species from any site of the body should be considered and...
monitored in hospitalized patients\textsuperscript{[22-25]}.

In this study, we analyzed the frequency and distribution of \textit{C. albicans} and NAC species over a five-year period in a tertiary pediatric care hospital. We observed an absolute predominance of \textit{C. albicans} (68.9\%) in general and in both normally sterile (60\%) and non-sterile (71.1\%) specimens/sites, which is in keeping with other studies reporting a high prevalence of this species\textsuperscript{[4,13,19,20,26-28]}. However, the annual isolation ratio of \textit{C. albicans} (\textit{C. albicans} / NAC species ratio) did not follow a homogeneous trend. It changed from 64.4\% in 2012 to 75.1\% in 2016 with some fluctuations.

In the present study, urinary tract specimens (urine, urinary catheter and suprapubic urine samples) were the major source of \textit{Candida} isolation (1357 of 2755 isolates, 49.2\%), which is due to the higher number of these specimens (more than 50\% of annual microbiology laboratory specimens). Generally, \textit{C. albicans} was the most frequent species (64.9\%) in urinary tract specimens, which is in agreement with other studies\textsuperscript{[17,19,20]}. However, in suprapubic urine samples, NAC species were the prevailing isolated \textit{Candida} (10/17, 58.8\%). The dominance of NAC species is observed in other studies as well\textsuperscript{[29,31]}. Since urinary tract infections represent the most frequent diagnosis of invasive \textit{Candida} infections, candiduria should be considered. However, except for suprapubic urine samples, candiduria could not be directly linked to urinary tract infection, and more studies are required for distinguishing between colonization and infection\textsuperscript{[29]}.

A total of 181 \textit{Candida} isolates were recovered from sputum, tracheal aspirate and bronchoalveolar lavage. It should be noted that \textit{Candida} pneumonia is a rare infection of the lungs, with the majority of cases occurring secondary to hematological dissemination of \textit{Candida} organisms, usually from the gastrointestinal tract or skin\textsuperscript{[32]}. However, critically ill pediatric patients bedridden in ICUs under ventilation, or patients with serious underlying conditions such as cystic fibrosis and cancers, because of therapies with broad spectrum antibiotics, oral and inhaled steroids and chemotherapy, are more likely to be colonized with \textit{Candida} species in their respiratory tract\textsuperscript{[30]}. \textit{C. albicans} is a common colonizer and potential pathogen found in respiratory specimen cultures of cystic fibrosis patients\textsuperscript{[34]}. As the majority of respiratory specimens in our center were from cystic fibrosis patients, the dominance of \textit{C. albicans} (154/181, 85.1\%) was confirmed in this study, as well.

Generally, an increasing trend for NAC species in blood samples has been observed over time and even frequencies higher than 50\% for NAC species have been reported in some pediatric settings\textsuperscript{[27,28,33,36]}. Similarly, in the present study, approximately the lowest overall rate of \textit{C. albicans} isolation (54\%) was observed in blood specimens. Furthermore, even the dominance of NAC species was observed in 2013 and 2015 with isolation rates of 53.1\% and 61.4\%, respectively. These findings are almost in accordance with the previous study carried out on candidemia in this center\textsuperscript{[20]}.

\textit{C. albicans} was five times more frequent than NAC species (15 vs. 3) among cerebrospinal fluid specimens. Isolation of \textit{Candida} species from cerebrospinal fluid represents an episode of disseminated candidiasis, which most often occurs in neonates. It is strongly associated with the use of the ventricular shunt\textsuperscript{[37]}. It should be highlighted that isolation of \textit{Candida} species from blood and other normally sterile body fluids is of great clinical importance and should be taken into account\textsuperscript{[24]}.

In the present study, the majority of \textit{Candida} strains (52.1\%) were isolated from children (1-18 years old) (Figure 1), while in previous cross-sectional studies carried out in this center, infants (1-12 months) were the most common source of \textit{Candida} isolation\textsuperscript{[19,20]}. Likewise, Oeser \textit{et al}\textsuperscript{[38]} and Nucci \textit{et al}\textsuperscript{[39]} in their studies reported the highest rate of candidemia in infants aged <1 year. This variation in results could be due to the type of specimens included in each study. In this study, data of all specimen types were included, some of which were dominantly taken from children (Figure 3).

Although \textit{C. albicans} was the dominant species in all age groups throughout the study, the ratio of \textit{C. albicans} to NAC species was not constant (neonate: 2.6; children: 2.5; infant: 1.8). Even higher isolation rate of NAC species was observed for infants in 2013 (51.7\%). However, the absolute isolation of \textit{C. albicans} from neonates has been reported by Oeser \textit{et al}\textsuperscript{[30]}. These proportions could change based on specimen types, study populations and geographical origin.

Globally, the distribution of \textit{Candida} species differs according to the type of patients, their underlying diseases and risk factors. Subsequently, the distribution differs in various hospital wards\textsuperscript{[39]}. In the present study, the number of \textit{C. albicans} recovered from all hospital wards was dramatically higher than NAC species (Figure 2). The majority of \textit{Candida} isolates (n=930, 33.8\% of total isolates) were recovered from the ICU wards. This finding is in agreement with the statement that ICU stay is an independent risk factor for invasive candidiasis development\textsuperscript{[30]}. However, it is claimed that the incidence of candidemia has increased over the last decade in internal medical wards and the burden of candidemia is shifting to general departments\textsuperscript{[34,35]}. Also, it is reported that candidemia in internal medical wards have unique characteristics and high mortality rate\textsuperscript{[40]}. Accordingly, \textit{Candida} species should be considered in all hospital wards.
Collectively, the present study provided a general view of frequency and distribution of *C. albicans* and NAC species based on the specimen types, age groups and hospital wards. It could be considered as the main advantage of this study because there were no comprehensive data in pediatric patients in Iran.

However, NAC species did not identify to the species level, which is a disadvantage for this study. Taken together, it seems that Candida isolation have an increased trend over time, however we could not find a significant increase throughout the study period. Accordingly, further studies are needed to prove this claim. Also, identification of Candida isolates to the species level and determination of their antifungal susceptibility patterns could be beneficial for appropriate treatment of patients.

CONCLUSION

*C. albicans* was the dominant species in Children’s Medical Center. However, the proportion of NAC species was higher in some specimen types, and the frequency of Candida species was different in various wards. It indicates that clinicians should be aware about the distribution of Candida species in their hospital, and even in various wards. It provides a basic information for appropriate treatment of patients.

ACKNOWLEDGMENT

Conflict of Interest: None.

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REFERENCES


Predictive value of bone scintigraphy in the diagnosis of prostate cancer bone metastases and comparison of verification methods

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Objective: There is no definitive consensus on the methods to verify suspicious lesions in bone scintigraphy (BS) for bone metastases in patients diagnosed with prostate cancer (PCa). In this study, we aimed to compare the accuracy rates of imaging modalities used for patients with suspected lesions in BS.

Design: Retrospective cross-sectional study

Setting: Tertiary university hospital

Subjects: One hundred and twenty-six PCa patients with bone metastases

Intervention: BS was applied to all patients for bone metastases screening. Patients underwent computerized tomography, X-ray, magnetic resonance imaging (MRI) and positron emission tomography for bone metastasis verification for suspicious lesions in BS.

Main outcome measures: Comparison of metastasis detection rates of the imaging modalities and the evaluation of sensitivity of BS according to the location and the number of lesions.

Results: MRI provided the highest rate of metastasis confirmation (81.3%). We found that the rate of detection of metastases in thoracal vertebrae, pubic bones, femur, L3-5 vertebrae and multiply involved cases was statistically significant (P<.05). Metastasis verification rate in non-vertebral lesions was significantly higher than vertebral lesions (58.2% vs 25.9%, P=.018).

Conclusion: MRI is the most accurate method providing metastasis verification for suspect foci in BS. As the number of lesions increases and in the involvement of the non-vertebral locations, the ability of BS to distinguish true metastases from false-positive metastases increases. Prospective, randomized trials are needed to routinely recommend MRI as a first-line procedure for the diagnosis of bone metastases.

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INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer of men and is the second most common cause of cancer-related deaths. The majority of cases diagnosed with PCa are asymptomatic. In these cases, the diagnosis is based on abnormal prostate-specific antigen (PSA) and/or digital rectal examination findings. After making a PCa diagnosis by ultrasound guided biopsy, the primary aim is to stage the disease correctly. PCa staging is performed according to the TNM staging system of the American Joint Cancer Committee[1]. Pre-treatment parameters are used in the clinical staging of PCa in order to predict the prognosis, evaluate the extent of the disease and decide on appropriate treatment. These include serum PSA and its derivatives, digital rectal examination, biopsy-detected Gleason Score, positive core number, tumor length in the cores and imaging findings[2]. In low-risk localized disease, imaging is not necessary for staging purposes[3]. According to the guidelines of the
European Association of Urology, additional imaging should be utilized if it changes the treatment plan of the patient[6].

There is no consensus on the standard procedures for the detection of metastatic disease. For this reason, in a joint opinion study taking into account the guidelines used, the Radiographic Assessments for Detection of Advanced Recurrence group recommends bone scintigraphy (BS), and abdomen, pelvis and thorax computerized tomography (CT) for initial evaluation. Additional recommended evaluation tools are direct X-ray imaging, magnetic resonance imaging (MRI) and 18F sodium fluoride (NaF)-Positron Emission Tomography (PET)[4]. Another imaging modality is prostate-specific membrane antigen (PSMA) PET/CT. Using a radiotropic substance named Gallium 68, PSMA-11 is very effective in diagnosing prostate cancer-related lymph nodes, soft tissue and bone metastatic disease. There is a great deal of evidence in the literature on the clinical success of PSMA PET/CT for staging and disease location in biochemical recurrence in high-risk prostate cancer[6]. BS is the most commonly used method to detect bone metastases due to PCa. BS using Tc99m is sensitive to osteogenic activity, and it is possible to evaluate the whole body with this method. However, there are some limitations. BS shows the tumor’s secondary effects on the bone, rather than its own proliferation. Trauma and many other non-cancerous foci may cause false positive results[6]. It does not show microscopic involvement and its sensitivity and specificity are low for osteolytic lesions. Its diagnostic significance is affected by PSA level, clinical stage and the tumor’s Gleason score.

In the presence of suspicious lesions, confirmation with X-ray imaging, CT, MRI and PET/CT may be required. In the current literature, there is no definitive suggestion regarding which imaging method should be used in the first plan for these lesions. In the present study, we aimed to compare the accuracy rates of various imaging methods used for metastasis verification in patients with suspicious lesions after PCa diagnosis and to evaluate the clinico-pathologic factors predicting metastasis in these patients. In addition, the sensitivity of BS according to location and number of lesions was assessed.

SUBJECTS AND METHODS

Study population

In this study, data of 126 patients who were diagnosed with PCa by transrectal ultrasound-guided biopsy between January 2010 and January 2017 and underwent BS for cancer staging, were analyzed. Patient’s age, PCa characteristics, location and number of lesions involved in BS, the imaging method used for verification and the metastasis status as a result of verification were recorded from patient files and analyzed.

Imaging methods used in the diagnosis of bone metastases

Whole-body bone scintigraphy

A single-headed gamma camera with low-energy high-resolution parallel-hole collimator was used for imaging and the patients were injected intravenously with diprophosphate compounds (MDP or HMDP) labeled with Tc-99m at 15-30 mCi (according to patient’s weight) for scintigraphic examination. Two to three hours after the injection, whole body images were taken from all patients in anterior and posterior projections, and spot planar images were taken from suspicious areas if necessary. Foci of increased activity involvement (such as degenerative changes) were interpreted as suspected metastatic lesions.

X-ray imaging

A cassette or detector was selected at the point where it will not cut the targeted area. The tube-cassette distance was determined as 100 cm. The centralization was made to the center of the target and perpendicular to the film. The patient was instructed not to move after adjusting the patient position and collimating in the required measurements. Radiographs were obtained with anteroposterior and lateral views with a high kilovoltage up to 120 kV. The X-ray graphy was performed with an average of 50 KV and 8 MaS.

Computerized tomography

A 64-slice scanner (Somatom Sensation 64; Siemens Healthcare) or a 16-slice scanner (Somatom Sensation 16; Siemens Helathcare) was used for CT. The iodinated contrast agent iomeprol was applied for better soft tissue resolution. Axial and coronal images were reconstructed in the bone windows with varying thicknesses from 1.25 mm to 5 mm.

Magnetic Resonance Imaging

A 1.5-T scanner (MAGNETOM Avanto; Siemens Healthcare) or a 3.0-T scanner (MAGNETOM Skyra; Siemens Healthcare) device was used for MRI images. Images were taken before and after administration of gadolinium contrast agent. Cortical bone invasion was suspected in the absence of a typical hypointense signal of the bone cortex in T1- and T2-weighted images. Bone marrow involvement was confirmed in the presence of a hypointense signal at T1, a hyperintense signal at T2, or contrast enhancement. In addition, bone invasion was considered when there was a diffusion restriction with a signal increase in the diffusion-weighted imaging and/or a decrease in the apparent diffusion of the coefficient value.
Positron Emission Tomography

Imaging was performed with a dual-modality two-detector row PET-CT scanner following injection of [18F]-fluoro-2-deoxy-D-glucose. The patients were recommended to fast for six hours before the procedure to provide blood glucose levels below 150 mg/dl. Intravenous buscopan was applied to prevent the first pass effect of [18F]-fluoro-2-deoxy-D-glucose to smooth muscle. 20 mg furosemide was administered to increase renal excretion of the tracer and prevent accumulation in benign cells. One hour after the administration of [18F]-fluoro-2-deoxy-D-glucose, a low-dose CT scan including neck, thorax, abdomen and pelvis was performed to optimize PET signaling. Then, an emission examination was performed using an integrated GSO crystal-based PET system with 3D Row Action Maximum Likelihood algorithm reconstruction. Subsequently, diagnostic contrast-enhanced CT imaging was performed in the venous phase with administration of 120 ml of intravenous contrast agent. PET and CT images were then fused using a special software program. An average of 24 mSv ionization radiation dose was calculated for the entire examination.

Outcome assessment

The accuracy rates of the imaging modalities performed for the verification of the lesions involved in BS and the metastasis detection rates according to the location and number of the lesions were compared. The study was conducted in accordance with the Helsinki declaration, and the hospital’s ethics committee for clinical trials approved the study (decision number: 17-3 / 1, date: 31.03.2017).

Statistical analysis

Chi-square test was used to analyze the relationship of locations with metastasis status. Logistic regression analysis was performed according to the Forward Stepwise method. SPSS 23.0 package program was used for all statistical analyzes. A value of $P<.05$ was considered statistically significant.

RESULTS

Bone metastasis due to PCa was verified with other imaging modalities in 65 of 126 patients (51.6%) with suspicious involvement in BS. A total of 89 different locations were detected in the BS and the total number of lesions was 294. The number of positive lesions in the BS of patients ranged from 1 to 16 for a single patient and 38 patients had more than one involvement, and metastasis was confirmed in 89.5% of these patients. BS revealed 112 vertebral and 182 non-vertebral involvement and metastasis verification rate was 58.2% in non-vertebral locations, while it was 25.9% in vertebral locations ($P=.018$). The involved lesions in BS whose metastasis status was significant according to locations are given in Table 1. The specificity and sensitivity of BS for metastasis diagnosis were 60.8% and 85.2% in patients with multiple lesion involvement, respectively ($P<.001$). MRI was the imaging modality that provided the highest metastatic confirmation rate for the lesions involved in scintigraphy (81.3%). The rates of metastasis detection according to different imaging protocols are given in Table 2.

<table>
<thead>
<tr>
<th>Imaging method</th>
<th>Metastasis status</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (%)</td>
<td>Positive (%)</td>
</tr>
<tr>
<td>CT</td>
<td>39 (51.3)</td>
<td>37 (48.7)</td>
</tr>
<tr>
<td>CT + X-ray graphy</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>X-ray graphy</td>
<td>12 (70.6)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>MRI</td>
<td>3 (18.8)</td>
<td>13 (81.2)</td>
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<tr>
<td>MRI + CT</td>
<td>2 (40)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>MRI + X-ray graphy</td>
<td>1 (25)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>PET-CT</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>PET-CT + MRI</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>61 (48.4)</td>
<td>65 (51.6)</td>
</tr>
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</table>

CT: computerized tomography; MRI: magnetic resonance imaging; PET: positron emission tomography
All of the patients had adenocarcinoma histopathology. The most frequent Gleason score was 4 + 5 = 9/10 (38.1%) and the most commonly used verification method was CT (60.3%). BS provided 78.6% specificity and 90.8% sensitivity for the diagnosis of metastases in patients with more than one lesion involvement. In addition, its negative predictive value was 67.5% and positive predictive value was 49.2% ($P= .015$). In cases with more than 3, 5 and 9 lesion involvement in BS, the incidence of metastasis was found to be significantly higher than the cases with less lesion and as the number of positive lesions increased, the rate of metastasis increased (Table 3). Sensitivity and specificity of BS were 76.5% and 82.7% ($P= .036$) for vertebral involvement, and 92.4% and 78.6% for non-vertebral involvement respectively ($P= .028$).

<table>
<thead>
<tr>
<th>Number of positive lesions</th>
<th>Metastasis status</th>
<th>$P$</th>
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<tbody>
<tr>
<td></td>
<td>Negative (%)</td>
<td>Positive (%)</td>
</tr>
<tr>
<td>≤3</td>
<td>42 (71.2%)</td>
<td>17 (28.8%)</td>
</tr>
<tr>
<td>≥4</td>
<td>19 (28.4%)</td>
<td>48 (71.6%)</td>
</tr>
<tr>
<td>≤5</td>
<td>50 (65.8%)</td>
<td>26 (34.2%)</td>
</tr>
<tr>
<td>≥6</td>
<td>11 (22%)</td>
<td>39 (78%)</td>
</tr>
<tr>
<td>≤9</td>
<td>54 (65.9%)</td>
<td>28 (34.1%)</td>
</tr>
<tr>
<td>≥10</td>
<td>7 (15.9%)</td>
<td>37 (84.1%)</td>
</tr>
</tbody>
</table>

### DISCUSSION

PCa causes systemic metastases most often in the bones, and early involvement of other sites is rare. Visceral metastases (lung, liver, etc.) arise in the late stages of the disease and bone metastases are present in 90% of patients who die from the disease[7]. When a diagnostic examination of the bones is needed, the Technetium-99 radionuclide bone scanning continues to be the standard procedure[8,9]. Its high sensitivity, accessibility and cost-effectiveness are the key advantages[10]. The most important drawback of BS is its low specificity due to the non-tumor specificity of the radioactive adsorbent. However, bone scan is only indicated for symptomatic patients and asymptomatic men who are at high risk for occult metastases (prognostic groups IIb, III, or IV; serum PSA >20 ng/ml or a T2 primary tumor with serum PSA >10 ng/ml or a Gleason 8 tumor or a T3 or T4 tumor)[11]. In our study, patients mostly had advanced stage tumors; 56.3% of them had a tumor with a Gleason score of 8 and above.

It is a very common scenario that bone metastases are suspected in the BS reports and recommended to be verified by other radiological methods. The fact that BS can give false positive results due to trauma and many other non-cancerous lesions reveals the necessity of verifying methods for metastasis diagnosis and direct X-ray imaging, CT, MRI and PET/CT are available options for this purpose. Although there are numerous studies evaluating all these modalities in the case of bone metastases in patients with PCa, their efficacy is still unclear and there is no consensus on their utilization. In this study, we aimed to determine the clinicopathologic factors predicting bone metastases in patients who underwent BS after PCa diagnosis and to compare the verification methods. To our knowledge, this is the first clinical trial evaluating the diagnostic accuracy of BS according to the locations and number of lesions involved in the skeletal system.

BS positivity rate is lower than 1% in low-risk patients. A large retrospective study conducted in United Kingdom showed that PSA level and Gleason score were the independent predictors of positive BS. The authors concluded that its negative predictive value was 100% when PSA <20 ng/ml and Gleason score <8[12]. The American Urological Association and European Association of Urology guidelines also confirm these results. Another study showed that 25% of patients had bone metastases with PSA <20 ng/ml and Gleason score <7[13]. Similar to the results of these studies, in our study, the sensitivity and specificity of BS for predicting metastases were increased in patients with PSA <20.7 ng/mL and Gleason score >8. Therefore, it is logical to perform an initial BS in patients with a palpable mass, Gleason score 7 and above and PSA >10 ng/mL[4]. BS should be performed in symptomatic patients regardless of PSA level, Gleason score and clinical stage[3].

The relationship between the number of lesions involved and the status of metastasis has been examined in the literature, but there is no study analyzing the success of imaging methods according to the location of the lesion. Gutzeit et al[14] showed that the ability of whole body MRI to detect malign lesions in patients with more than 10 metastatic lesions was superior to that of BS, although the sensitivity of the two methods was similar in patients with less than 5 lesions[14]. In this study, we performed an analysis of the metastasis status at each locus involved in BS and found that the detection rate of metastases in patients with thoracic vertebrae, pubic bones, femur, L3-5 vertebrae and multiple bone involvement was statistically significantly higher than other locations.

Verification with other imaging modalities may be required in the presence of suspected lesions in BS. It has been shown that PET/CT using NaF or 18F coline has a higher sensitivity and specificity than scintigraphy[4]. In a large meta-analysis, MRI and choline PET/CT have been found to be more accurate in detecting bone metastases in patients with prostate cancer than single photon emission computed tomography and BS[5]. Whole body MRI has been shown to accurately
demonstrate bone and lymph node metastases when using diffusion weighted imaging. Lecouvet et al have shown that diffusion-weighted whole-body MRI detects a higher rate of metastatic bone lesions than conventional BS\(^{[16]}\). In their studies involving 100 high-risk or relapsed patients, diffusion-weighted whole-body MRI was found to detect metastases with 99% sensitivity and 99% specificity\(^{[16]}\). In high-risk patients, whole body MRI (T2 weighted) and axial MRI have higher sensitivity and specificity than BS and targeted radiography. The accuracy of MRI in detecting bone metastases was found as good as 18F-NaF PET/CT\(^{[17]}\). MRI may be a better option because of its availability and low radiation dose. MRI can also provide useful information about soft tissues\(^{[16]}\). However, cost-effectiveness and availability are still significant disadvantages. Therefore, the first choice is still BS\(^{[3]}\).

PSMA is a cell surface protein that is highly expressed in PCs compared to other tissues. This protein provides a promising target for specific imaging and treatment depending on the transmembrane location after ligand binding\(^{[18]}\). Gallium 68-PSMA PET/CT is highly sensitive for the imaging of lymph nodes and bone metastases in patients with PCs. Early reports have shown that this method provides better contrast enhancement in the lesions than choline PET\(^{[19]}\). In a recent study including 140 PCs patients, it was shown that Gallium 68-PSMA PET/CT demonstrated a higher rate of bone metastasis involvement than low-dose CT\(^{[20]}\). If supported by prospective studies, PSMA PET/CT has the potential to be a routine screening method for staging and treatment planning in PCA patients. A major disadvantage of this method is its high cost. This is an important factor limiting its routine utilization. For this reason, this assay seems to be an extreme way to be routinely used for screening purposes in PCs patients for the time being. We were not able to use this diagnostic test for screening in our patients because PSMA PET/CT was not covered by the Social Security Institution routine back-payment system and the need for some strict indications for the imaging in the period that we have planned our study. In our patients, the most commonly preferred radiologic verification method was CT, which was used in 60.3% of the patients. However, MRI was the imaging method which detected metastases with the highest rate (81.3%). Our findings support the use of MRI as a first-line diagnostic tool for the detection of bone metastases in high-risk PCs patients. The strategy of single-step use of MRI in high-risk patients with PCs was previously described by Lecouvet et al\(^{[16]}\). However, the long application period of 40-50 minutes of this method prevents its widespread usage. With the development in MRI equipment, it has been possible to perform the test in under 30 minutes.

In our study, as the number of lesions involved in BS increased, the rate of metastasis detection increased. The specificity of BS in detecting metastases in all locations was 82.8% and sensitivity was 90.8%. Early detection of bone metastases in the PCs is crucial for the selection of appropriate treatment, the detection of the tumor stage, the assessment of the prognosis of the patient and the effectiveness of the treatment protocols\(^{[21-23]}\). In a patient with PCs, the extent of metastatic bone disease is an independent prognostic factor\(^{[16]}\). The false-negative bone scans that may occur in BS may result due to the absence of reactive changes and the rapid growth of pure osteolytic metastases\(^{[25,26]}\).

In our patients, the rate of detection of metastasis in non-vertebral locations in BS was higher than in vertebral locations (58.2% vs. 25.9%). In the literature, it has been suggested that MRI has low sensitivity for metastases detection in small curved smooth bones such as ribs, which is a significant limitation, and the reason for this is the black appearance of the cortical bone in the T1 and T2 weighted sequences\(^{[27]}\). In some studies on MRI and bone single photon emission computed tomography, imaging protocols were limited to the entire axial skeleton and spine and skull, ribs, and extremities were overlooked. The reason for this is that in PCs, which predominantly metastasizes to the spine and pelvis, the possibility of metastasis at these sites without axial skeletal metastasis is insignificant\(^{[28,29]}\).

The field of imaging for PCs metastases has evolved dramatically in the last few years. Although the gold standard today for staging is either PSMA or NaF PET/CT, these methods were not included because of the retrospective nature of the study. The cohort size is also relatively modest. These were the limitations of our study.

In the majority of men diagnosed with PCs, the primary location of metastases is the axial skeletal system and these lesions may lead to pain, weakness and functional impairment. In our study, we found that BS was more sensitive in non-vertebral locations than in vertebral locations, which is the most frequent metastasis site of PCs, and it is possible to say that BS is not very reliable in vertebral involvement according to this result.

**CONCLUSIONS**

MRI seems to be the most appropriate method for metastasis verification in suspected lesions detected in BS in high-risk patients with PCs. As the number of lesions and non-vertebral involvement increases, the power of BS distinguishing true metastases from false-positive metastases increases. BS may be insufficient for screening purposes in the axial skeletal system which is the most common metastasis site of PCs.
Randomized, prospective clinical trials are required to routinely recommend MRI as a first-line imaging method for the diagnosis of bone metastases.

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REFERENCES

Original Article

Colonoscopic, genetic and laboratory characteristics of Colchicine-resistant Familial Mediterranean Fever

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ABSTRACT

Objective: To determine the relation between inflammatory bowel disease (IBD) and cases with Familial Mediterranean Fever (FMF) not responding to colchicine therapy by evaluating endoscopic and histopathological characteristics

Design: Prospective study

Setting: Pediatric Gastroenterology Clinic, Cukurova University Medical Faculty, Turkey, between 2012 and 2015

Subjects: Twenty-eight children

Intervention: Twenty-eight cases that applied to our institution were diagnosed with FMF on the basis of Tel-Hashomer criteria, were using colchicine therapy, and presented with fever, abdominal pain, diarrhoea and dyspeptic problems. The cases were investigated in terms of demographics, clinical and family history, nutritional status, accompanying diseases and perianal lesions.

Main outcome measure: Type of FMF gene mutations was investigated and inflammation was detected through colonoscopic morphology or histopathology.

Results: Histopathological analysis of biopsy samples taken from the colon and terminal ileum of the cases in Group 1 (n=5) revealed goblet cell loss and crypt hyperplasia, indicating active colitis compatible with IBD. Appearance of the colon mucosa was normal in all cases, although areas of multiple ulcers were observed in some parts of the ileum in two cases.

Conclusion: In cases of FMF with chronic abdominal pain and dyspeptic symptoms, persistently high erythrocyte sedimentation rate and low hemoglobin levels may be an indicator of IBD. Although colonoscopic imaging of patients with FMF is normal, it is important to perform a biopsy in order to identify histopathological inflammation.

KEY WORDS: children, colchicine, familial Mediterranean fever, inflammatory bowel disease, MEFV mutation

INTRODUCTION

Familial Mediterranean Fever (FMF) is the prototype of periodic inflammatory clinical syndromes characterized by acute and painful inflammation in the joints, chest and abdomen, and also by febrile episodes. Tel-Hashomer criteria were used for the diagnosis of FMF. Although there are well-defined criteria for the diagnosis of FMF, clinical heterogeneity causing diagnostic difficulties is frequently observed[1]. The heterogeneity in the FMF genes affects the disorder's clinical manifestations[2]. In some cases, abdominal pain, dyspeptic complaints and high acute-phase reactants persist in spite of colchicine treatment. Previous studies have reported diagnosis of inflammatory bowel disease (IBD) in patients with FMF, and a close overlap association between FMF and IBD has been represented. The prevalence of inflammatory diseases, including IBD, is increased in FMF[3-5]. The FMF causing gene, known as MEFV, was first described in 1997. MEFV molecular analysis is a useful approach in clinical practice to identify the

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atypical form(s) of the disease\textsuperscript{[2]}. For the FMF patients with IBD who do not respond to colchicine treatment, homozygous M694V mutation has been observed as the genetic background\textsuperscript{[3-10]}. IBD is characterized by an irregular mucosal immune response of the gastrointestinal system. Although its pathogenesis is not fully understood, environmental contributors, genetic background, immune factors, endogenous and exogenous triggers, and complex interactions of intestinal flora all play a role\textsuperscript{[11]}. IBD and FMF are inflammatory diseases that proceed with relapses, as well as neutrophil infiltrations, in the damaged location. Epidemiological data show that IBD is more common and more severe in non-Ashkenazi Jews, especially in the families of and in patients with FMF. These data support the modifying effects of the genes (MEFV) that are responsible for FMF\textsuperscript{[12-16]}. The aim of this prospective study was to determine the relation between IBD and cases of FMF that do not respond to colchicine therapy by evaluating endoscopic, histopathological, genetic analysis and laboratory characteristics.

SUBJECTS AND METHODS
Twenty-eight cases that came to the Cukurova University Medical Faculty, Pediatric Gastroenterology Clinic, Turkey, between January 2012 and January 2015, were diagnosed with FMF on the basis of Tel-Hashomer criteria, were using colchicine (despite taking colchicine at a high dose (2 mg/day)), and presented with fever, abdominal pain, diarrhoea and/or dyspeptic problems. The cases were investigated in terms of demographics, clinical and nutritional status, accompanying diseases and perianal lesions. Family history were investigated because IBD is a familial disease. Data related to dyspepsia were chosen according to the ROME III criteria\textsuperscript{[17]}. An individual was classified as having dyspepsia if they reported experiencing at least one of the following symptoms during the previous three months, with the first instance occurring at least six months earlier: (a) bothersome postprandial fullness; (b) early satiety; (c) epigastric pain; or (d) epigastric burning. Tel-Hashomer criteria were used for the diagnosis of FMF\textsuperscript{[18]}. For definitive diagnosis, two major criteria or one major and two minor criteria are required. For a probable diagnosis, one major criterion and one minor criterion are sufficient. Colchicine resistance was defined by >1 attacks per month in compliant patients receiving the maximally tolerated dose for >6 months\textsuperscript{[19]}. Patients were also investigated in terms of hemogram, biochemistry, C-reactive protein, erythrocyte sedimentation rate (ESR), fibrinogen, imaging methods (abdominal ultrasonography, abdominal tomography, barium intestine and colon graphs for assessing the main abdominal complications of inflammatory bowel diseases such as strictures, fistulas and lead-pipe appearance), anti-neutrophilic cytoplasmic antibody and anti-Saccharomyces cerevisiae antibody. All patients also underwent ophthalmological examination. Some ocular manifestations of IBD can lead to significant visual morbidity and temporally associated complications can also be a herald of disease control. Furthermore, ocular manifestations of IBD can occasionally manifest before the usual intestinal manifestations, leading to an earlier diagnosis.

Type of FMF gene mutations in all patients in the study was investigated by applying real-time polymerase chain reaction method. Moreover, HLA-B5 was also examined. After routine bowel cleansing preparations, the colonoscopies were performed with a Pentax EG-2730 K gastroscope and colonoscope (Pentax, Tokyo, Japan). Propofol and midazolam were used for sedation. In cases in which inflammation was detected through colonoscopy imaging or histopathology, infections (viral, bacterial, parasitic), Behçet’s disease, tuberculosis, immune deficiencies and food allergy were excluded on the basis of clinical and laboratory findings. Cases were divided into two groups based on detection of inflammation through colonoscopy as inflammation positive Group 1 and inflammation negative Group 2.

Statistical analysis
Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 software (IBM; Armonk, NY, USA). The results are expressed as mean ± standard deviation. The chi-square test and Student’s t-test were used for comparisons. A P-value <.05 was regarded as significant.

Ethics
Families and patients were informed about endoscopy, colonoscopy and enteroscopy procedures, and the related written informed consents were obtained. The Cukurova University School of Medicine local ethics committee approved this retrospective study.

RESULTS
All cases, in both groups, exhibited abdominal pain. Nausea was the second most common symptom. Clinical symptoms of cases are displayed in Table 1. Another clinical symptom, chronic diarrhoea, was observed in one case in Group 1 and three cases in Group 2. The mean age was 13.2±3.9 years in Group 1 (M/F: 2/3) and 10.6±4.2 years in Group 2 (M/F: 3/8), and both groups were compared in terms of clinical and laboratory findings. No significant difference was
found between the groups for age, age distribution, and gender (P > 0.05). Patients’ mean length of colchicine use was 14±6 months, with a mean dosage of 2 mg/day.

No pathology was detected or no stool culture was produced in the four cases with diarrhoea. No family history, perianal lesion, rectal bleeding or bloody diarrhoea was present in either group. No significant difference in clinical symptoms was determined between the groups.

A total of 28 patients were included in the present study. Gastroscopic and colonoscopic procedures were carried out according to the complaints, physical examination and laboratory values of the patients. Both gastroscopic and colonoscopic procedures were carried out in 16 patients. The other 12 patients underwent endoscopic procedures only. Based on histopathological analysis of the colon and terminal ileum, goblet cell loss crypt, hyperplasia and cryptitis and mixed-type inflammation in colonic segments indicating active colitis and ileitis that is compatible with IBD was found in five patients from Group 1 (31%).

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Group 1 (n=5)</th>
<th>Group 2 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (100%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (80%)</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (40%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (20%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (20%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>-</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Eruption</td>
<td>-</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Family history</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stool microscopy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Period of attacks (days) mean ± SD</td>
<td>6±2.3</td>
<td>2.5±0.5</td>
</tr>
<tr>
<td>Number of attacks (years) mean ± SD</td>
<td>17.8±1.7 times</td>
<td>0.6±0.2 times</td>
</tr>
</tbody>
</table>

We investigated the presence of IBD in patients who were followed up with a diagnosis of FMF and found that IBD accompanied FMF in five of 28 patients with a diagnosis of FMF. Appearance of the colon mucosa was normal in all cases, although areas of multiple ulcers were observed in some parts of the ileum in two cases. Haemoglobin and mean corpuscular volume values in Group 1 were significantly lower (P=0.03 and P=0.014, respectively) compared with that in Group 2, whereas platelets and ESR values were significantly higher (P=0.02 and P=0.01, respectively; Table 2).

<table>
<thead>
<tr>
<th>MEFV Gene Analysis</th>
<th>Group 1 (n=5)</th>
<th>Group 2 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M694V (Homozygote)</td>
<td>4 (80%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>M680I (Homozygote)</td>
<td>1 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>E148Q (Homozygote)</td>
<td>-</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>R202Q (Homozygote)</td>
<td>-</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>R314R (Heterozygote)</td>
<td>-</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>G138G (Homozygote)</td>
<td>-</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>A165A (Heterozygote)</td>
<td>-</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Negative mutation</td>
<td>-</td>
<td>3 (27%)</td>
</tr>
</tbody>
</table>

Abdominal ultrasonography and ophthalmological examination were normal in all cases. Anti-Saccharomyces cerevisiae antibody positivity was determined in only one (1/5; 20%) of the cases. Based on genetic analysis of the cases in Group 2 following mutations have been revealed: homozygous M694V mutation in two cases (2/11; 18%), homozygous E148Q mutation in one case (1/11; 9%), homozygous R202Q mutation in three cases (3/11; 27%), A165A in three cases (3/27), and R314R mutation in only two cases (2/11; 18%). MEFV mutation was negative in three cases in Group 2 (Table 3).

DISCUSSION

Although FMF is diagnosed clinically, in cases of accompanying disorders such as IBD and vasculitis, atypical clinical pictures can emerge [20]. Previous reports have demonstrated that various diseases such as polyarteritis nodosa, Henoch-Schönlein purpura, prolonged febrile myalgia syndrome, Behçet’s disease and IBD may accompany FMF [20-23]. Gastrointestinal
system involvement in FMF has been described in the literature, and some reports have stated that the onset of FMF can manifest with gastrointestinal symptoms\cite{25,26}. FMF is a widespread disease in Turkey, with an estimated prevalence of 1/1000 and a carrier rate of 1/5 (20%)\cite{5,24}. The incidence of M694V gene mutation in healthy and symptomatic individuals is 3% and 51%, respectively\cite{5,24}. Throughout Europe, IBD affects 0.5% to 1% of the population at any given time, and the disease begins in childhood in 30% of patients\cite{11,25,26}. Sawczenko et al reported that 12 of 78 patients with FMF also had IBD\cite{9}. In this study, FMF Study Group reported that 4 of the 2716 cases (0.1%) had IBD (11%), M694I (7%) and E148Q (2%)\cite{5}. Yılmaz et al reported a carrier rate of 20% in their healthy control group (E148Q (12%), M680I (5%), M694V (83%) and M726A (2%))\cite{24}. They also verified that the most common mutation in the Turkish population is M694V (51.6%)\cite{24}. According to genetic analysis of our study, homozygous M694V mutation was detected in four (4/5; 80%) cases in Group 1 (IBD-FMF) and homozygous M680I mutation was determined in one (1/5; 20%) case. Our findings are compatible with the previous reports. As another line of evidence, Fidder et al reported that FMF attacks are more frequent and severe in cases with comorbid CD. The MEFV gene mutation carrier rate was 25.7%, which is higher than the general Turkish population\cite{3}. One of the mutations responsible for the disease is M694V, which was observed in 10.6% of cases with IBD alone, a higher level than the carrier population in Turkey\cite{3}. In cases of coexisting FMF and IBD, the incidence of M694V mutation has been reported at 43.7-70%\cite{3,9,10}.

The most frequent mutations in the Turkish FMF population are M694V (45%), M680I (13%), V726A (11%), M694I (7%) and E148Q (2%)\cite{3}. Yılmaz et al reported a carrier rate of 20% in their healthy control group (E148Q (12%), M680I (5%), M694V (83%) and M726A (2%))\cite{24}. They also verified that the most common mutation in the Turkish population is M694V (51.6%)\cite{24}. According to genetic analysis of our study, homozygous M694V mutation was detected in four (4/5; 80%) cases in Group 1 (IBD-FMF) and homozygous M680I mutation was determined in one (1/5; 20%) case. Our findings are compatible with the previous reports. As another line of evidence, Fidder et al reported that FMF attacks are more frequent and severe in cases with FMF-CD, and that the risk of amyloidosis is also higher\cite{14}. Sarı et al indicated that three patients with infantile ulcerative colitis who were resistant to treatment had M694V mutation\cite{14}. In our study, attacks were more frequent and more severe in Group 1, although amyloidosis was not determined in any patient. The haemoglobin and mean corpuscular

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**Table 4: Colonoscopy, histopathology, and MEFV gene analysis of the cases in Group 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (Year)</th>
<th>Fever</th>
<th>Abdominal Pain</th>
<th>Number of attacks (year)</th>
<th>Period of attacks (day)</th>
<th>Mutation</th>
<th>Colonoscopy imaging</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>17</td>
<td>Yes</td>
<td>Yes</td>
<td>18</td>
<td>5</td>
<td>M694V (Homozygote)</td>
<td>Multiple ulcer in ileum</td>
<td>Chronic active ileitis</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>20</td>
<td>4</td>
<td>M694V (Homozygote)</td>
<td>Normal</td>
<td>Goblet cell loss crypt, hyperplasia and cryptitis and mixed-type inflammation in colonic segments indicating active colitis</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>13</td>
<td>No</td>
<td>Yes</td>
<td>15</td>
<td>4</td>
<td>M680I (Homozygote)</td>
<td>Normal</td>
<td>Goblet cell loss crypt, hyperplasia and cryptitis and mixed-type inflammation in colonic segments indicating active colitis</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>13</td>
<td>No</td>
<td>Yes</td>
<td>18</td>
<td>7</td>
<td>M694V (Homozygote)</td>
<td>Multiple ulcer in ileum</td>
<td>Chronic active ileitis</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>18</td>
<td>10</td>
<td>M694V (Homozygote)</td>
<td>Normal</td>
<td>Goblet cell loss crypt, hyperplasia and cryptitis and mixed-type inflammation in colonic segments indicating active colitis</td>
</tr>
</tbody>
</table>
CONCLUSION

FMF is a common disease in Mediterranean countries such as Turkey, and the association of IBD in cases of FMF has recently increased. Although colonoscopic imaging in all FMF patients is normal, it is important to perform a biopsy in order to identify histopathological inflammation. We believe that the gene mutations associated with inflammatory bowel diseases may have a modifying effect on both disorders. In cases of FMF resistant to colchicine treatment, possibility of underlying IBD should be considered, especially in countries where FMF is prevalent. Genetics and laboratory tests help in identifying patients at risk of IBD associated to FMF.

ACKNOWLEDGMENT

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REFERENCES

The effect of retrobulbar block on bi-hemispheric cerebral oxygen saturation and early period postoperative cognitive function with lidocaine and levobupivacaine in elderly patients undergoing ophthalmic surgery: A randomised controlled trial

ABSTRACT

Objectives: To measure the changes in cerebral oxygen saturation (rSO\textsubscript{2}) and Mini-Mental State Examination (MMSE) test scores after a retrobulbar block

Design: A prospective double-blinded randomised controlled trial

Setting: Medical faculty hospital, Department of Ophthalmology, Ondokuz Mayis University, Samsun, Turkey

Subjects: Sixty-six patients (age >60 years) undergoing vitreoretinal surgery (duration <1 hour)

Interventions: The retrobulbar block was performed with lidocaine and levobupivacaine.

Main outcome measures: Bilateral rSO\textsubscript{2} measurements were performed before and after the retrobulbar block and during the postoperative period. The MMSE was performed preoperatively and postoperatively to evaluate the short-term cognitive function. Sensory and motor block durations, pain, akinesia and conjunctival feeling scores, patient-surgeon satisfaction and complications were also recorded.

Results: The rSO\textsubscript{2} was higher in both hemispheres (for both the intraoperative and postoperative periods) in group L (lidocaine) compared to group LB (levobupivacaine). There were no differences between the groups regarding the short-term MMSE scores. The L group showed a faster sensory block onset than the LB group, but the difference was not statistically significant. However, the motor block onset/end times and the sensory block end times were significantly greater in group LB. Moreover, the surgeon and patient satisfaction scores were higher in group LB.

Conclusions: Higher rSO\textsubscript{2} values were observed in patients with a lidocaine-induced retrobulbar block than those with levobupivacaine. No effect on the MMSE scores was seen. Overall, further studies that investigate long-term MMSE scores are necessary to demonstrate that the elevation in rSO\textsubscript{2} does not affect the MMSE score.

INTRODUCTION

Ophthalmic surgery is a common surgical procedure and is mostly performed with regional anaesthesia\textsuperscript{[1]}. Regional anaesthesia techniques were first conducted by Herman Knapp in the last quarter of the 19\textsuperscript{th} century, where he used cocaine to generate a retrobulbar block\textsuperscript{[2]}. Regional anaesthesia has become increasingly popular for ophthalmic surgery as it avoids the risks associated with general anaesthesia (e.g. laryngospasm, coughing, nausea and vomiting and in some instances major perioperative complications), provides fast surgical anaesthesia and recovery, and enables adequate akinesia and analgesia\textsuperscript{[3]}.

Cardiac and neurologic complications are more...
common in the perioperative period among elderly patients who undergo intraocular surgery due to cardiovascular system diseases they often have. In addition, the baseline rSO₂ decreases with advanced age. Significant reduction in intraoperative rSO₂ is associated with increased risk of perioperative stroke, prolongation of hospital stay and postoperative cognitive dysfunction. For this reason, it is crucial to monitor the intraoperative oxygen dynamics.

Cerebral oximetry is a non-invasive monitoring technique utilising near-infrared spectroscopy (NIRS) that can show oxygenation and perfusion in the capillary circulation of the brain. It also measures the continuous intraparenchymal oxygenation in the frontal cortex. The principle of the technique is based on an optical technique that measures oxygenated and deoxygenated haemoglobin concentrations with 700-900 nm light waves. Therefore, NIRS might be useful to monitor ischaemia in the brain and also neurological complications that may occur during surgery. Currently, there are only a few previous studies that have investigated the effects of ophthalmic regional anaesthesia techniques, which are anatomically very close to the central nervous system focusing on the cerebral oxygenation.

Levobupivacaine is the S(-) enantiomer of bupivacaine. It has a favourable cardiovascular and neurological toxic side effect profile and is generally associated with high patient-surgeon satisfaction. Therefore, this local anaesthetic is widely used for eye surgery. Lidocaine also has a rapid onset of action with a moderate duration, low side effects and typically sufficient efficacy. In this study, we investigated and compared these two commonly used anaesthetic agents.

Cognitive functions are defined as the necessary brain activities that enable a person to carry on his/her life and fulfil daily activities and responsibilities. There are short examination methods and screen tests designed to assess cognitive functions. The Mini-Mental State Examination (MMSE) test, in which patient compliance is high, is one of the most commonly applied tests to assess cognitive function (for further details, see the Appendix). The assessments within the first postoperative month measure the loss of short-term function, whereas tests conducted after the second to third month are designed to evaluate the long-term or permanent dysfunctions.

The primary aim of this study was to investigate the effects of lidocaine and levobupivacaine used for a retrobulbar block on the rSO₂ and the short-term cognitive function (MMSE). Additionally, we also assessed the sensory and motor block times, pain, akinesia and conjunctival feelings scores, patient-surgeon satisfaction and complications.

SUBJECTS AND METHODS
This study was conducted in the medical faculty hospital at the Department of Ophthalmology with the approval of the medical faculty and the surgical research centre’s ethics committee (B.30.2.ODM.0.20.08/1142).

Study participants
All study participants provided informed consent. A total of 66 patients undergoing vitreoretinal surgery – either cataractectomy, trabeculectomy, vitrectomy and keratoplasty, with a total duration <60 minutes – who were subjected to a retrobulbar block, were investigated. Additionally, patients were only included in the study when classified as category I–III according to the American Society of Anaesthesiologists classification system, they were 60 or older in age and they had no cognitive dysfunction. Patients were excluded when they had either a contraindication for retrobulbar block, a preoperative systolic blood pressure of 180 mmHg, a diastolic blood pressure of above 100 mmHg, uncontrolled diabetes, a body mass index ≥30 kg/m², a MMSE ≤24, advanced organ failure or haemoglobin <9 gr/dL.

Randomisation
For the investigation, the patients were randomly divided into two groups using a sealed-envelope method: group L, which contained patients undergoing a retrobulbar block with lidocaine (n=33), and group LB, which contained patients undergoing a retrobulbar block with levobupivacaine (n=33). Randomisation was performed by a physician, who did not take part in the patient follow-up, using sealed envelopes that were numbered according to the computer-generated random number list. The medication (5-mL injector) was given to the practitioner by an independent assistant – both were unaware of the medication given to the patients. The medication preparation and retrobulbar block application were each time conducted by the same person to ensure standardisation.

Patient monitoring and retrobulbar block application
The patients did not undergo premedication in order to accommodate the postoperative MMSE evaluation. For intraoperative sedation, remifentanil (Ultiva®, GlaxoSmithKline, Brentford, UK) was used as an infusion with a 0.05-0.1 mcg/kg/min dose range. The mean arterial pressure (MAP) and heart rate (HR) values were allowed to vary up to 20% based on the patient’s preoperative values. Based on these deviations, the remifentanil infusion rate was increased or decreased at the determined dose interval. When the hypotension MAP [<60 mmHg] or bradycardia HR [<50 pulse/min] lasted longer than three minutes, 5 mg ephedrine was used to
treat the hypotension and 0.5 mg atropine to treat the bradycardia. Based on these required measures, the patients were excluded from the study when ephedrine or atropine was used more than twice. The sedation levels of the patients were followed using the Ramsay Sedation Scale; a score of 2-4 was accepted as a sufficient sedation level. Since the faces of the patients would be covered with sterile cloth, they were given 4 L/min of oxygen (100%) via a nasal cannula regardless of the oxygenation status.

The retrobulbar block was performed with 5 mL of 2% lidocaine hydrochloride (Aritmal®, Osel, Istanbul, Turkey) in group L patients and 5 mL of 0.5% levobupivacaine (Chirocaine®, AbbVie, Chicago, USA) in group LB patients. The retrobulbar block was performed by the same practitioner who used an inferotemporal approach (as described by Sanderson) using 27-gauge disposable needles (Atkinson Retrobulbar Needle®, ASICO, USA)\(^{[18]}\). Any complications following the retrobulbar block were recorded.

**MAP, HR and oxygen saturation record periods**

MAP, HR and oxygen saturation were recorded in the preoperative period; at 1, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes during the intraoperative period and at 10, 20, 30 and 40 minutes postoperatively in the recovery room.

**Determination of the rSO\(_2\) and MMSE**

The NIRS device probes (INVOS-3100A®, Somanetics Inc., Troy, MI, USA) were placed with at least 2 cm above the right and left eyebrows and 3 cm away from the midline of the forehead – all in accordance with the instructions of manufacturer\(^{[19]}\). The patient’s forehead was cleaned with acetone alcohol before the sensor pads were glued to the skin and then wrapped with a bandage so that the sensors were not affected by ambient light. The patient was then transferred to the operating table for measurements of the bilateral rSO\(_2\). Preoxygenation was performed for three minutes using 4 L/min oxygen (100%) via a nasal cannula. The basal oxygenation values were determined by taking the average of the last 30-second measurements. The rSO\(_2\) values were recorded 1, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes after the retrobulbar block and 10, 20, 30 and 40 minutes after the completion of the procedure. If the measured value fell below 25% of the basal value and lasted longer than 30 seconds during the operation, it was reported as a reduced rSO\(_2\)\(^{[20]}\). In this case, the patient underwent ventilation by increasing the amount of given oxygen. The patient was put into normotension (administration of vasopressors, such as ephedrine, and/or infusion of isotonic fluids), and adjustments were made in cases of external factors causing arterial or venous obstruction in the neck.

Cognitive functions were assessed by the same technician using the MMSE during the preoperative period, 40 minutes after the operation and seven days after the operation (short-term)\(^{[15]}\). A reduction of two or more points in the MMSE score compared to the preoperative value was considered as a reduction in cognitive function. A decrease of more than 24 points was considered as a loss of cognitive function\(^{[27]}\).

**The onset and end times for the sensory and motor block**

The sensory and motor block onset times were recorded, as well as the end time. The onset time of the sensory block was recorded when the patient did not feel a piece of cotton against the cornea anymore. The onset time of the motor block was recorded when the patient’s eye movements diminished in all four quadrants. The time when these functions were recovered was recorded as the block’s end time.

**The akinesia score and visual analogue scale (VAS) score**

The akinesia score was assessed between 0–12 points after 10 minutes of the block’s application\(^{[21]}\). Eye movements were measured at three points in each of the four quadrants: (3) full eye movement, (2) partial movement unsuitable for surgery; (1) partial movement but suitable for surgery; and (0) no movement. The sum of the movement scores across all four quadrants was recorded as the akinesia score. An eye capable of full movement was scored as 12, and an immobile eye was scored as 0. The retrobulbar block was considered successful when the akinesia score was 4 or less. The anaesthesia block efficiency was further measured by the conjunctival feeling score using the cotton contact test (0: normal, 1: less sensitive and 2: a complete sensory loss)\(^{[22]}\). If the score was higher than 0, the retrobulbar block was considered successful.

During the operative procedure, a VAS score was used to assess intraoperative pain. The patients were asked to rate their pain from 0 (no pain) to 10 (the strongest known pain). If the VAS score was 4 or less, the retrobulbar block was considered successful.

If the akinesia score was ≥5 and/or the VAS score was ≥5 and/or the conjunctival score was 0 after performing the block, then the retrobulbar block was considered unsuccessful. In this case, the patient was given two drops of topical proparacaine HCl (Alkain®, Alcon-Couvreur, Belgium) at 5-minute intervals and underwent the surgical procedure. These cases were excluded from the study analysis.

**Patient-surgeon satisfaction**

Surgeon satisfaction was queried at the end of the case and patient satisfaction at the end of the day.
Patient and surgeon satisfaction were evaluated using a 0 to 10 satisfaction scale (0 = dissatisfied and 10 = very satisfied).[23] After the procedure, the patients were transferred to the recovery room and monitored for 40 minutes for any complications. In cases where no complications were apparent, the recovery was evaluated using a modified Aldrete scoring system. If the score was 9-10, patients were transferred to the general hospital staff. Patients with a VAS score >4 after the sensory block underwent intravenous treatment with 0.3 mg/kg meperidine. If there was no desired change in the VAS value after 30 minutes, 75 mg diclofenac sodium was additionally administered by intravenous bolus injection.

**Statistical analysis**

Based on the article by Casati et al.[24], the power analysis for a one-sample t-test to identify differences in the rSO2 value was determined at 99.9% for 66 patients with 95% reliability and 5% error.

The data were analysed using the Statistical Package for the Social Sciences Version 23.0 software (IBM SPSS Statistics Inc., IBM Corp., Armonk, NY, USA). The normal distribution of the quantitative data was evaluated with the Kolmogorov Smirnov test. For the analysis of normally distributed data, the independent-samples t-test and repeated measure analysis of variance were used. The Mann-Whitney U test, a nonparametric method, was used for the comparison of non-normally distributed data. The chi-square test was used for the assessment of qualitative data. The onset and end times for the sensory and motor block were compared between the groups using the Mann-Whitney U test. The level of statistical significance was accepted with a P-value of <.05.

**RESULTS**

**Demographic data and haemodynamic parameters**

Table 1 shows the following demographic data: age, gender, American Society of Anaesthesiologists classification score and the duration of the surgery. The mean age of group L was higher than that of group LB, but there was no difference in the other demographic parameters. There were also no differences for the haemodynamic parameters, including HR, MAP or oxygen saturation between the groups or within the groups.

![Fig. 1: Right hemisphere rSO2 (%) values by group (Preop: preoperative; Postop: postoperative; rSO2: cerebral oxygen saturation).](image1)

![Fig. 2: Left hemisphere rSO2 (%) values by group (Preop: preoperative; Postop: postoperative; rSO2: cerebral oxygen saturation).](image2)

**Table 1: Patient demographic characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group L (n=33)</th>
<th>Group LB (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>67 (60-84)</td>
<td>63 (60-75)</td>
<td>.008</td>
</tr>
<tr>
<td>ASA classification</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>.051</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>55 (15-60)</td>
<td>50 (15-55)</td>
<td>.076</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 (19-29)</td>
<td>25 (18-27)</td>
<td>.620</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>13/20</td>
<td>14/19</td>
<td>.360</td>
</tr>
</tbody>
</table>

BMI: Body mass index; F/M: Female/Male; ASA: American Society of Anaesthesiologists

The rSO2 and MMSE values

Next, the effect of local anaesthetics on rSO2 values was determined. In group L, the rSO2 values were found higher than in group LB (P < .001) (Figure 1 and 2); there was no difference within the groups. Regarding the MMSE values, there was no difference found within the group or between the groups (Table 2).

**Table 2: MMSE scores of the groups (Mean ± SE)**

<table>
<thead>
<tr>
<th>MMSE Scores</th>
<th>Group L (n=33)</th>
<th>Group LB (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop.</td>
<td>25.3 ± 1.0</td>
<td>25.5 ± 1.0</td>
</tr>
<tr>
<td>Postop. 1. day</td>
<td>25.3 ± 1.0</td>
<td>25.4 ± 1.0</td>
</tr>
<tr>
<td>Postop. 7. day</td>
<td>25.4 ± 1.0</td>
<td>25.5 ± 1.0</td>
</tr>
</tbody>
</table>

Preop: preoperative; Postop: postoperative; MMSE: Mini Mental State Examination test

**The onset and end times for the sensory and motor block**

Group L had a faster sensory block onset than group LB, but the differences were not statistically significant (Table 3). However, the motor block onset/end times and the sensory block end times were significantly greater in group LB (P < .001) (Table 3).
The conjunctival feeling score, akinesia score, patient-surgeon satisfaction and VAS score

There was no significant difference regarding the conjunctival feeling score and the VAS score between group L and group LB (P =.801 and P =.406, respectively) (Table 4). However, the akinesia score was found lower in group LB, and the patient and surgeon satisfaction scores were higher in group LB (P =.012 and P =.001, respectively) (Table 4). However, the akinesia score was found lower in group LB, and the patient and surgeon satisfaction scores were higher in group LB (P =.012 and P =.001, respectively) (Table 4).

Complications

The complications seen in the groups were bradycardia, hypotension, dizziness and headache. There was no difference in the incidence of complications found between groups (Table 5).

DISCUSSION

The primary aim of this study was to investigate the effects of local anaesthetics used for a retrobulbar block on rSO2 and short-term cognitive functions. The rSO2 values were found higher during the follow-up in group L (with lidocaine as the retrobulbar block inducer). Previous studies have reported that lidocaine slows the cerebral metabolism without altering the brain’s blood flow and has a neuroprotective effect [25,26]. Rasool et al have reported that lidocaine reduces the mitochondrial oxygen consumption in a direct proportion to dose in porcine brain tissue[28]. Therefore, reduced oxygen consumption due to suppressed brain metabolism may explain the slight elevation in rSO2 observed in group L in the present study.

Levobupivacaine (used to induce the retrobulbar block in group LB) has a vasoconstrictor activity and increases intracellular calcium at low doses (plasma concentration of 10^-6–10^-3 mol/L)[29,30]. In a pharmacokinetic study by Birt et al, the maximum plasma concentration of 3 mL of 0.75% levobupivacaine after the peribulbar block was 0.7 × 10^-6–0.9 × 10^-6 mol/L[31]. We estimate that 5 mL of 0.5% levobupivacaine reached similar plasma concentrations in our study. Accordingly, vasoconstriction in the cerebral vascular bed is very likely. Overall, the difference in the rSO2 value between group L and group LB could be explained by the effect of lidocaine on the cerebral metabolism and the effect of levobupivacaine on the arterial system.

Preoperative MMSE scores were similar to the 1st and 7th day postoperative values in both groups. A decreased rSO2 which indicates cerebral desaturation, was not seen in our patients. Prior studies have reported a correlation between rSO2 values and MMSE scores [10,32]. For example, Yao et al found that the decrease in rSO2 values correlated with postoperative MMSE scores while evaluating rSO2 values and MMSE scores in patients who would undergo coronary artery bypass graft surgery[10]. Additionally, Suehiro et al demonstrated an inverse correlation between rSO2 values and MMSE scores in patients with one-lung ventilation and found a correlation between the increase in cerebral desaturation duration during one-lung ventilation and the decrease in MMSE scores[32]. Similarly, in our study, there was a correlation found between the rSO2 values and the MMSE scores.

In our study, longer motor block onset-end times, longer sensory block end times and better akinesia scores were found in group LB compared to group L. In a study by Aksu et al, which compared levobupivacaine and lidocaine, there was no difference reported between the motor and sensory block onset times; however, they were longer in the levobupivacaine group[31]. Furthermore, in another study by Aksu et al,
the authors compared levobupivacaine, bupivacaine and lidocaine, and their results showed that the motor and sensory block times were longer in the levobupivacaine and bupivacaine groups compared to the lidocaine group\(^{33}\). This study also reported that the motor block onset times were similar in all three groups. In both studies by Aksu et al, the motor and sensory block onset times were assessed after five minutes of orbital pressure after the retrobulbar injection. We suspect that the onset of the blocks occurred during this process. In our study, no pressure was applied to the orbital area after retrobulbar injection, and the block onset times were measured immediately afterwards. These methodological differences may account for the differences between the present study and the ones reported by Aksu et al. In a review by Simonson on retrobulbar blocks, the author noted that the sensory and motor block onset time of lidocaine was three minutes and its end time two hours\(^{34}\). The same review reported that the sensory and motor block onset time of bupivacaine was 5-10 minutes and the end time six hours. Furthermore, the use of bupivacaine resulted in successful akinesia. Together, these results correlate with the values in our study. The similarity in the sensory block onset time may be the result of the relatively subjective test that we applied (cotton contact test)\(^{22}\). Alternately, the von Frey method, which uses a nylon thread with a special holder to touch the eye, may provide improved objective measurements. This recently developed technique, together with a Cochet-Bonnet aesthesiometer and a non-contact corneal aesthesiometer, may further improve objective corneal sensitivity examinations\(^{35}\). However, we used a cotton contact method with lower sensitivity since these devices were not available in our clinic.

The improved akinesia in group LB may be associated with the increased potency of levobupivacaine\(^{36}\). Previous studies have shown that akinesia scores are generally better with levobupivacaine treatment, probably as a result of its increased potency. For instance, in a study by Aksu et al which compared levobupivacaine, bupivacaine and lidocaine for retrobulbar block, the akinesia score was found better in the levobupivacaine and bupivacaine groups compared to the lidocaine group\(^{33}\). Furthermore, Ghali et al compared levobupivacaine and ropivacaine for the peribulbar block and obtained enhanced akinesia with levobupivacaine\(^{37}\). Based on these previous studies, we find that our findings are consistent with them.

In this study, we also investigated patient and surgeon satisfaction. The obtained scores were found higher in group LB than in group L. In the study conducted by Aksu et al, patient and surgeon satisfaction scores were higher in the levobupivacaine group (5 mL, 0.5%) when compared to the lidocaine group (5 mL, 2%) – both with patients undergoing a retrobulbar block\(^{11}\). In a similar study by the same group, patient and surgeon satisfaction scores in the levobupivacaine and bupivacaine groups were better than the lidocaine group\(^{38}\). Together with our findings, we conclude that the longer action time of levobupivacaine prolongs the duration of postoperative analgesia, resulting in an increase of patient satisfaction and that it provides better akinesia scores, resulting in increased surgeon satisfaction.

There was no difference in complication incidence between the two groups in our study. Hypotension, bradycardia and dizziness occurred shortly after the block application. We attributed these complications to the vasovagal reflex, which can occur in patients due to needle phobia\(^{18}\). Another complication seen in our study was headache. This symptom might be caused due to the pressure of the anaesthetic volume to the eyeball\(^{38}\).

Our study had the following limitations: (1) The cotton contact test is a subjective measure of sensory block onset and may reduce the reliability and reproducibility of these results, and (2) the NIRS method, used to measure \(rSO_2\), does not fully reflect the global cerebral oxygenation as it assesses the local cerebral blood flow in the frontal area. Therefore, based on these limitations, additional arterial-jugular venous blood gas analysis and/or techniques that measure the cerebral blood flow such as positron emission tomography, magnetic resonance imaging or ultrasonography are recommended to assess the global oxygenation more detailed\(^{39}\).

**CONCLUSION**

In this study, higher cerebral oxygen saturation was observed in patients undergoing retrobulbar block with lidocaine (group L) compared to those treated with levobupivacaine (group LB), but there was no difference in short-term MMSE scores between the treatment groups. However, further studies investigating long-term MMSE scores are necessary to demonstrate that this elevation in cerebral oxygen saturation does not affect the MMSE scores.

On the other hand, surgeon and patient satisfaction scores were increased when using levobupivacaine, which provides better akinesia and a longer duration of postoperative analgesia than lidocaine. For this reason, levobupivacaine may be preferred in vitreoretinal surgeries that require retrobulbar anaesthesia.

**ACKNOWLEDGMENT**

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of Ondokuz Mayis University, Samsun, Turkey, under project number PYOTIP.1904.15.009.

**Presentation:** Preliminary data for this study were submitted oral presentation at the Regional Anesthesia Congress, 18-21 MAY 2017, Antalya, Turkey.

**Trial registration:** ClinicalTrials.gov NCT03189329, registered June 15, 2017, retrospectively registered.

**Conflicts of interest:** The authors declare that they have no conflicts of interest.

**REFERENCES**

31. Birt DJ, Cummings GC. The efficacy and safety of 0.75% levobupivacaine vs 0.75% bupivacaine for peribulbar anaesthesia. Eye (Lond) 2003; 17(2):200-206.


APPENDIX

Background of the MMSE

The MMSE test, developed by Folstein et al in 1975 to assess cognitive functions, is widely utilised for clinical evaluation, research, community surveys and epidemiologic studies. This test can quickly and easily assess language, memory, attention and concentration, visual-spatial skills, executive functions, computation, abstract thinking, and orientation skills[15]. The maximum total score for the MMSE test, which can usually be applied within 5-10 minutes, is reported to be 30 and with a cut-off point around 23 to 24, which can discriminate between cognitive impaired and non-cognitive impaired patients. The MMSE scores are categorised to stratify subjects into normal (30-24), mild (23-18) and severely impaired (17-0)[40].

MMSE scoring (adapted from Rovner & Folstein)[41]

<table>
<thead>
<tr>
<th>Mini-Mental State Examination (MMSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient name....................................................</td>
</tr>
<tr>
<td>Date of birth........................... Date of test...............</td>
</tr>
</tbody>
</table>

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

<table>
<thead>
<tr>
<th>Section</th>
<th>Questions</th>
<th>Maximum points</th>
<th>Patient score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>“Can you tell me today’s (date)/(month)/(year)?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Which (day of the week) is it today?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Can you also tell me which (season) it is?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“What city/town are we in?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“What is the name of the district?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“What is the (county)/(country)?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“What (building) are we in and on what (floor)?”</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Registration</td>
<td>“I should like to test your memory.” (Name 3 common objects: e.g. “ball, car, man”)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>“Can you repeat the words I said.” (Score 1 point for each word) (Repeat up to 6 trials until all three are remembered)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Record number of trials needed here:...........................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention and Calculation</td>
<td>“I would like you to count backward from 100 by sevens.” (93, 86, 79,72, 65, …)</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Stop after five answers. Alternative: “Spell WORLD backwards.” (D-L-R-O-W)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall</td>
<td>“Earlier I told you the names of three things. Can you tell me what those were? ”</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
### Language and Praxis

<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naming</td>
<td>Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.</td>
<td>2</td>
</tr>
<tr>
<td>Repeating</td>
<td>“Repeat the phrase: ‘No ifs, ands, or buts.’”</td>
<td>1</td>
</tr>
<tr>
<td>Reading</td>
<td>“Please read this and do what it says.” (Written instruction is “Close your eyes.”)</td>
<td>1</td>
</tr>
<tr>
<td>Writing</td>
<td>“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)</td>
<td>1</td>
</tr>
<tr>
<td>Three stage command</td>
<td>“Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper.)</td>
<td>3</td>
</tr>
<tr>
<td>Construction</td>
<td>“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)</td>
<td>1</td>
</tr>
<tr>
<td>Total Score</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>
The reno-protective role of Angiotensin 1-7 in Cisplatin induced nephrotoxicity

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2Department of Clinical Pathology, Isfahan University of Medical Sciences, Isfahan, Iran
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4Isfahan MN Institute of Basic and Applied Sciences Research, Isfahan, Iran

Objective: To determine the protective role of angiotensin 1-7 (Ang1-7) against Cisplatin (CP) induced nephrotoxicity

Design: Case-control animal experimental study

Setting: Water and Electrolytes Research Center/Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran

Subjects: 35 male (331±7.4 g) and female (196.5±5.9 g) Wistar rats

Interventions: The rats were subject to treatment with vehicle, single dose of CP alone (7.5 mg/kg) or a single dose of CP plus daily infusion of Ang1-7 (30 µg/kg/day). The measurements were performed one week after CP administration.

Main outcome measures: Serum levels of blood urea nitrogen (BUN), creatinine (Cr) and malondialdehyde, kidney tissue damage score and normalized kidney weight

Results: The increased kidney tissue damage, kidney weight, and the serum levels of BUN and Cr induced by CP was attenuated significantly by Ang1-7 (P <.05) in male rats. However, the protective role of Ang1-7 against CP induced nephrotoxicity was not detected in female rats.

Conclusion: Ang1-7 may act as suitable supplement to attenuate CP induced nephrotoxicity in male rats, possibly due to its effect on kidney circulation.

INTRODUCTION

Nephrotoxicity, the major side effect of cisplatin (CP), is one of the most important limitations of CP therapy. Administration of supplement agents was suggested to avoid/limit the CP side effect of nephrotoxicity. The laboratory investigations in animal models have been performed to suggest different supplements against CP-induced nephrotoxicity[1-8], while CP-induced nephrotoxicity is also altered by gender and sex hormones[9-12].

Renin angiotensin system is also affected by CP, and the protective role of losartan as angiotensin II receptor 1 antagonist against CP induced nephrotoxicity has been reported before[9,13,14]. Another important component of renin angiotensin system is Angiotensin 1-7 (Ang1-7), which is available in the kidney[13]. Usually, the action of this peptide in vascular system is against angiotensin II functions, and it may reduce renal angiotensin II receptor 1[16]. Accordingly, it was hypothesized that Ang1-7 could protect the kidney against CP-induced nephrotoxicity, and to test this hypothesis, male and female rats were subjected to receive CP accompanied with Ang1-7 and were compared with negative and positive control groups.

SUBJECTS AND METHODS

Thirty-five male (331±7.4 g) and female (196.5±5.9 g) Wistar rats in six groups were used in this study. The male rats received saline as vehicle (Group 1, n=7), single dose of CP (7.5 mg/kg, Mylan Drug Company,
Athens, Greece) (Group 2, n=5), or single dose of CP plus daily injection of Ang1-7 (30µg/kg/day.ip) (Group 3, n=7). The female rats in groups 4, 5 and 6 (n=5, 5, 6) were treated in the same manner as Groups 1-3. One week later, blood samples were obtained and the animals were sacrificed humanly. The kidney tissues were fixed in formalin 10% to prepare for H&E staining, and the tissue damage was scored as kidney tissue damage score by a pathologist who was not familiar to study protocol.

The serum levels of blood urea nitrogen and creatinine were measured using quantitative diagnostic kits (Pars Azmoon, Iran). The malondialdehyde level in the serum also was measured by the manual method.

**Statistical analysis**

The data reported as mean±SEM were analyzed by the analysis of variance test and least significant difference as post hoc to compare the groups. The Kruskal–Wallis and Mann–Whitney U tests also were

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**Fig 1:** The serum levels of blood urea nitrogen (BUN) and creatinine (Cr), the percentage of weight change and the kidney weight (KW) per 100 g of body weight (BW) in the experimental groups. The CP and CP+Ang1-7 indicate the groups treated with cisplatin, cisplatin plus angiotensin1-7. The P value was obtained by ANOVA for each gender. The symbols (* or #) indicate significant differences (P<.05) from vehicle or CP groups in each gender using LSD as post hoc test.
Fig 2: The samples images of kidney tissue in all the experimental groups. The CP and CP+Ang1-7 indicate the groups treated with cisplatin or cisplatin plus angiotensin1-7 respectively. CP induced tubular damage were shown widely in both male and female rats, and the damage was attenuated in male rats when Ang1-7 was accompanied with CP (left panel). Such attenuation was not seen in female rats (right panel).
used to compare the kidney tissue damage score between the groups. The P values less than 0.05 were considered statistically significant.

RESULTS
The serum levels of blood urea nitrogen and creatinine were increased significantly ($P<0.05$) in male rats treated with CP alone, and these markers levels were attenuated by Ang1-7, but such observation was not detected in female rats (Fig. 1). CP increased normalized kidney weight and kidney tissue damage score significantly ($P<0.05$) in both male and female rats, and Ang1-7 attenuated both parameters only in male rats (Fig. 1). No significant difference in the serum levels of malondialdehyde were found between the groups and gender. The samples of kidney tissues are shown in Figure 2.

DISCUSSION
In this report, we showed that Ang1-7 could potentially protect the kidney against CP induced nephrotoxicity in male rats, while such a result was not detected in female rats. Previously, we reported that the action of Ang1-7 in renal system was gender related$^{[17,18]}$. The kidney related side effects of CP also perform gender dependently$^{[6,19]}$. It seems the mechanism is related to Ang1-7 effects on renal blood flow. Ang1-7 increases renal blood flow by decreasing renal vascular resistance$^{[19]}$ even when its specific receptor (Mas) was not presented$^{[17]}$. Possibly, the increased renal blood flow by Ang1-7 promotes the glomerular filtration rate, which primarily reduces during CP therapy$^{[1]}$.

CONCLUSION
In this short article, we introduce Ang1-7 as a potential supplement against CP-induced nephrotoxicity. More research is needed to verify the current result and to find the exact related mechanism for future of Ang1-7 as therapeutic agent during cancer drug therapy.

ACKNOWLEDGMENTS
Conflict of interest: The authors have declared that no conflict of interest exists.

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REFERENCES


Original Article

Doppler ultrasonographic findings in cases with Hashimoto thyroiditis

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3Department of Internal Medicine, Düzce, Düzce University Medical Faculty, Düzce, Turkey
4Department of Internal Medicine, Sinop State Hospital, Sinop, Turkey

ABSTRACT

Objective: To investigate the effect of thyroid-stimulating hormone (TSH) levels on hemodynamic indexes in color doppler ultrasonography in patients with Hashimoto’s disease

Design: Prospective observational study

Setting: Departmant of Endocrinology, Medical Park Hospital, Ordu, Turkey

Subjects: One hundred and twelve patients

Intervention: The patients were divided into two groups: Group 1, TSH: 0.35-4.94 mIU/L; and Group 2, TSH >4.94 mIU/L. The mean peak systolic velocity (mPSV), mean end diastolic velocity (EDV) and mean resistive index (RI) of the inferior thyroid artery were measured using doppler ultrasonography at the appropriate angle (45-60°C).

Main outcome measure: The mPSV, EDV and RI of the inferior thyroid artery

Results: A total of 48.21% of the patients (n=54) were in Group 1 and 51.78% of them (n=58) were in Group 2. In our study, we found that as the TSH levels increased, the thyroid blood flow and RI decreased in patients with Hashimoto’s disease and with clinical and subclinical hypothyroidism compared with normal ones.

Conclusion: The TSH level in Hashimoto’s disease and the vascular RI increases as the parenchymal damage increases.

KEY WORDS: doppler ultrasonography, Hashimoto’s disease, hemodynamic parameters

INTRODUCTION

Hashimoto’s thyroiditis (HT) is an autoimmune disease characterized by chronic lymphocytic infiltration of the thyroid gland due to genetic and environmental influences and the formation of antibodies against thyroid antigens. Ultrasonographic findings during the progression of autoimmune disease vary greatly in parallel with the dynamic nature and histopathologic changes of the disease[1-2].

Color doppler imaging in Hashimoto’s disease (HD) appears to be a promising diagnostic imaging modality. In particular, changes in resistivity index (RI) values in patients with normal grayscale findings require the addition of color doppler ultrasonography to routine ultrasound examinations of these patients. However, the use of color doppler ultrasonography in thyroid disease is a relatively new and promising concept[3].

Ultrasonographic (US) diffuse hypoechoic, heterogeneous, hypervascular, hypovascular areas are seen in patients with HD with the progress of the effects of autoimmunity on the thyroid gland. The aim of this study was to investigate the effect of thyroid-stimulating hormone (TSH) level on hemodynamic indexes in color doppler ultrasonography in patients with HD.

SUBJECTS AND METHODS

This is a prospective observational study which was conducted from May 2017 to March 2018 in Endocrinology Department of Medical Park Hospital. Ethical approval was obtained from Ordu University...
of Medical Sciences Ethics Committee (Number: 239846807, dated 8 May 2017).

The study was conducted on a total of 112 patients. The mean peak systolic velocity (mPSV), mean end diastolic velocity (EDV) and mean RI were measured by using clinical and serological data of the patients with HD, anti-thyroid peroxidase autoantibodies (TPOAb), anti-thyroglobulin antibody (TgAb), TSH, B-mode ultrasonography and doppler ultrasonography at the appropriate angle in the inferior thyroid artery (45-60 °C).

The patients were divided into two groups: Group 1, TSH: 0.35-4.94 mIU/L; and Group 2, TSH: >4.94 mIU/L. Exclusion criteria were other autoimmune disease strains, pregnancy and immunosuppressive drug use, and being under 18 years of age. The HD was diagnosed with clinically obvious hypothyroidism, diffuse goiter presence on B-mode ultrasonography, TPOAb and/or TgAb positivity.

In the study, the hormonal data of serum TSH (reference range: 0.35-4.94 mIU/L), free T3 (reference range: 2.63-5.70 pmol/L), free T4 levels (reference range: 9.01-19.05 pmol/L), TgAb (cut-off level: 4.11 IU/mL), TPOAb (cut-off level: 5.61 IU/mL) were examined with automated chemiluminescent immunoassay kits (Abbott, IL, USA). Thyroid ultrasonography was performed with a high-resolution apparatus (The Philips Affiniti 70 ultrasound; Philips North America Corporation 3000 Minuteman Road M/S 109 Andover, MA 01810, USA) equipped with a 5-12 MHz broadband linear array probe. All practices were performed by an experienced healthcare staff. Analysis of the data was performed using the SPSS Software, version 10.0 (SPSS Inc, Chicago, IL). Mean ± standard deviation was calculated for descriptive analysis and one-way analysis of variance was used to compare the groups. The Kruskal Wallis test was used for further analyses among the groups. Categorical variables were assessed by Pearson Chi-square test. Statistical significance was accepted as \( P < .05 \).

RESULTS

A total of 112 patients were included in the study. The mean age of the patients was 32±11.6 years in Group 1 and 34.2±9.7 years in Group 2, and all the patients were female. Of the 112 patients, 48.21\% (n=54) was in Group 1 and 51.78\% (n=58) was in Group 2. The general characteristics of the groups according to TSH levels are shown in Table 1. Doppler US showed an inferior thyroid artery mPSV of 38.4±6.8 cm/s in Group 1 and 29.3±7.6 cm/s in Group 2 (\( P = .049 \)).

The inferior thyroid artery EDV was 16.27±2.8 cm/s in Group 1 with normal TSH and 11.67±3.68 cm/s in Group 2 with high TSH level (\( P = .023 \)). In the group with high TSH level, the measured RI values were statistically higher than the group with a normal TSH level (\( P < .001 \)). Doppler US parameter values between groups according to TSH levels are shown in Table 2.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (n=54)</th>
<th>Group 2 (n=58)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year) mean, SD</td>
<td>32.5±11.6</td>
<td>34.2±9.7</td>
<td>.528</td>
</tr>
<tr>
<td>TSH mean, SD</td>
<td>2.1±0.85</td>
<td>15.3±3.9</td>
<td>.002</td>
</tr>
<tr>
<td>TPOAb mean, IU/mL</td>
<td>89.8±15.4</td>
<td>354.3±43.52</td>
<td>.041</td>
</tr>
<tr>
<td>TgAb mean, IU/mL</td>
<td>45.2±15.1</td>
<td>134.7±27.9</td>
<td>.654</td>
</tr>
</tbody>
</table>

DISCUSSION

In our study, we examined the effect of euthyroid and hypothyroidism on thyroid parenchymal blood flow in HT patients, one of the autoimmune thyroid diseases. Studies have shown that the superior thyroid artery mPSV can effectively distinguish the underlying cause of thyrotoxicosis\[^4\]. In patients with diffuse autoimmune thyroiditis, color doppler US is generally accepted to increase intra-parenchymal blood-flow at the onset and peak of the disease\[^5\]. We found that as TSH levels increased in our study, thyroid blood flow decreased in patients with HD with clinical and subclinical hypothyroidism clinic compared with normal ones.

Thyroid parenchymal bleeding is one of the distinguishing features of thyroid diseases. Left inferior thyroid artery mPSV has a specificity of 91.7\% for HD disease, which is faster than 26.11 cm/s\[^6\]. Also, in our study, the left inferior thyroid artery mPSV was determined as 38.4±6.8 cm/s and 29.3±7.6 cm/s in Group 1 and Group 2 respectively. Inferior thyroid artery mPSV values in HT disease were found to be consistent with the literature. In our study, we found that thyroid blood flow was higher in normal TSH patients with HD. For patients with high TSH levels, inferior thyroid artery mPSV was 29.3±7.6 cm/s.
cm/s and slower flow was detected. This low flow rate was statistically significant among the groups (P=0.049). The decrease in TSH elevation and thyroid blood flow may be explained by higher TPOAb and TgAb levels in individuals in Group 2, impairment of immunomodulation, endothelial dysfunction and more severe chronic parenchymal inflammation. The reason for the inclusion of young patients (Group 1: 32±11.6 years and group 2: 34.2±9.7 years) in the study is that doppler is performed for the newly diagnosed patients and the occurrence of the causes for the disruption of endothelial structure at earlier ages is rare.

Previous studies have shown that there are differences in the parameters of thyroid gland bleeding in people with euthyroidism, thyroiditis and Graves’ disease [5-7]. In our study, we found the inferior thyroid artery EDV was 16.27±2.8 cm/s in Group 1 and 11.67±3.68 cm/s in Group 2 (P=0.023).

When examined with color doppler US, inferior thyroid artery RI was 0.579±0.15 in normal TSH patients (Group 1) and 0.621±0.21 in patients with clinical and subclinical hypothyroidism (Group 2). In previous studies, a higher RI indicates a higher impedance vascular bed blood flow. In cases such as liver cirrhosis, renal atherosclerosis, renal transplant rejection, parenchymal infiltration and edema, resistance to vascular flow due to fibrosis develops, and this can be detected non-invasively by increased RI in doppler US [8-10]. It correlates positively with parenchymal diseases and microvascular resistance. It has been shown that lack of thyroid hormone causes hypertension, increases vascular resistance, reduces vascular volume, renal blood flow and renal sodium reabsorption [11,12]. Based on this information, clinical and subclinical hypothyroidism in HT patients may have reduced parenchymal blood flow by disturbing endothelial function and causing more parenchymal injury.

CONCLUSION

The increase in TSH levels in patients with HD showed that parenchymal bleeding of the gland was reduced and microvascular resistance was increased. RI increase is known to be associated with carotid artery stenosis, renal disease rejection and serious parenchymal diseases. Based on this information, in HD compared to the ones with normal TSH level, more severe parenchymal damage can be detected with an increase in RI in the subclinical and clinical hypothyroidism cases. Measurement of hemodynamic parameters may also provide additional information for the diagnosis in cases of B-Mode ultrasonographic patterns, similar to those seen in clinically challenging cases.

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REFERENCES

11. Chang YC, Chang CH, Yeh YC, Chuang LM, Tu YK. Subclinical and overt hypothyroidism is associated with reduced glomerular filtration rate and proteinuria: a large cross-sectional population study. Sci Rep 2018; 8:2031.
Original Article

Patterns and predictors of malignancy in ovarian cysts with benign pre-operative diagnosis in Jordanian women

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Kuwait Medical Journal 2020; 52 (4): 398 - 405

ABSTRACT

Objectives: To study clinic pathological parameters of presumed benign ovarian cysts at our institute

Design: Retrospective study

Setting: Jordan University Hospital, Amman, Jordan

Subjects: Seven hundred and sixty-four presumed benign ovarian cysts were studied. Inclusion depended on clinicosonographic findings and Risk of Malignancy Index <200. Data including age, symptoms, ultrasound, serum cancer antigen 125 (CA125), and final histopathology diagnoses were collected.

Intervention: Compare pre-operative results with post-operative histopathological diagnosis

Main outcome measures: Examine clinic pathological features and predictors of malignant diagnosis in ovarian cysts with pre-operative benign diagnosis using descriptive statistics and correlations

Results: Mean age was 33.6±10.68 years; 92.8% in reproductive years. Most common presentation was menorrhagia (47.6%). Mean sonographic diameter was 5.1±3.76cm. Ultrasound characteristics were complex in 2.4%. Serum CA125 was elevated in 12.2%, most frequently in endometriotic cysts (68.3%). Histopathologically, cysts were neoplastic (349, 45.7%); physiologic (315, 41.2%); endometriotic (96, 12.6%); and four were uncharacterized (0.5%). Most common histological type was luteal cyst (28.7%). Discordance with pre-op diagnosis was 3.4% (including 21 borderline (2.7%), and five malignant tumors (0.7%)). Discordance was significantly related to cyst diameter (P=.000); sonographic complexity (P=.000); but not to symptoms (P=.927) or CA125 (P=.212). Highest discordance was observed in patients’ ≥50 years (4.4%; P=.054), and lowest in patients <20 years (0%).

Conclusion: Compared to previous studies, we had similar percentage of malignancy, but higher percentage of borderline tumors. Although quantitatively limited, risk of malignancy in ovarian cysts with pre-op benign diagnosis should be expected, especially with older age, cyst diameter and complexity.

INTRODUCTION

Ovarian masses are a common gynecological problem that can occur at any time during a woman’s life. The prevalence of an ovarian mass on ultrasound examination varies broadly among different studies, with a higher occurrence in reproductive-age women than in asymptomatic postmenopausal women[1].

The etiology varies from physiologic cysts in some individuals to aggressive malignant conditions in others. Symptoms associated with adnexal masses, such as ovarian cysts, are rather non-specific and primarily include irregular vaginal bleeding and pelvic and abdominal pain[2]. Furthermore, pelvic examination has low sensitivity and specificity for detecting ovarian masses. Use of cancer antigen 125 (CA125) level alone is not recommended to distinguish between a benign and malignant mass, as it may be elevated in many other conditions[1].

Pelvic ultrasound is the first-line method for evaluating an adnexal mass with high sensitivity and specificity[3]. Sonographic characteristics are important to note because large size, complexity, projections,
septation, irregularity or bilaterality may indicate cancer[3].

Histopathological examination of the resection specimen is the definitive diagnostic tool[4]. Accuracy of ultrasound examination and concordance with histopathological diagnosis are critical to reduce over-treatment and under-treatment, and has been studied among different populations in English literature. However, this issue has not been explored in our population previously. The aim of the current study was to examine the clinicopathological features and predictors of a malignant diagnosis in ovarian cysts with pre-operative benign diagnosis in a major Jordanian tertiary care center.

SUBJECTS AND METHODS

The current study was approved by the Faculty of Medicine and Scientific Research Deanship’s Research Ethics Committee and the hospital IRB committee. This retrospective study was conducted at our University Hospital and covered the period from January 2007 to December 2016. A total of 764 cysts were included; these cysts were presumed to be benign based on clinico-sonographic impression along with Risk of Malignancy Index (RMI) of <200. All patients underwent diagnostic and/or therapeutic surgical procedures at our institution, including laparotomy, laparoscopy and cystectomy, or salpingoopherectomy. RMI[5] is currently a widely used method in evaluating the oncogenic potential of ovarian masses. It incorporates three criteria including: menopausal status (if premenopausal, M=1; if postmenopausal, M=3), ultrasound malignant characteristics (if none of these characteristics are found, U=0; if one, U=1; if two or more, U=3), and the CA125 level (U per ml [kU/L]) in the following formula: M*U*CA125. RMI was calculated for all cases, and a value of ≥200 was used as an exclusion criterion[5]. Cases were included regardless of patient age, fertility, co-morbidities or surgical procedure used. Fresh frozen section was not performed, as the inclusion criteria of study cases depended on the clinical impression of “benign” ovarian cyst. Whenever the clinicians had a suspicious case, it was excluded from the study.

The clinical decision of laparoscopy versus laparotomy intervention was based on ultrasound characteristics of the cyst and the patient’s age, co-morbidities, desire for fertility preservation and personal preference. The patients’ medical records were used to obtain clinical data, including age at time of cyst diagnosis, presenting symptoms, pelvic examination notes, previous medical and gynecological history, hormonal treatment, family history of relevant conditions or gynecological malignancy, fertility and follow-up notes.

The hospital database was used to retrieve biochemical test results for tumor marker CA125 from blood taken around the time of the cyst diagnosis.

Sonographic features of the cysts including maximum diameter, bilaterality, complexity, septation and the presence of any extra-adnexal masses or ascites were identified from the gynecology clinic ultrasound examination notes. The level of experience of the examining clinician was not taken into consideration; most cases were initially evaluated by senior gynecology residents then confirmed by a gynecology consultant.

Histopathological diagnoses and morphological features were obtained from histopathology reports of Department of Pathology at our institute for all harvested specimens. Corresponding formalin-fixed, paraffin-embedded, and hematoxylin and eosin-stained sections for each specimen were reviewed by a pathologist.

The clinical, radiological, biochemical and histopathological characteristics of those ovarian cystectomy cases were studied. Cases were initially divided into groups according to the patient’s age (Table 1). Discrepancies between clinico-sonographic diagnoses and final histopathological diagnoses (behavior) were analyzed and correlated to age groups, cyst diameters, CA125 levels and sonographic features. Statistical analyses were performed using the Statistical Package for Social Sciences software version 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics and correlations were performed using Student’s T- tests and analysis of variance, with P <.05 considered significant.

RESULTS

Clinical features

The patients’ ages ranged from 12 to 74 years (mean: 33.6 years), 8.6% were <20 years old; 238 patients (31.2%) were 20 to <30 years; 218 patients (28.5%) were 30 to <40 years; 197 patients (25.8%) were 40 to <50 years; 17 patients (5.9%) were ≥50 years of age. Seven hundred and nine patients (92.8%) were in reproductive life, whereas 55 (7.2%) were in menopause as reported by patients. The surgical procedures employed included laparoscopy (n=685; 89.7%), laparotomy (n=68; 8.9%), total abdominal hysterectomy (n=1; 0.3%); cesarian section (n=1); and laparotomy, bilateral salpingoopherectomy and total abdominal hysterectomy (n=8; 0.5%). Two patients (0.3%) underwent laparotomy followed by laparoscopy for recurrent cysts; one patient (0.1%) underwent laparotomy twice; and one patient (0.1%) underwent right ovarian cystectomy and left ovarian wedge resection. Regarding clinical presentations, the cysts were symptomatic in 735 patients (96.2%),
whereas they were an incidental finding in 29 patients (3.8%). For symptomatic cases, the most common clinical presentation was menorrhagia (n=364; 47.6%), followed by abdominal or pelvic pain (n=331; 43.3%), and abdominal mass (n=34; 4.5%). One patient complained of abdominal distension, lower limb swelling, irregular cycles and left loin pain. With the exception of three patients, most patients with recurrent ovarian cysts reported similar symptoms for both cysts. Among those with variable symptoms, one patient described abdominal pain with the first cyst and lower back pain with the second, another patient described menorrhagia with one cyst and pain with the second, and the third patient described an abdominal mass with the first cyst and pain with the second. Clinical and sonographic findings and CA125 serum levels are summarized in Table 1.

### Sonographic characteristics

Cyst diameters ranged from 1 cm to 27 cm (mean: 5.1 cm) as measured by ultrasound. 74.5% of cysts (n=569) were ≤6 cm in diameter; and 91.4% cysts were <10 cm (n=698) and only 18 cysts were >15 cm. The majority of cysts were unilateral (95.4%), including 407 right-sided cysts (53.3%) and 322 left-sided (42.1%). Only 35 (4.6%) were bilateral. Cysts were described as simple or complex according to a set of ultrasound characteristics as per gynecological clinic ultrasound notes. ‘Simple’ was used to describe a cyst that was solitary, unilateral and unilocular with anechoic fluid in cyst cavity and thin walls. Cysts were ‘complex’ if they were multilocular, had solid components or septation, or associated with extra-adnexal disease or ascites. The majority of the studied cysts (97.6%) had simple ultrasound findings, whereas 2.4% were considered complex.

### CA125 serum level

The tumor marker serum level was evaluated at time of cyst diagnosis and was found to be within normal in 87.8% and elevated (>35 U/ml) in 93 cases (12.2%). The strongest association was with endometriotic cysts, as 41 out of 96 endometriotic cysts (68.3%) had elevated CA125.

### Histopathological findings

According to histopathological diagnosis, cysts were specified a behavior as either benign or non-benign (including borderline or malignant).

Cysts were histopathologically classified into the following categories: neoplastic (n=349; 45.7%); physiologic (n=315; 41.2%); endometriotic (n=96; 12.6%); and infracted/ hemorrhagic uncharacterized (n=4; 0.5%).

Clinical and sonographic characteristics and CA125 serum levels of the study sample are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Age (year)</td>
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<tr>
<td>&lt;20</td>
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</tr>
<tr>
<td>20 to &lt;30</td>
<td>238</td>
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<td>30 to &lt;40</td>
<td>218</td>
<td>28.5</td>
</tr>
<tr>
<td>40 to &lt;50</td>
<td>197</td>
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<tr>
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<tr>
<td>≥35</td>
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<td>right</td>
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<td>0.3</td>
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<td>0.5</td>
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<td>0.1</td>
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<tr>
<td>Incidental</td>
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<td>3.8</td>
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<td>Abdominal/ pelvic pain</td>
<td>331</td>
<td>43.3</td>
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<td>Menorrhagia</td>
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<tr>
<td>Abdominal mass</td>
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<td>4.5</td>
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<td>Abdominal swelling</td>
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<tr>
<td>irregular cycles</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Lt loin pain</td>
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<td>0.1</td>
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<tr>
<td>low back pain</td>
<td>1</td>
<td>0.1</td>
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<tr>
<td>1st Menorrhagia, 2nd pain</td>
<td>1</td>
<td>0.1</td>
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<tr>
<td>1st Abdominal Mass, 2nd pain</td>
<td>1</td>
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</table>


diagnoses of presumed benign ovarian tumors were concordant in 738 cases (96.6%). The discordant cases (3.4% of all) included borderline (n=21; 2.7%) and malignant tumors (n=5; 0.7%). The borderline neoplastic cysts included 16 serous and five mucinous tumors. The five malignant cases included three endometrioid carcinomas, one serous carcinoma, one signet ring carcinoma, and one mixed germ cell tumor (Fig 1). Seven hundred and forty-five (97.5%) cysts were of a pure histotype, whereas 24 were mixed lesions, including 13 mixed neoplastic and physiologic cysts/paratubal cysts; seven mixed endometriotic and physiologic cysts; and four mixed neoplastic and endometriotic cysts.
Based on the specific histological typing, the most common cysts were luteal cysts (28.7%), followed in frequency by cystic teratoma (15.4%) and serous cystadenomas (14.1%). The histopathological characteristics of the cysts are summarized in Table 2.

Table 2: Histopathological characteristics of the study sample

<table>
<thead>
<tr>
<th>Histological type</th>
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<th>Percentage</th>
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<tbody>
<tr>
<td>Follicular</td>
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<td>12.3</td>
</tr>
<tr>
<td>Luteal cyst</td>
<td>219</td>
<td>28.7</td>
</tr>
<tr>
<td>Endometriotic</td>
<td>96</td>
<td>12.6</td>
</tr>
<tr>
<td>Paratubal cysts</td>
<td>39</td>
<td>5.1</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>108</td>
<td>14.1</td>
</tr>
<tr>
<td>Cystadenofibroma</td>
<td>22</td>
<td>2.9</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Teratoma</td>
<td>118</td>
<td>15.4</td>
</tr>
<tr>
<td>Serous borderline</td>
<td>16</td>
<td>2.1</td>
</tr>
<tr>
<td>Mucinous borderline</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>Malignant serous</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Malignant germ cell</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Malignant endometrioid</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Uncharacterized</td>
<td>4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Discordance between pre-operative clinico-sonographic diagnoses and histopathological diagnosis

Next, we examined factors that may have significant impact on the accuracy of sonographic pre-operative diagnoses.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Number</th>
<th>Benign</th>
<th>BLT*</th>
<th>CA†</th>
<th>BLT</th>
<th>CA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 yr</td>
<td>66</td>
<td>66</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 to &lt;30 yr</td>
<td>238</td>
<td>231</td>
<td>6</td>
<td>1</td>
<td>2.5</td>
<td>0.4</td>
<td>2.9</td>
</tr>
<tr>
<td>30 to &lt;40 yr</td>
<td>218</td>
<td>209</td>
<td>7</td>
<td>2</td>
<td>3.2</td>
<td>0.9</td>
<td>4.1</td>
</tr>
<tr>
<td>40 to &lt;50 yr</td>
<td>197</td>
<td>189</td>
<td>7</td>
<td>1</td>
<td>3.6</td>
<td>0.5</td>
<td>4.1</td>
</tr>
<tr>
<td>≥50 yr</td>
<td>45</td>
<td>43</td>
<td>1</td>
<td>1</td>
<td>2.2</td>
<td>2.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Total</td>
<td>764</td>
<td>738</td>
<td>21</td>
<td>5</td>
<td>2.7</td>
<td>0.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

*borderline; †cancer; ‡discrepancy with histopathological diagnosis
cm in diameter (\(n=284; 90.2\%\)) and none were \(\geq 15\) cm (\(P=0.063\)). Seventy-four endometriotic cysts (77.1\%) and 160 neoplastic cysts (45.8\%) were \(<6\) cm in diameter.

Cysts larger than \(10\) cm in diameter were most frequently neoplastic in nature (\(n=55; 84.8\%\)), with teratoma being the most common post-operative histopathological diagnosis (\(n=22; 33.3\%\)) among them.

Cyst complexity by ultrasound was also significantly associated with the behavior of the lesion (\(P=0.000\)). By ultrasound, 97.6\% of all samples were ‘simple’ cysts; the majority of which (97\%) were diagnosed as benign based on histopathology, whereas 2.1\% were borderline tumors and 0.4\% were malignant based on histopathology. Although cysts classified as ‘complex’ by ultrasound constituted only 2.4\% of all cases in the current study, complexity was detected in 28.6\% (6/21) and 80\% (4/5) of cases that by histopathology turned out to be borderline and malignant cysts, respectively.

CA125 levels were significantly associated with general cyst type (Pearson Chi\(^2\)=.000), being elevated in 18 patients with physiologic cysts (12.4\%), 41 patients with endometriotic cysts (68.3\%), and 34 patients with neoplastic cysts (17.9\%). There was no significant association between CA125 levels and cyst histological behavior (\(P=0.212\)). Of the 93 patients with elevated CA125, 90 (96.8\%) were diagnosed with benign disease and three (3.2\%) were diagnosed with borderline tumors upon histopathological examination. Interestingly, none of the five patients diagnosed with malignancy had elevated CA125 levels, even the patient with serous carcinoma.

Statistical relationships are summarized in Table 4.

**Table 4:** Statistical relationships between cyst histopathological behavior and different study parameters using ANOVA for age groups, and bivariate correlation for remaining variables (*Correlation is significant at 0.01(2-tailed))

<table>
<thead>
<tr>
<th>Correlation to Parameter</th>
<th>Significance to Behavior</th>
<th>Significance to Cyst diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.321)</td>
<td>(0.171)</td>
</tr>
<tr>
<td>Age group</td>
<td>(0.223)</td>
<td>(0.327)</td>
</tr>
<tr>
<td>Actual age of patient</td>
<td>(0.000^*)</td>
<td>---</td>
</tr>
<tr>
<td>Cyst diameter</td>
<td>(0.212)</td>
<td>(0.666)</td>
</tr>
<tr>
<td>CA125 level</td>
<td>(0.000^*)</td>
<td>(0.000^*)</td>
</tr>
<tr>
<td>Ultrasound features</td>
<td>(0.927)</td>
<td>(0.001^*)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>---</td>
<td>(0.000^*)</td>
</tr>
<tr>
<td>General type</td>
<td>---</td>
<td>(0.000^*)</td>
</tr>
<tr>
<td>Histologic type</td>
<td>---</td>
<td>(0.000^*)</td>
</tr>
</tbody>
</table>

By contrast, CA125 levels did correlate significantly with specific histological type (\(P=0.000\)). Interestingly, the strongest association was with endometriotic cysts (41; 68.3\%).

The 21 cases with borderline malignancy had the following profile: age ranged from 20 to 50 years (mean: 34 years); cyst diameters ranged from 4 to 20 cm (mean: 7 cm); 3/21 were bilateral (14.3\%); CA125 levels ranged from 12.6 to 109.4 (mean: 28.2 U/ml). RMI ranged from 9 to 127 (mean: 62.4). Six out of them showed complex ultrasound features (28.6\%) including four multilocular/ septated, one showing “thick wall” and one labelled as “heterogeneous”.

For the five malignant cases, the age ranged from 27 to 56 years (mean: 34 years); the cyst diameters ranged from 7 to 18 cm (mean: 11 cm); 2/5 were bilateral (40\%); CA125 serum levels ranged from 13 to 33 U/ml (mean: 14.6); RMI ranged from 18.5 to 122.4 (mean: 99). Four out of five cases showed complex ultrasound findings (80\%) including solid component in 2 and septation in another 2. In the case with signet cell carcinoma, the ovarian cyst was the first presentation for the patient, the diagnosis of signet ring carcinoma prompted the clinical and radiological search for an extra-ovarian primary site; so investigations including upper and lower gastrointestinal endoscopy were performed and were all negative. The diagnosis of primary ovarian signet ring cell carcinoma was given.

**DISCUSSION**

Ovarian masses, including cysts, are common gynecological conditions seen among women of all age groups. They may be incidental findings during a routine gynecological checkup, or more frequently, symptomatic, leading the patient to seek medical attention either in family medicine- based disciplines or specialized gynecological clinics. The major concern of the clinician is to rule out ovarian malignancy, a common cancer type in women and one of the leading causes of cancer deaths worldwide\(^[1]\).

The prevalence of an adnexal cyst on ultrasound examination varies broadly among different studies with a higher occurrence in reproductive-aged women\(^[2]\) than in asymptomatic postmenopausal women during routine gynecological checkup\(^[3]\). Up to 10\% of women will have surgery for an ovarian finding in their lifetime\(^[4]\).

The clinical presentation of an adnexal mass includes abnormal vaginal bleeding, bloating, enlarged abdominal girth, dyspareunia, urinary symptoms, and pelvic and abdominal pain\(^[5]\). The initial clinical evaluation for an adnexal mass includes comprehensive medical history taking and pelvic examination. Unfortunately, the sensitivity of pelvic examination for detecting an adnexal mass is generally poor\(^[3]\), especially in early cases or small-sized cysts.

Vaginal pelvic ultrasound is currently the first and most frequently used imaging method in evaluating a case of presumed benign ovarian tumor, and in many
of the cases (those consisting of a pure fluid unilocular mass less than 7 cm in diameter) is sufficient to typify the mass\[6\], with reported sensitivity and specificity of >90%. The main advantages of this technique are reproducibility, consistency and reduced costs compared with other investigations\[2\]. The major ultrasound features that help to identify benign cysts are unilocular fluid-containing masses, homogeneous low-to-medium echoes in the cystic mass and the absence of a solid component\[7\]. A fishnet or reticular pattern (network of curvilinear or thin linear internal echoes) is strongly suggestive of a hemorrhagic cyst\[8\].

The risk of ovarian malignancy increases with ovarian mass (>6 cm), bilateralism, septation and the presence of ascites\[4,9\]. Disadvantages of ultrasonography include its dependence on the level of experience of the technician and the relatively low accuracy in evaluating larger masses.

Following ultrasound, magnetic resonance imaging is the next best imaging technique to characterize an adnexal mass\[10\], especially for large masses, and is thought to show malignant characteristics more evidently\[6\].

Ultrasound-guided puncture is not recommended for diagnosing ovarian cysts because the sensitivity is limited by inconclusive or inadequate results\[11\] and because of the high risk of intra-operative rupture of malignant ovarian epithelial neoplasms\[12\].

CA125 is well known to be elevated in ovarian malignancies and CA125 levels (measured as U/ml with a cutoff of greater than 35 U/ml) may assist in evaluating an ovarian mass\[6\]; however, it should not be used as a screening technique due to its low specificity, as CA125 levels may be elevated in a number of conditions other than ovarian cancer\[6\]. CA125 levels are normally higher in pre-menopausal women than in post-menopausal women. Based on the results of one meta-analysis of 49 cohort studies and two case-control studies, diagnostic ultrasound for post-menopausal women with CA125 levels >35 U/ml has an overall sensitivity of 79% and a specificity of 78%\[6\]. At a CA125 level of 100 U/ml, a premenopausal woman has only a 21.1% likelihood of having a malignant ovarian tumor, whereas a post-menopausal woman with same level has a 74.3% likelihood of an ovarian malignancy\[6\].

Common benign gynecological conditions leading to elevated CA125 include endometriosis, large uterine fibroids, menstruation, pelvic inflammatory disease and previous hysterectomy\[6\]. Even non-gynecological benign conditions can raise CA125 levels, for example liver cirrhosis with or without ascites, lung disease and obesity. Moreover, other malignancies can cause high serum levels of CA125, such as breast cancer, endometrial cancer, lung cancer, pancreatic cancer and peritoneal implants of non-ovarian cancers\[14\].

To take a more quantitative approach, multiple risk scoring systems have been designed to distinguish between benign and malignant adnexal masses\[4\]. One of the most widely used methods is RMI\[5\]. There is a commonly accepted RMI threshold of 200\[5\], above which the individual is at high risk for malignancy. Some studies recommended a higher threshold in Asian populations\[15\]. We used the RMI formula in the current study as part of the clinical evaluation of presumed benign ovarian cysts; all cases with an RMI ≥200 were initially excluded.

The guidelines for the diagnosis and treatment of benign ovarian cysts are dependent on the age of the patient and maximum diameter and sonographic characteristics of the mass. The main concern, as stated previously, is the risk of malignancy.

Regarding patient age at diagnosis, a retrospective study reported that 25% of adnexal masses in patients younger than 18 years were malignant\[16\]. The detection of an adnexal mass in a pre-menarchal patient, whether symptomatic or not, should be evaluated by a gynecologist. In the current study, none of the patients younger than 20 years old had a discordant malignant diagnosis.

In pre-menopausal women, physiologic cysts including follicular and corpus luteum cysts are the most common adnexal masses\[16\]. Management of such cysts depends on cyst complexity and symptoms. For asymptomatic simple unilocular ovarian cysts less than 10 cm in diameter, a premenopausal patient can be observed or placed on oral combined contraceptives\[8\], which offer benefits beyond contraception, such as treatment and prevention of several gynecological disorders, including functional ovarian cysts. This conservative approach is based on the observation that risk of malignancy in unilocular ovarian cystic tumors less than 10 cm in diameter in women 50 years old or younger is extremely low\[6\]. A drawback of surgical intervention is the overall recurrence rate of 2-5% after cystectomy for functional ovarian cysts\[7\]. In addition, many of the conservatively managed functional ovarian cysts resolve spontaneously as determined by serial transvaginal ultrasound follow-ups\[2\].

In cases where a conservative approach is preferred, repeated ultrasound examination should be used to monitor presumed benign adnexal masses\[4\]. The guidelines are variable as to how often and how long to monitor\[17\]. If an adnexal mass persists for more than 12 weeks, surgery by a gynecologist is indicated. This is important as knowledge of physiological cyst morphology and speed of development will help to avoid unnecessary surgery.
Cysts in postmenopausal women are generally treated with greater caution. Surgical management is preferred over conservative management in cases of persistent or complex cysts[15].

In symptomatic cysts, laparoscopy rather than laparotomy is the preferred approach for surgical treatment[14]. A conservative surgical treatment (cystectomy) is favored to oophorectomy in pre-menopausal women without previous history of cancer[17].

Advantages of laparoscopy over laparotomy are diverse. First, laparoscopy is associated with less in-hospital stay, recovery time and costs, and lower rates of post-operative complications such as fever, urinary tract infection, postoperative pain and adhesion formation[17,18]. Second, it is the favored method when fertility is an issue[18]. One disadvantage of laparoscopic oophorectomy or cystectomy, however, is the potential for intra-operative spillage of the cancer cells if the mass is malignant[1]. Even in cases of suspected adnexal torsion, laparoscopic surgical exploration is recommended[19].

Conservative untwisting without oophorectomy is recommended for non-menopausal women regardless of the estimated duration of the twist and the macroscopic appearance of the ovary[19].

Adnexal cysts may also occur in pregnant women (incidence ranging from 2% to 5%)[20]. Expectation is recommended for asymptomatic unilocular fluid cystic masses less than 6 cm[15]. Simple cysts measuring less than 5 cm are the most common adnexal masses with an intrauterine pregnancy (76%) and malignant masses are the least common ovarian masses detected during pregnancy (less than 1%)[21].

In all cases where surgery is the focus, the disadvantage of a potential drop of the ovarian reserve needs to be reasonably weighed with the benefits of surgery.

Upon literature review for studies of similar interests, the risk of an unexpected malignancy in a clinically presumed benign cyst is small (0.04% to 1.9% in some studies)[22-24], however, it is still an issue and only a histopathological examination can provide a definitive characterization of an adnexal mass. A recent systematic review and meta-analysis of 34 large-sized studies evaluating histopathological diagnoses of ovarian cysts pre-operatively called as simple unilocular cysts states that the rates are generally low, and in particular lower for premenopausal women (0.3%) than postmenopausal ones (1.9%; Pearson chi-square \( P=.002 \)), and in cysts \(<5\) cm than those \(\geq5\) cm ((1.1%; 95% CI: 0.74-1.66 including borderline malignancy: 0.6%)[24].

In the current study, our results are comparable to literature regarding factors with impact on risk of an unexpected malignancy in a clinically presumed benign, with decreasing accuracy with increasing age, cyst diameter and complexity. However, our rates of an unexpected malignancy are somewhat higher, especially for borderline tumors. The explanation for this may be due to the fact that most previous studies were limited to anechogenic unilocular ovarian cysts, while our cases included some complex ovarian cysts. Moreover, many of those review and meta-analysis papers are published in English, so non-English publication results are ambiguous to us. Another reason may be the heterogeneity in defining simple versus complex ultrasound examination among different studies, and among practicing sonographic examiners involved in our cases, along with variable individual technical skills and interpretation.

Limitations of the current study include that it was conducted at a single center, as well as lack of proper follow up data of the cases.

CONCLUSION

We conclude that despite occurring at a low rate, discrepancies between preoperative clinicosonographic evaluations and final histopathology diagnoses are known to exist. We believe that a decision for surgical management based on a preoperative clinical-sonographic impression may result in under-treatment (for unrecognized borderline or malignant disease), or over-treatment (with unnecessary oophorectomy for an otherwise benign condition).

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REFERENCES


Original Article

Comparison of different methods in sonographic estimation of fetal weight in diabetic pregnant women on insulin therapy

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Kuwait Medical Journal 2020; 52 (4): 406 - 411

ABSTRACT

Objective: The aim of the study to compare the accuracy of different ultrasonographic weight estimating equations for predicting the fetal weight in pregnant patients on insulin therapy.

Design: Prospective clinical study

Setting: Erciyes University Obstetric Clinic Perinatology Unit, Turkey

Subjects: One hundred and eleven diabetic pregnant women using insulin

Intervention(s): The fetal weight estimations were calculated off-line using the two previously investigated methods (Hadlock 1 and Shepard) and abdominal circumference (AC).

Main outcome measure(s): The accuracy of different weight estimating equations for predicting fetal weight in pregnant patients on insulin therapy

Results: Hadlock 1 and Shepard methods had estimated fetal weight values close to the actual birth weight whereas AC had not. The success rates and the sensitivity of the methods for detecting macrosomic fetuses weighing over 4000 g in insulin using diabetic women were low and the rates were 0.65 (95% CI: 0.40-0.84), 0.13 (95% CI: 0.01-0.40) and 0.55 (95% CI: 0.31-0.76), for the Hadlock 1, AC and Shepard formulae respectively (P<.05).

Conclusion(s): The study showed that Hadlock 1 and Shepard methods were significantly better for estimating fetal weight than AC. The success rates of the methods for detecting macrosomic fetuses weighing over 4000 g were similar, but the methods did not have high sensitivity.

KEY WORDS: abdominal circumference, diabetes mellitus, Hadlock 1, Shepard, weight estimation

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases affecting hundreds of millions of people worldwide[1]. The presence of maternal DM during pregnancy has important consequences for both mother and baby. Women with DM are at risk for pre-eclampsia and primary caesarean operation, while their infants tend to experience higher rates of fetal anomalies and fetal macrosomia[2]. The primary concern about the birth of a macrosomic fetus is related to adverse maternal outcomes including cervical and vaginal laceration, uterine rupture, pelvic floor injuries and postpartum haemorrhage; and neonatal outcomes such as birth asphyxia, shoulder dystocia, brachial plexus injuries and meconium aspiration syndrome[3].

Accurate prediction of fetal weight is critical in preventing labour complications and permits obstetricians to plan the delivery. Due to the inherent subjective nature of fetal weight estimation with Leopold manoeuvres, they are not useful for detecting macrosomic fetus in pregnancies with DM. Prenatal ultrasound appears to be the best method for performing weight estimation up to 3500g. However, when used for the detection of fetal macrosomia, ultrasound biometry is characterized by low sensitivity and low predictive value[4]. Fetal
biparietal diameter (BPD), head circumference (HC), femur length (FL) and abdominal circumference (AC) are essential parameters for the prediction of fetal weight in ultrasound examination. Recent studies determined that the combination of these parameters may be more accurate when compared with a single parameter[5]. Lots of equations have been developed by experts and programmed into ultrasound for automatic calculation of fetal weight according to the given parameters.

Despite the fact that there are studies comparing the different equations for estimating the fetal weight accurately in uncomplicated pregnancies, there is no study in pregnant patients on insulin therapy. In this study, we aimed to compare the accuracy of different weight estimating equations for predicting fetal weight in pregnant patients on insulin therapy.

SUBJECTS AND METHODS

This is a prospective longitudinal study which was conducted in Erciyes University Hospital, Kayseri, Turkey between January 2013 and June 2015 with 111 diabetic, insulin using pregnant women. Women with a singleton pregnancy complicated by DM and using insulin therapy during the pregnancy were invited to have an ultrasound examination between 37+0 and 37+6 weeks gestation to estimate fetal weight. Patients signed a written informed consent for examination. Those with congenital structural/chromosomal abnormalities, multiple gestations and intrauterine fetal deaths were excluded from the study. Pregnant patients were hospitalized at 36 weeks of gestation and glycemic control and fetal wellbeing tests were performed daily. Gestational diabetes mellitus (GDM) was diagnosed based on Carpenter-Coustan criteria. When two values were above the limit, the diagnosis of GDM made. All patients were managed by an obstetrician and endocrinologist. In patients with GDM, if one to two weeks of trial of dietary management failed, insulin therapy was started by the managing endocrinologist. In patients with GDM, short acting insulin therapy was used between two or four daily doses. In patients with pregestational diabetes, insulin therapy was started when pregnancy was diagnosed. Insulin therapy was used at four daily doses. In patients with pregestational diabetes, insulin therapy was started when pregnancy was diagnosed. Insulin therapy was used at four daily doses. In patients with pregestational diabetes, insulin therapy was started when pregnancy was diagnosed. Insulin therapy was used at four daily doses. In patients with pregestational diabetes, insulin therapy was started when pregnancy was diagnosed.

The scans were performed trans abdominally by a single obstetrician (M.S.K) with a Voluson 730 Pro equipped with a 5- to 8-MHz transabdominal transducer (GE, Healthcare). All fetal parameters (BPD, HC, AC and FL) were measured with standard 2D techniques in frozen images. The BPD was measured from the outer edge of the proximal parietal bone to the inner edge of the distal parietal bone at the level of the paired hypoechoic thalami and cavum septum pellucidum[6]. The HC was measured with an ellipse measurement tool from the occipital to the frontal part of the outer counter of the fetal skull bone in the same frozen image as used for the BPD. FL was measured as the length of the ossified diaphysis of the fetal femur from the greater trochanter to the femoral condyles and the AC was measured as the extent of the outer border of the fetal abdomen at the level of umbilical vein entrance to the liver sinus (kidneys should not be visible) at the transverse plane. It is our institutional policy to perform cesarean section in diabetic pregnant patients with estimated fetal weight greater than 4000 grams. Due to the risk of sudden fetal death, we delivered the pregnant patients requiring insulin therapy at 38+3 weeks. Fetal macrosomia was defined above 4000 grams. All babies were weighed by the same scale at birth.

The fetal weight estimations were calculated off-line using the two investigated methods and AC (Table 1).

Statistical analysis

The baseline characteristics of the study cohort were reported using descriptive statistics. Comparisons between the precision of the actual birth weight and the three fetal weight estimating equations were made by using Passing-Bablok regression analysis and the Bland-Altman graphics were created. By examining the confidence intervals of the coefficients obtained by regression analysis, systematic and proportional error probabilities were investigated. In the case where the constant coefficient does not contain 0, the existence of a systematic error and the case where the regression coefficient does not include 1, the existence of a proportional error is accepted. Receiver operating characteristic analysis were applied in easy ROC software. Sensitivity, specificity, positive and negative predictive values were calculated with 95% confidence intervals[7].

<table>
<thead>
<tr>
<th>Name</th>
<th>Contents</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadlock I</td>
<td>BPD, HC, AC, FL</td>
<td>10^\left(1.3596+0.0064^*HC+0.0424^*AC+0.174^*FL+0.00061^*BPD^*AC–0.00386^*AC^*FL\right) [g, cm]</td>
</tr>
<tr>
<td>AC</td>
<td>AC</td>
<td>\pi \left(\text{APAD}+\text{TAD}\right)/2 = 1.57 \left(\text{APAD}+\text{TAD}\right)</td>
</tr>
<tr>
<td>Shepard</td>
<td>BPD, AC</td>
<td>10^\left(-1.7492+0.166^*BPD+0.046^*AC–0.002+546^*AC^*BPD\right) [g, cm]</td>
</tr>
</tbody>
</table>

AC: abdominal circumference; BPD: biparietal diameter; FL: femur length; HC: head circumference; APAD: anteroposterior abdominal diameter; TAD: transverse abdominal diameter.
RESULTS

One hundred and eleven insulin using diabetic pregnant women were scanned for estimated fetal weight between 37 and 37+6 weeks gestation. The demographic and clinical data are shown in Table 2.

<table>
<thead>
<tr>
<th>Demographic parameters</th>
<th>Mean ± Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>33.1±6.3</td>
<td>18-47</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>33.8±6.4</td>
<td>24.2-38.8</td>
</tr>
<tr>
<td>Parity</td>
<td>3.4±1.8</td>
<td>1-10</td>
</tr>
<tr>
<td>Insulin dosage (units per day)</td>
<td>34.6±3.1</td>
<td>4-160</td>
</tr>
<tr>
<td>HbA1c levels</td>
<td>5.6±1.0</td>
<td>4-8.9</td>
</tr>
<tr>
<td>Chronic Hypertension</td>
<td>12/111 (10.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3527.3±582.5</td>
<td>1560-5190</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>94/111 (84.6%)</td>
<td>-</td>
</tr>
<tr>
<td>&gt;4000g birth weight</td>
<td>20/111 (18%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Demographic and clinical data of study population

The median age of the women was 33.1±6.3 years (range: 18-47 years). All of the patients were on insulin therapy and twelve women were using antihypertensive drugs for chronic hypertension. Fifty-six insulin using diabetic patients (56/111, 50.4%) were diagnosed as GDM A2, 37 patients (37/111, 33.3%) were Type 2 and 18 patients (18/111, 16.2%) were Type 1 DM. The mean insulin dosage was 34.6±31.1 (range: 4-160) units per day. All HbA1c tests were done at 37 weeks gestation and the mean HbA1c level was 5.6±1.0% (range: 4-8.9%). Mean fasting glucose value was 108.7±15.8 mg/dL (range: 80-150).

The actual birth weight had a mean of 3527.3±582.5 (range: 1560-5190) grams. The Hadlock 1 method had a mean estimate of 3553.5±585.4 g. AC had a mean estimate of 3502.5±421.8 g and the Shepard method had a mean estimate of 3570.4±553.8 g. Hadlock 1 and Shepard methods had estimated fetal weight

- Fig 1: Bland-Allman versus Passing-Bablok Graphics. a) Actual Birth weight and Hadlock 1 Bland-Allman Graphic; b) Actual birth weight and AC Bland-Allman Graphic; c) Actual Birth weight and Shepard Bland-Allman Graphic; d) Actual Birth weight and Hadlock 1 Passing-Bablok Graphic; e) Actual Birth weight and AC Passing-Bablok Graphic; f) Actual Birth weight and Shepard Passing-Bablok Graphic

<table>
<thead>
<tr>
<th>Name</th>
<th>B0 (95% CI)</th>
<th>Systematic Error</th>
<th>B1 (95% CI)</th>
<th>Proportional error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadlock 1</td>
<td>285.70 (-187.60/659.85)</td>
<td>-</td>
<td>0.92 (0.81/1.06)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Circumference</td>
<td>1287.05 (883.30/1587.63)</td>
<td>+</td>
<td>0.64 (0.55/0.76)</td>
<td>+</td>
</tr>
<tr>
<td>Shepard</td>
<td>412.00 (-399.92/848.76)</td>
<td>-</td>
<td>0.89 (0.77/1.02)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Comparison of the mean of actual birth weight and estimated fetal weight of three equations with Passing-Bablok regression analysis
values close to the actual birth weight. There was no systematic and proportional error between these methods. AC had systematic and proportional error and had not estimated fetal weight values close to the actual birth weight. Table 3 shows the Passing-Bablok regression analysis and Figure 1 shows the Bland-Altman graphics. Twenty (20/111, 18%) of the insulin using diabetic women delivered a macrosomic infant weighing >4000 grams, and 5.4% (6/111) delivered an infant weighing >3900 grams. The Hadlock 1, AC and Shepard methods determined the delivery of thirteen, twelve and eleven infants weighing >4000 grams, respectively. The success rates and the sensitivity of the methods for detecting macrosomic fetuses in insulin using diabetic women were low and the rates were 0.65 (95% CI: 0.40-0.84), 0.13 (95% CI: 0.01-0.40) and 0.55 (95% CI: 0.31-0.76), for the Hadlock 1, AC and Shepard methods respectively (P>0.5). Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio of positive and negative test results.

### DISCUSSION

The presence of DM during pregnancy can lead to many problematic outcomes for the baby. Preterm delivery, neonatal hypoglycaemia, polycythaemia, hypocalcaemia, respiratory distress syndrome, small/ large for gestational age, fetal macrosomia, operative delivery and shoulder dystocia dependant on fetal macrosomia are the main problems seen in diabetic infants.

Fetal macrosomia is typically defined as a birth weight above the 90th percentile for gestational age or >4000g. Macrosomic fetuses in diabetic pregnancies develop a unique pattern of overgrowth, involving the central deposition of subcutaneous fat in the abdominal and interscapular areas. They have larger shoulder and extremity circumferences, a decreased head-to-shoulder ratio and thicker upper-extremity skin folds. Since fetal head size is not increased, but shoulder and abdominal girth can be markedly augmented, the risk of shoulder dystocia and brachial plexus injury is more common[8]. Multiple cohort studies have found that macrosomic neonates have an increased risk of abnormal labor, shoulder dystocia, operative delivery and birth trauma[9].

It is important to predict accurate fetal weight for planning the delivery and preventing fetal complications related to birth injury. Clinical and ultrasonographic examinations are the most commonly used methods for this purpose. Fundal height measurement and symphysis-fundal height distance are more commonly used for detecting fetal macrosomia with low sensitivity (10-43%) and positive predictive value (28-53%). The low sensitivity of clinical methods are due to oligohydramnios/polyhydramnios, maternal obesity, incoherent fundal height measurement, the effect of obstetricians experience and abnormal fetal position[10]. Kayem et al compared the diagnostic value of fundal height and ultrasonographic measured fetal AC in the prediction of actual fetal weight at 37-40 weeks gestation. The authors revealed that the ultrasonographic measurement of fetal AC had a better correlation with actual fetal weight than clinical fundal height measurement[11]. Ultrasonographic biometry for estimating fetal weight and fetal macrosomia is more objective than clinical methods. Investigators have suggested many ultrasound equations for predicting fetal weight. However, only a few studied suggestions were used in clinical practice. In this study, we compared three different fetal ultrasonographic fetal weight estimation equations for accuracy of fetal birth weight in insulin using diabetic pregnancies. Hadlock 1 and Shepard methods had estimated fetal weight values close to the actual birth weight. There was no systematic and proportional error between these methods. AC had systematic and proportional error and had not estimated fetal weight values close to the actual birth weight.

Fetal ultrasound provides a combination of biometric data, such as the BPD, AC, HC and FL, which are also used to estimate the fetal weight separately. The most widely used equations are Shepard, Hadlock 1 and single AC. Recent studies revealed that the estimation of fetal weight according to multiple parameters is much more accurate than

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**Table 4: Sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio of positive and negative test results**

<table>
<thead>
<tr>
<th>Name</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR-</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadlock 1</td>
<td>0.65 (95% CI:0.40-0.84)</td>
<td>0.94 (95% CI:0.87-0.98)</td>
<td>0.72 (95% CI:0.46-0.90)</td>
<td>0.92 (95% CI:0.85-0.96)</td>
<td>0.37 (95% CI:0.20-0.67)</td>
<td>11.8 (95% CI:4.7-29.4)</td>
</tr>
<tr>
<td>Abdominal Circumference</td>
<td>0.13 (95% CI:0.01-0.40)</td>
<td>0.97 (95% CI:0.92-0.99)</td>
<td>0.50 (95% CI:0.06-0.93)</td>
<td>0.87 (95% CI:0.79-0.93)</td>
<td>0.88 (95% CI:0.72-1.0)</td>
<td>6 (95% CI:0.90-39.8)</td>
</tr>
<tr>
<td>Shepard</td>
<td>0.55 (95% CI:0.31-0.76)</td>
<td>0.91 (95% CI:0.83-0.96)</td>
<td>0.57 (95% CI:0.33-0.79)</td>
<td>0.90 (95% CI:0.82-0.95)</td>
<td>0.49 (95% CI:0.30-0.80)</td>
<td>6.2 (95% CI:2.8-13.5)</td>
</tr>
</tbody>
</table>

PPV: positive predictive value; NPV: negative predictive value; LR-: likelihood ratio of negative test; LR+: likelihood ratio of positive test; CI: Confidence interval
that with a single parameter. AC is a highly related single parameter for fetal weight estimation[9]. Shi et al determined the reliability of the fetal AC measured by ultrasound as a predictor of birth weight. They revealed that AC is useful in screening for macrosomia and avoiding shoulder dystocia[12]. In another study, Smith et al compared AC and actual fetal birth weight in nondiabetic women and concluded that the AC parameter alone is useful to estimate fetal weight[13]. Conversely to previously reported studies, we determined that single AC measurement did not have effective success on fetal weight estimation compared with Hadlock and Shepard methods. Therefore, in diabetic pregnancies using insulin, it is not a very appropriate method to determine the weight estimate using only AC. With the addition of BPD to the AC measurement, it may be a good idea to estimate the weight without losing time for the FL and HC measurements.

Shepard et al developed an equation which included BPD and AC in 1982 and they concluded that this method is useful to estimate fetal weight[14]. Kurmanavicius et al published a comparison of different methods for fetal weight estimation in 5612 women. They concluded that Hadlock 1 and Hadlock 2 (AC, FL) provide the closest results in all patients. They also demonstrated that the Shepard formula generally overestimates the fetal weight[15]. In our study, the Shephard formula gave close but sometimes higher estimated fetal weights than the actual birth weight in insulin using diabetic women. There was no statistical difference between the estimated fetal weight of the Shepard method and the actual fetal birth weight.

The estimated fetal weight values of the Hadlock 1 method were closest to the Shepard method estimated values. Equations with the addition of the HC parameter have been reported to find better estimates of fetal weight because of variations in the shape of the fetal head, which can result in inaccurate estimation of actual fetal weight[16]. However, Faschingbauer et al found that methods including HC show underestimation of fetal weight values because of the increasing descent of the fetal head into the maternal pelvis[17]. In our study, we did not find any discrepancy among the three methods. An explanation for this result may be the ultrasound examination time. We conducted all ultrasonographic exams between 37+0 and 37+6 weeks gestation before initiation of labour.

The perinatal mortality rate had an odds ratio of 2.3 when the birth weight was over the 97th percentile[18], and infants with birth weights greater than 4500g had a perinatal mortality rate twice that of normal-weight infants[19]. The new method that was first used by Hart et al demonstrated that the formula including fetal biometry and maternal weight had the lowest mean absolute percentage error to estimate fetal weight over 4000g infants[20]. Lindel and Marsal compared two-dimensional ultrasonography and three-dimensional ultrasonography techniques for fetal weight estimation in prolonged pregnancies. They concluded that both techniques have similar values for fetal weight estimation[21]. In the present study, twenty (20/111, 18%) of the insulin using diabetic women delivered a macrosomic infant weighing >4000 grams, and 5.4% (6/111) delivered an infant weighing >3900 grams. The success rates and the sensitivity of the methods for detecting macrosomic fetuses in insulin using diabetic women were low and the rates were 0.65 (95% CI: 0.40-0.84), 0.13 (95% CI: 0.01-0.40) and 0.55 (95% CI: 0.31-0.76), for the Hadlock 1, AC and Shepard methods respectively (P>.05).

CONCLUSION

The present prospective comparative study showed that Hadlock 1 and Shepard equations were superior to AC for estimating fetal weight in insulin using diabetic patients. The success rates of the methods for detecting macrosomic fetuses weighing over 4000g are similar, but the formulae do not have high sensitivity.

ACKNOWLEDGMENT

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REFERENCES


A single developing country’s Hematology-Oncology Centre retrospective analysis of the Janus Kinase 2 V617F mutation in Philadelphia negative myeloproliferative neoplasms

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Objective: Myeloproliferative neoplasms are heterogeneous clonal hematological stem cell diseases. The activating Janus kinase 2 (JAK2) V617F mutation has been shown to be associated with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). In this retrospective study, we aimed to determine the frequency of JAK2 V617F mutation in patients having myeloproliferative neoplasms at one Hematology-Oncology Centre in Erbil, Northern Iraq.

Design: Retrospective cohort study

Setting: Department of Hematology, Nanakali Hospital for Blood Diseases and Cancer, and Department of Clinical Biochemistry, College of Medicine, Hawler Medical University, Erbil, Iraq

Subjects: Medical records of 185 patients with myeloproliferative neoplasms over more than seven years were reviewed.

Intervention: The blood samples were subjected to analysis for JAK2 V617F mutation detection using amplification refractory mutation system polymerase chain reaction.

Main outcome measures: The frequency of mutated JAK2 V617F

Results: The JAK2 V617F mutation was detected in 145 (78.3%) patients and heterozygous mutant forms were found in 81 (55.9%) of the total cases with myeloproliferative neoplasms. The frequency of the JAK2 mutation was 93 (86.9%) in PV, 35 (71.4%) in ET, and 17 (58.6%) in PMF. The mutation was more common in males (60%) in PV.

Conclusion: The JAK2 V617F mutation rates in the current cohorts were not very different from what have been previously reported. It is essential to perform JAK2 mutation testing in all suspected cases of myeloproliferative neoplasms.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) are divided into two main groups according to the revised World Health Organization classification in 2016: the classical Philadelphia chromosome negative MPNs which are polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) with the overproduction of mature erythroid and myeloid progeny, and Philadelphia chromosome positive chronic myelogenous leukemia[12].

In 2005, the c.1849G→T transversion mutation in exon 14 of the Janus kinase 2 (JAK2) gene on chromosome 9p24 that had a high rate of incidence in MPN patients was discovered. This mutation causes a single substitution of valine to phenylalanine at position 617 (JAK2 V617F) in the antiregulatory JH2...
(pseudokinase domain) is associated with MPNs and it is the main diagnostic indicator of MPN. The gain of function mutation causes a constitutive activation of the JAK2 causing enhanced hematopoiesis, which results in the phosphorylation of signal transducer and activator of transcription in the absence or presence of low levels of hematopoietic growth factors[3].

The family of non-receptor tyrosine kinases, known as Janus kinases (JAKs), includes JAK1, JAK2, JAK3 and tyrosine kinase 2, are essential for the differentiation, proliferation of erythroid, megakaryocytic lineages and apoptosis. JAK2 plays an important role in the JAK / signal transducer and activator of transcription pathway that is involved in the signaling via cytokines such as erythropoietin, thrombopoietin or granulocyte-monocyte colony stimulating factor residues[4].

The structure of JAK2 is characterized by the presence of seven defined regions of conserved homology, denoted as JAK homology domains 1-7. Janus homology domain 2 which lacks kinase activity (pseudokinase) has an inhibitory effect on the JAK2 kinase domain[5].

Several mutations of the JAK2 gene in exons 12-15 have been identified in MPN patients, given that the JAK2 V617F mutation in exon 14 is present in about 95% of PV cases and 50-60% of ET or PMF cases[6]. There are increased reports of prevalence of JAK2 V617F mutation in the last decade. However, there is a lack of information about the prevalence of JAK2 V617F mutation in MPN patients who have been treated at our Centre. Therefore, we deemed it necessary to review and study our patient’s records to determine the rate of prevalence of JAK2 mutation, and to describe patient’s demographic data, clinical and laboratory findings.

**SUBJECTS AND METHODS**

This retrospective study was carried out at Nanakali Hemato-Oncology Teaching Centre in Erbil. Records of 185 patients with MPNs who were registered and treated at Nanakali Centre from October 2010 to December 2017 were reviewed. The patients were categorized as follows; 107 with PV, 49 with ET and 29 with PMF. Hematological diagnosis followed the 2008 and revised 2016 World Health Organization diagnostic criterion[1]. The included patients were made fully anonymous before accessing their files. Twenty-four patients were excluded from this analysis; eight had escaped the follow-up and sixteen had chosen to be treated outside the country after they were diagnosed.

Data were collected through direct interview with the patients and ethical approval was obtained from Ethics committee for the study protocol from the College of Medicine at Hawler Medical University-Erbil, Iraq; and informed consent form was taken from all patients.

### Table 1: Age and gender among MPN patients with PV, ET and PMF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PV</th>
<th>ET</th>
<th>PMF</th>
<th>Total MPNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>107 (57.8%)</td>
<td>49 (26.4%)</td>
<td>29 (15.6%)</td>
<td>185</td>
</tr>
<tr>
<td>Age (year; mean±SD)</td>
<td>49.7±2.3</td>
<td>51.2±2.8</td>
<td>54.3±4.3</td>
<td>50.8±3.2</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Male</td>
<td>75 (70%)</td>
<td>19 (38%)</td>
<td>17 (58%)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (29%)</td>
<td>30 (61%)</td>
<td>12 (41%)</td>
<td>74 (40%)</td>
</tr>
</tbody>
</table>

MPN: myeloproliferative neoplasm; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis

Demographic data, presenting symptoms, examination findings and routine laboratory results were retrieved from patient’s records. The blood samples were subjected to analysis for JAK2 V617F mutation[7]. All patients had complete blood count and some had bone marrow studies aspirate and biopsy studied. Detection of JAK2 was performed for all patients using amplification refractory mutation system polymerase chain reaction as described earlier. Since our laboratory does not perform exon 12, CALR and MPL mutations for diagnosis of PV, ET and PMF in JAK2 negative patients, the hematologists in our Centre mainly decided on the clinical basis to make final diagnoses.

Data were analyzed using the Statistical Package for the Social Sciences (version 19.0). The different variables were compared to each other and results were provided as mean ± standard deviation for

### Table 2: Frequencies of JAK2 V617F mutations among PV, ET and PMF patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PV</th>
<th>ET</th>
<th>PMF</th>
<th>Total MPNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of JAK2 V617F positive (%)</td>
<td>93/107 (86.9%)</td>
<td>35/49 (71.4%)</td>
<td>17/29 (58.6%)</td>
<td>145/185 (78.3%)</td>
</tr>
<tr>
<td>Number of Homozygous (%)</td>
<td>42 (39.3%)</td>
<td>16 (45.7%)</td>
<td>6 (33.3%)</td>
<td>64 (44.1%)</td>
</tr>
<tr>
<td>Number of Heterozygous (%)</td>
<td>51 (47.7%)</td>
<td>19 (54.3%)</td>
<td>11 (64.7%)</td>
<td>81 (55.9%)</td>
</tr>
<tr>
<td>Thrombosis Yes (%)</td>
<td>13 (12.1%)</td>
<td>4 (8.2%)</td>
<td>0 (0%)</td>
<td>17 (9.2%)</td>
</tr>
<tr>
<td>No (%)</td>
<td>94 (87.9%)</td>
<td>45 (91.8%)</td>
<td>29 (100%)</td>
<td>168 (90.8%)</td>
</tr>
</tbody>
</table>

JAK2: Janus kinase 2; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis
RESULTS

During the period between October 2010 and December 2017, 185 patients with MPNs were diagnosed, admitted and treated at Nanakali Hemato-Oncology Teaching Centre in Erbil. The mean age of the patients was 50.8±3.2 years (PV: 49.7 years; ET: 51.2 years; PMF: 54.3 years). Males constituted 60% of the entire cohort (111 patients), while 74 patients (40%) were females (Table 1).

The overall frequency of the JAK2 V617F mutation was 145 (78.3%) among patients diagnosed with MPNs. The prevalence of the mutation in the different subtypes were 93 (86.9%) in PV, 35 (71.4%) in ET and 17 (58.6%) in PMF. The mutated JAK2 V617F was found in homozygous state in 64 patients (44.1%) and in heterozygous state in 81 (55.9%) (Table 2).

One patient was transformed into acute myeloid leukemia and thrombosis was observed in 17 (9.2%) MPN patients. The mean duration of disease for PV patients was 11.1±1.8 and 5.9±1.5 (P=0.13), for ET patients was 3.2±1.3 and 6.1±1.7 (P=0.10), and for PMF patients was 6.3±1.6 and 3.8±1.3 (P=0.07) in JAK2 V617F negative and positive MPN patients.

Table 3: Demographic and hematological parameters in patients with PV, ET and PMF with JAK2 V617F mutation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PV</th>
<th>ET</th>
<th>PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JAK2 - ve</td>
<td>JAK2 + ve</td>
<td>P</td>
</tr>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>93</td>
<td>.008</td>
</tr>
<tr>
<td>Age (year, mean±SD)</td>
<td>45.7±1.2</td>
<td>50.0±1.3</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>48-59</td>
<td>40-63</td>
<td></td>
</tr>
<tr>
<td>Gender (n)</td>
<td>Male</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>WBC (X10³/L, mean±SD)</td>
<td>5.1±0.2</td>
<td>10.2±8.1</td>
<td>.60</td>
</tr>
<tr>
<td>RBC (X10¹²/L, mean±SD)</td>
<td>4.3±0.1</td>
<td>5.8±0.9</td>
<td>.05</td>
</tr>
<tr>
<td>Hb (g/dl, mean±SD)</td>
<td>15.2±1.6</td>
<td>16.3±0.8</td>
<td>.45</td>
</tr>
<tr>
<td>HCT (X10¹²/L, mean±SD)</td>
<td>44.0±0.1</td>
<td>48.1±0.1</td>
<td>.22</td>
</tr>
<tr>
<td>Plt (X10³/L, mean±SD)</td>
<td>481±62</td>
<td>506±269</td>
<td>.96</td>
</tr>
<tr>
<td>Duration of disease (month) (mean±SD)</td>
<td>11.1±1.8</td>
<td>5.9±1.5</td>
<td>.13</td>
</tr>
</tbody>
</table>

Table 4: Rate of JAK2 mutation detection in some regional and international studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Countries</th>
<th>Year</th>
<th>PV %</th>
<th>ET %</th>
<th>PMF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>Iraq</td>
<td>2018</td>
<td>86.9</td>
<td>71.4</td>
<td>58.6</td>
</tr>
<tr>
<td>Gari et al[27]</td>
<td>Saudi Arabia</td>
<td>2012</td>
<td>91</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Jaradat et al[28]</td>
<td>Jordan</td>
<td>2015</td>
<td>70</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Yidiz et al[29]</td>
<td>Turkey</td>
<td>2017</td>
<td>73</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>Abkar et al[31]</td>
<td>Sudan</td>
<td>2016</td>
<td>81.7</td>
<td>56.4</td>
<td>51.1</td>
</tr>
<tr>
<td>Zhang et al[32]</td>
<td>China</td>
<td>2015</td>
<td>82</td>
<td>53.1</td>
<td>40</td>
</tr>
<tr>
<td>Sazawal et al[33]</td>
<td>India</td>
<td>2010</td>
<td>82</td>
<td>70</td>
<td>52</td>
</tr>
<tr>
<td>Horn et al[34]</td>
<td>Germany</td>
<td>2006</td>
<td>96</td>
<td>74</td>
<td>62</td>
</tr>
<tr>
<td>Fantasia et al[35]</td>
<td>Italy</td>
<td>2013</td>
<td>100</td>
<td>76.3</td>
<td>55.5</td>
</tr>
<tr>
<td>Krawlives et al[36]</td>
<td>Switzerland</td>
<td>2005</td>
<td>65</td>
<td>57</td>
<td>23</td>
</tr>
</tbody>
</table>

JAK2: Janus kinase 2; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis

DISCUSSION

In the current retrospective study, we have described the demographic and laboratory findings as well as the JAK2 V617F mutation detection of patients with MPNs who have been treated at Nanakali Hemato-Oncology Teaching Centre in Iraqi Kurdistan. Male to female ratio was 1.5:1; however, we found male predominance in PV (M:F=2.3:1), this coincides with many reports which showed male predominance in PV, ET and PMF: 82, 53.1 and 40% respectively.

Detection of somatic single nucleotide polymorphism of JAK2 V617F mutation is the most commonly described mutation in BCR-ABL-negative MPNs; it is detected in approximately 70% of MPN patients and the prevalence of this mutation varied between the different subtypes of MPNs[9]. Several mutations of the JAK2 gene in exons 12-15 have been identified in MPN patients. However, the JAK2 V617F mutation is normally distributed variables and the paired t-test was used.
mutation in exon 14 is present in about 95% of PV cases, and 50-60% of ET or PMF cases[6]. In a review study on MPNs carried out in 2013, it was found that since 2005 when screening of JAK2 mutation was begun, the rate of diagnoses has changed. It was reported that the rates of correct diagnosis for PV and ET patients have changed; PV decreased by 21% and ET increased by 31%[10].

In our study, detection of JAK2 V617F mutations in exon 14 was found positive in 78.3% patients with MPNs (which included the homozygous mutant 51.6% and heterozygous mutant 65.2%). No local study was found to compare our results to apart from Al-Thwani et al[11], which reported a prevalence of the JAK2 V617F mutation in 90.6% among PV patients in Baghdad.

Table 4 shows the rate of JAK2 mutation among some regional and international studies. We found that our results are in agreement with that of Abkar et al[12], Zhang et al[13] and Sazawal et al[14]. However, other studies reported lower prevalence mutation rates[15-17] or higher as reported by Horn et al[18], who found JAK2 V617F mutation in 96% cases with PV, 74% cases with ET and 62% cases with PMF, while some other studies reported results slightly different from the present study[19-21].

The difference in the results could be due to ethnic variation, causing differences in the sensitivity of detecting JAK2 V617F mutation[22].

Our study reported one patient transformed into acute myeloid leukemia, most appropriately referred to as MPN-blast phase, although this transformation is very rare. On the other hand, thrombosis was observed in 17 MPN patients from this study results. Similar results were found by Sazawal et al[14]. Thrombosis probably results from metabolic imbalance accompanying hyperproliferation of hematopoietic cells.

In the present study, the mean age of the patients with MPNs was 50.8 years, and this result coincides with that of Al-Thwani et al[11], who reported approximate mean ages. We observed a significant association between age of the patients and JAK2 V617F mutation positivity in PV and ET, but not in PMF patients (P=.008, P=.02, P=.57 respectively).

There was a significant difference in the red blood cell count in PV and ET groups, but not in PMF, in relation to JAK2 V617F positivity; on the other hand, we did not find any significant differences in the white blood cell (WBC), hemoglobin (Hb), hematocrit and platelet counts between V617F positive and V617F negative patients for PV, ET and PMF. Several studies reported no significant association between mutated JAK2 V617F and WBC, Hb, hematocrit and platelet counts in MPN patients[23,24]. However, other studies reported significant association between JAK2 V617F mutation and high WBC, Hb and hematocrit, with normal or decreased platelet counts[25,26]. Batebi et al in 2012 reported a significant association between mutated JAK2 V617F and WBC count, though the Hb and platelet counts did not show any differences between[27].

In our study, we noted that the mutation of the JAK2 V617F gene is more common among older age and in the male gender. The overall prevalence of JAK2 V617F mutation among MPN patients in Northern Iraq was 78.3% and their subtypes were consistent with the other previously published studies of MPN patients in Asia, Africa, Europe and USA. Our study suggested that screening for JAK2 V617F mutation is useful for incorporation into the initial evaluation for the diagnosis and therapeutic approach of MPNs.

CONCLUSION

The Janus Kinase 2 V617F mutation rates in the current cohorts were not much different from what have been previously reported. It is essential to perform JAK2 mutation testing in all suspected cases of myeloproliferative neoplasms.

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Conflict of Interest: Authors declare that they have no conflicts of interest.

Authorship Contributions: These authors contributed equally to this work.

REFERENCES


5. Michiels JJ; Goodheart Institute and Foundation; Freedom of Science and Education Thrombocythemia Vera Study Group; TVSG and European Working Groups on Myeloproliferative Neoplasms (EWG.


Original Article

Assessment of vitamin-D levels in premenstrual syndrome and premenstrual dysphoric disorder

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ABSTRACT

Objective: To evaluate the vitamin D levels in patients with premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)
Design: Cross-sectional study
Setting: Obstetrics and Gynecology outpatient clinics, Acibadem Hospital, Istanbul, Turkey
Subjects: The study population included 125 women aged 18-47 years who presented with various complaints and regular menstrual cycle. A control group was formed of 159 premenopausal women without premenstrual symptoms.
Intervention: Serum samples were tested during the luteal phase of menstrual cycle
Main Outcome Measure: Study groups were formed as none/mild PMS; moderate to severe PMS; PMDD group by using the premenstrual symptoms screening tool, and a control group; biochemical analyses of serum 25(OH)D₃ (vitamin D) were performed using the electrochemiluminescence immunoassay method.

Results: The mean age of the participants was 30.52±6.44 years. The distributions of diagnoses were 51.2%, 33.6% and 15.2% in the PMS none/mild, the PMS moderate/severe, and the PMDD group, respectively. Vitamin D levels were found as sufficient (≥20 ng/dL) in 46.2%, deficient (10-20 ng/dL) in 43%, and severely deficient (<10 ng/dL) in 10.7% of the control group, and in the patient group these rates were non-deficient in 13.4%, deficient in 27.7%, and severely deficient in 58.7%.

Conclusions: The study showed that vitamin D levels were significantly lower in the study patients compared with the control group. Although the vitamin D level was lower in the PMS groups than in the PMDD group, the difference did not reach statistical significance. Further studies are needed to elucidate the exact role of vitamin D in PMS/PMDD.

INTRODUCTION

Premenstrual syndrome (PMS) is described as a broad range of symptoms, including emotional, behavioral and physical changes, which occur several days to two weeks before menstruation and decrease after menses[1]. These symptoms are mostly irritability, anxiety, depression, headache, fatigue, increased appetite, weight gain, bloating and acne[2]. The occurrence of these symptoms, which disappear by the follicular phase, corresponds to the luteal phase of the menstrual cycle[3]. The prevalence of the disease is estimated to be approximately 70-90% in women of reproductive age[4]. Premenstrual dysphoric disorder (PMDD) is another clinical entity, which is a combination of anxiety and depressed mood that begins during the luteal phase and improves after the onset of menses, and approximately 3-8% of women suffer from PMDD[5]. Current scientific evidence suggests that PMDD is a clinical entity distinct from PMS, and it was included in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) as a treatment-responsive depressive disorder[6].

PMS and PMDD are significant problems that impair the quality of life of women and cause significant work problems and withdrawal from social life[7,8].

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The mechanisms underlying these clinical conditions have not yet been completely understood, but they are thought to be psycho-endocrine disorders. The cyclic ovarian activity and the effects of estradiol and progesterone on serotonin and gamma-aminobutyric acid are the suspected culprits in the etiology of PMS. Nevertheless, there is no strong evidence that reproductive hormones are the only factors responsible for this clinical condition[9].

New roles of vitamin D in physiological events are currently still being revealed. Vitamin D is known to be involved in the hypothalamic-pituitary-adrenal axis as a neurosteroid[10,11], to play a modulating role in the immune system by inhibiting aromatase and pro-inflammatory cytokines[12], and to stimulate ovarian steroidogenesis[13].

The accumulating evidence about the roles of vitamin D on the female reproductive system has drawn increasing attention to its role in the etiology of PMS and PMDD. Thus, we aimed to evaluate the levels of serum vitamin D in patients with PMS and PMDD.

SUBJECTS AND METHODS
Consecutive patients who attended the outpatient clinics of the Obstetrics and Gynecology Department of Acibadem Kozyatagi Hospital, Istanbul, between January 2017 and January 2018 with various complaints were assessed in terms of eligibility for inclusion in the study. This cross-sectional study was conducted in accordance with the Declaration of Helsinki and approved by the Research and Ethics Committee of Acibadem Hospital, Istanbul, Turkey (reference number 2017-11/7). All the study participants were informed about the study protocol and provided with written informed consent for participation.

The inclusion criteria were age 18-47 years, not taking any drugs including hormonal contraceptives, anti-depressants, or vitamins of herbal compounds, having normal serum levels of vitamin D-related biomarkers including serum calcium and parathormone, and having normal serum levels of thyroid-stimulating hormone and other biochemical markers. Exclusion criteria comprised irregular menstrual cycles, pregnancy in the last two years, breastfeeding, connective tissue disorders, and systemic diseases including cardiovascular, renal or gastrointestinal diseases, epilepsy, diabetes mellitus, thyroid and/or parathyroid dysfunction, or psychiatric diseases.

The study population included 299 women aged 18-47 years who presented with various complaints and had a regular menstrual cycle. Three patients who did not meet inclusion criteria and 12 patients who refused to participate in the study were excluded. The remaining 284 patients were enrolled in the study. The patient group consisted of 125 subjects with PMS/PMDD, the diagnosis of which was based on the DSM-IV. The rest of the enrolled patients (n=159) served as the control group. These control subjects lacked any PMS and/or PMDD symptoms. The study flow-chart depicting patient selection process is shown in Figure 1.

All study participants were evaluated using the DSM-IV diagnostic criteria of PMS/PMDD. The DSM-IV diagnostic criteria of PMS/PMDD are as follows[14]:
- Symptoms must be present during most of the
week prior to menstruation, diminish a few days after the onset of menstruation, and are completely absent the week following menstruation

- At least five or more symptoms must occur in most menstrual cycles (i.e., depressed mood, anxiety, marked affective lability, anger, fatigue, appetite changes, insomnia/hypersomnia, any physical symptom (e.g., headache, bloating), and feeling out of control), and one of these symptoms must be either depressed mood, anxiety/tension, marked affective lability, or anger/irritability

- Symptoms significantly interfere with relationships, school/work, or usual activities

- Symptoms are not an exacerbation of another mental or physical disorder

- This pattern of symptoms and behavior must be confirmed by prospective daily ratings for at least two consecutive menstrual cycles.

The patients were subcategorized by means of the Premenstrual Symptoms Screening Tool that was developed by Steiner et al.[15]. This scale includes two domains, the first of which includes 14 items related to psychological, physical, and behavioral symptoms, and the second domain (5 items) evaluates the impact of symptoms on women’s functioning, in line with DSM-IV criteria. The detailed scoring and interpretation of the results of this scale were described elsewhere[15]. We subcategorized study patients into three subgroups as none/mild PMS, moderate to severe PMS and PMDD.

The demographic characteristics of the entire study population were recorded. All biochemical measurements were performed during the late luteal phase of each patient’s menstrual cycle. Serum 25(OH)D3 (vitamin D) measurements were performed by the electrochemiluminescence immunoassay method (Roche Cobas C601; ECLI A). The participants were classified according to serum vitamin D level as non-deficient (≥20 ng/dL), deficient (10-20 ng/dL) and severely deficient (<10 ng/dL).

The Benefit from Ultraviolet Light Index (BFUI) reflects the degree of an individual’s exposure to sunlight[16]. This index was calculated as a ratio after completion of a questionnaire (appendix 1). The participants were asked about physical activity and were scored using the Metabolic Equivalent Task (MET) hours of activity, as described elsewhere[17]. BFUI and MET were used to control the likely changes in serum Vitamin D levels for sunlight exposure and activity level. This way we could attribute the observed changes in vitamin D levels to the presence or absence of PMS and PMDD more accurately.

### Statistical analyses

The conformity of the data to normal distribution was evaluated by the Shapiro-Wilk test. The Kruskal-Wallis H test was used with the Monte Carlo simulation results when more than two groups were compared with each other quantitatively. Dunn’s test was used for the binary comparison of the groups for the significant results. In the comparison of categorical variables, the Fisher-Freeman Halton test was used with the Monte Carlo Simulation technique, and the column ratios were compared with each other and expressed according to the Benjamin-Hochberg corrected P-value results. The quantitative variables were expressed as mean ± standard deviation and median range (maximum-minimum), and the categorical variables as n(%). The variables were analyzed at a 95% confidence level, and P<.05 was accepted as significant. The Statistical Package for Social Sciences (SPSS) 24.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the study data.

### RESULTS

The mean age of the participants was 30.52±6.44 years (range: 18-47 years). The gravidity of the participants ranged from 0 to 4. The mean level of serum vitamin D was 16.01±11.37 ng/dL. A considerable portion of the patients was nulliparous (n=131, 46.13%), and the rate of cesarean delivery was 53.29% among the whole group. The general characteristics of the participants are summarized in Table 1.

According to the Premenstrual Symptoms Screening Tool assessments, 84.8% of the women were diagnosed with PMS (51.2% with none/mild PMS, and 33.6% with moderate to severe PMS), and

<table>
<thead>
<tr>
<th>Table 1: Demographic characteristics of the participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>25(OH)D3 (ng/dL)</td>
</tr>
<tr>
<td>MET / wk</td>
</tr>
<tr>
<td>BFUI</td>
</tr>
<tr>
<td>Menarche age</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Gravidity</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>≥3</td>
</tr>
<tr>
<td>Delivery type</td>
</tr>
<tr>
<td>Caesarean section</td>
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<tr>
<td>NSV</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

SD: standard deviation; Min: minimum; Max: maximum; MET: metabolic equivalent task; wk: week; BFUI: benefit from ultraviolet light index; BMI: body mass index; NSV: normal spontaneous vaginal.
15.2% diagnosed with PMDD. The mean age (P=.827) and body mass index (BMI, P=.163) were comparable between the patient subgroups. Vitamin D levels were similar in the patient subgroups and were significantly lower in each patient group than in the control group (Figures 2 and 3). No differences were found between

Fisher Freeman Halton (Monte Carlo) / *: significant compared to the None/Mild group - ¶: significant compared to the Moderate-Severe group - §: significant compared to the premenstrual dysphoric disorder (PMDD) group; PMS: Premenstrual syndrome; PMDD: Premenstrual dysphoric disorder; na: not applicable

Table 2: Comparison of the clinical characteristics of the groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>None/Mild PMS</th>
<th>Moderate to Severe PMS</th>
<th>PMDD</th>
<th>Control</th>
<th>P-value</th>
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<tbody>
<tr>
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<td>30 (20/46)</td>
<td>31 (20/40)</td>
<td>30 (18/45)</td>
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</tr>
<tr>
<td>(Median (Min/Max))</td>
<td>7.23 (2.9/28.82)</td>
<td>10 (2.9/70.1)</td>
<td>7.87 (2.9/25.2)</td>
<td>19 (5/90)</td>
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<tr>
<td>25(OH)D Median (Min/Max)</td>
<td>19.7 (17.2/25.1)</td>
<td>19.35 (17.5/22.1)</td>
<td>19.8 (18.9/23.2)</td>
<td>20.8 (18.9/22.8)</td>
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<tr>
<td>MET/week Median (Min/Max)</td>
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<td>BMI Median (Min/Max)</td>
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<td>12 (10/14)</td>
<td>12 (9/14)</td>
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<tr>
<td>Menarche age Median (Min/Max)</td>
<td>23.1 (18.9/27.3)</td>
<td>23 (19.8/26.2)</td>
<td>22.6 (19.2/28.9)</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>0</td>
<td>29 (45.31)</td>
<td>22 (52.38)</td>
<td>8 (42.11)</td>
<td>7 (42.8)</td>
<td>0.079</td>
</tr>
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<td>8 (19.05)</td>
<td>4 (21.05)</td>
<td>5 (35.8)</td>
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</tr>
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<td>8 (19.05)</td>
<td>6 (31.58)</td>
<td>26 (16.35)</td>
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</tr>
<tr>
<td>≥3</td>
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<td>4 (2.52)</td>
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<td></td>
<td></td>
<td>0.972</td>
</tr>
<tr>
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<td>11 (55)</td>
<td>5 (45.45)</td>
<td>46 (53.49)</td>
<td>na</td>
</tr>
<tr>
<td>NSV</td>
<td>16 (45.71)</td>
<td>9 (45)</td>
<td>6 (54.55)</td>
<td>40 (46.51)</td>
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</tr>
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<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.773</td>
</tr>
<tr>
<td>No</td>
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<td>17 (89.47)</td>
<td>131 (82.39)</td>
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</tr>
<tr>
<td>Yes</td>
<td>13 (20.31)</td>
<td>9 (21.43)</td>
<td>2 (10.53)</td>
<td>28 (17.61)</td>
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</tr>
<tr>
<td>25(OH)D (ng/dL)</td>
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</tr>
<tr>
<td>&lt;10</td>
<td>41 (64.1)</td>
<td>20 (47.6)</td>
<td>11 (57.9)</td>
<td>18 (11.3)</td>
<td>¶ §</td>
</tr>
<tr>
<td>(10-20)</td>
<td>14 (21.9)</td>
<td>17 (40.5)</td>
<td>5 (26.3)</td>
<td>68 (42.8)</td>
<td>* ¶ §</td>
</tr>
<tr>
<td>≥20</td>
<td>9 (14.1)</td>
<td>5 (11.9)</td>
<td>3 (15.8)</td>
<td>73 (45.9)</td>
<td>* ¶ §</td>
</tr>
</tbody>
</table>

Kruskal Wallis Test (Monte Carlo) - Post Hoc Test: Dunn’s Test; Min: minimum; Max: maximum; MET: metabolic equivalent task; BFUI: benefit from ultraviolet light index; BMI: body mass index; PMS: Premenstrual syndrome; PMDD: Premenstrual dysphoric disorder; na: not applicable

Table 3: Distribution of gravidity, delivery type and smoking frequency between the groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>None/Mild PMS</th>
<th>Moderate to Severe PMS</th>
<th>PMDD</th>
<th>Control</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Gravidity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>29 (45.31)</td>
<td>22 (52.38)</td>
<td>8 (42.11)</td>
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<td>na</td>
</tr>
<tr>
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<td>6 (31.58)</td>
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<td>C/S</td>
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<td>5 (45.45)</td>
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<tr>
<td>NSV</td>
<td>16 (45.71)</td>
<td>9 (45)</td>
<td>6 (54.55)</td>
<td>40 (46.51)</td>
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<tr>
<td>Smoking</td>
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<td>0.773</td>
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<tr>
<td>No</td>
<td>51 (79.69)</td>
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<td>17 (89.47)</td>
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<td>9 (21.43)</td>
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<td>(10-20)</td>
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<td>5 (11.9)</td>
<td>3 (15.8)</td>
<td>73 (45.9)</td>
<td>* ¶ §</td>
</tr>
</tbody>
</table>

Appendix 1:
Benefiting from Ultraviolet Index (BFUI), which evaluates the degree of sunlight exposure, was calculated as the ratio of first two points.

2.1. Questionnaire

1. Point of exposure to sun:
   • People who are not directly exposed to sun. 1 point
   • People who are exposed to sun except 11–15 o’clock. 2 points
   • People who are permanently exposed to sun between 11 and 15 o’clock. 3 points
   • People who are exposed to sun all day long. 4 points 2. The level of sunshine prevention capacity of the outfit:
   • People whose daily clothes uncover his/her head, face, neck, arms, hands, legs and who bathes in the sun for at least a week in the summer, by wearing a bathing suit. 1 point
   • People whose daily clothes uncover his/her head, face, neck, arms and legs. 2 points
   • People whose daily clothes uncover his/her face, neck, hands and sometimes arms. 3 points
   • People who are covered up with daily clothes. 4 points

3. Benefiting from ultraviolet index (BFUI): Point of exposure to sun/point of the level of sunshine prevention capacity of the outfit.
Fig 2: Comparison of vitamin D levels between the groups

Fig 3: Comparison of physical activity between the groups
the groups with respect to BFUI and physical activity degree evaluated by the MET. However, the latter two scores were lower in the patient group compared with the controls. The comparisons of the clinical characteristics of the groups are shown in Table 2. Rates of cigarette smoking and obstetrics characteristics were no different between the patient subgroups and the controls (Table 3). Vitamin D levels were found as non-deficient (≥20 ng/dL) in 13.4%, deficient (10-20 ng/dL) in 27.7%, and severely deficient (<10 ng/dL) in 58.7% of the patient group, and in the control group, these rates were 46.2%, 43%, and 10.7%, respectively (Table 3, Figure 4). The prevalence of severe vitamin D deficiency was found to be significantly lower in all the patient subgroups than in the control group.

**DISCUSSION**

The results of the present study showed that the mean serum vitamin D levels were lower in patients with PMS/PMDD compared with the controls; however, the levels were similar in two subgroups of PMS and PMDD. Severe deficiency of vitamin D was significantly more common in the patient group than in the control group. Furthermore, these differences did not seem to originate from the previously established modifiers of serum vitamin D levels. Among these, only activity level was found to be significantly different between the patient and control groups.

It is well established that estradiol can augment the catalytic activity of vitamin D metabolizing enzymes including 1-α-hydroxylase and 24-hydroxylase and thereby decrease the serum level of 25(OH)D. Since ovarian hormones spike during the luteal phase of menstruation, consequent decreases occur in the vitamin D level. Thus, it has been hypothesized that this cyclic fluctuation of ovarian hormones with the corresponding fluctuation in serum vitamin D levels may exacerbate the symptoms of PMS. Vitamin D deficiency might also lead to several changes in inflammatory mediators and renin-angiotensin-aldosteron system, which can lead to alterations in fluid balance and blood pressure among many other changes.

Vitamin D has been extensively studied in the etiopathogenesis of several physiological processes and disorders. To date, numerous studies have been conducted to unravel the relationship between vitamin D and PMS symptoms. On the other hand, these studies have produced contradictory results. A very recent systematic review reported that low levels of serum vitamin D and calcium levels in the luteal phase of the menstrual cycle might be associated...
with the development and exacerbation of PMS symptoms. Besides, the administration of calcium and vitamin D supplements or the use of a diet rich in these substances eliminate or reduce the symptoms of PMS\(^\text{[29]}\). However, not all studies reported such a positive correlation between serum vitamin D levels and PMS symptoms. In one study including 117 premenopausal women, vitamin D levels were similar in symptomatic and non-symptomatic women with PMS\(^\text{[20]}\). In addition, no difference was found between vitamin D deficient and sufficient women according to the PMS symptom score.

In contrast to PMS, there is a scarcity of studies on the relationship between vitamin D and PMDD. Thys-Jacobs et al. found higher calcitriol levels in PMDD patients compared with the control subjects\(^\text{[26]}\). In this current study, different from previous studies in the literature, we included patients with PMDD in addition to PMS subgroups. Our findings showed that in patients with PMDD, serum 25(OH)D\(_3\) level was comparable with the PMS subgroups; however, the mean value was significantly lower compared with the control group.

Several factors have been shown to affect the serum vitamin D levels, including cigarette smoking, BMI, physical activity, sun exposure, menarche age, and number of pregnancies, among others. We also tried to control the potential effects of these factors on the relationship between PMS/PMDD and vitamin D levels.

Physical activity is known to affect vitamin D status\(^\text{[27]}\). Increased exposure to sunlight would increase the synthesis of vitamin D and thereby, the interactions between vitamin D levels and the symptoms. BFUI was found to be positively correlated with vitamin D levels\(^\text{[16]}\). In the current study, no significant differences were determined between the groups for BFUI. Thus, in our study, similar BFUI levels in patients and the controls provided that sun exposure was not a confounding factor in the evaluation of vitamin D levels. On the other hand, activity levels in all three patient subgroups were lower compared with the controls. Thus, this may have affected vitamin D results to some extent. In some studies, the menarche age of PMS patients has been found to be lower than that of controls\(^\text{[24]}\). Earlier menarche has been observed to be associated with several endpoints, such as PMS\(^\text{[29]}\). Moreover, a previous study reported that early menarche age might be related to vitamin D deficiency\(^\text{[29]}\). However, in the current study, menarche age was comparable in all the groups. As expected, menarche age could not be the only determinant in the occurrence of PMS. Other studies have also shown no differences in menarche age between PMS or PMDD and healthy women\(^\text{[28,30,31]}\).

Several studies have suggested that the serum vitamin D level is decreased as BMI and the degree of obesity increase\(^\text{[32-34]}\). In studies evaluating vitamin D levels in certain patient groups, BMI should also be considered as a confounding factor. In the current study, BMI values were found to be similar in the control and patient groups.

Apart from physical activity, which was higher in the patient group, other potential confounders were comparable between the patient and the control groups. Thus, to some extent, we can attribute the differences observed in our study to the presence of PMS/PMDD.

Several limitations of this present study deserve mention. First, we did not include patients with abnormal levels of serum calcium and/or serum parathyroid hormone. Thus, we might have missed many patients with severe vitamin D deficiency and subsequent secondary hyperparathyroidism, hence affecting the results. Second, vitamin D levels are also dependent on the amount of vitamin D in one’s diet. However, we could not control for this potential confounder in this present study. Lastly, there were relatively fewer patients in the PMS subgroups and PMDD group. The strength of this present study was that a validated scale, the Premenstrual Symptoms Screening Tool, was used in the assessment of premenstrual symptoms. Furthermore, ours is one among the few studies to investigate the level of serum vitamin D in patients with PMDD and make comparisons with PMS and control subjects. Moreover, we took into account the potential confounding factors that might affect serum vitamin D levels. Thus, the low levels of vitamin D are more likely to reflect the real differences between the PMS/PMDD patients and control subjects.

CONCLUSION

In conclusion, our results demonstrated a lower mean level of vitamin D in PMS and PMDD patients than controls. There were no differences between PMS subgroups and PMDD in this regard. Our findings support the previous reports that vitamin D deficiency might be associated with the development and exacerbation of symptoms of PMS/PMDD. Studies with larger sample sizes should be conducted, particularly to elucidate the relationship between vitamin D levels and PMDD.

ACKNOWLEDGMENT

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Contribution to the manuscript: Elif Meseci: Concept, design, data collection, data analysis, manuscript writing, editing.
References

Sources of funding: None

Conflict of interest: None

REFERENCES


Original Article

Type 2 diabetes mellitus and diabetic nephropathy with Angiotensin II type 1 receptor gene variants:
A case control study in a Turkish population

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ABSTRACT

Objective: This study was performed to determine the polymorphism frequencies of the Angiotensin II type 1 receptor (AT1) A1166C, and to examine the role of this polymorphism in type-2 diabetes (T2DM) and diabetic nephropathy (DN) development.

Design: This is a research study.

Setting: Clinic for Internal Medicine, Artvin State Hospital, Turkey

Subjects: The study consisted of 259 (135 T2DM and DN + 124 controls) persons referred to the Clinic for Internal Medicine, Artvin State Hospital.

Intervention: This study used peripheral blood samples.

Main outcome measures: Two hundred and fifty-nine genomic DNAs were analyzed. AT1 gene A1166C polymorphisms were determined using polymerase chain reaction (PCR), restriction fragment length polymorphism and electrophoresis. PCR products were digested with restriction enzyme HindIII and were analyzed in 2% agarose gel electrophoresis.

Results: The frequencies of A1166C genotypes were found to be 32.3% AC and 67.7% CC in controls and 73% AC and 27% CC in total patient group. Statistically, it was found that the AT1 gene A1166C polymorphism genotype was significantly different between the control group and the total patient’s group.

Conclusions: As a result, we can say that there is an interaction between the AT1 gene A1166C polymorphism with T2DM and DN.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health concern and is characterized by defects in both insulin secretion from pancreatic β-cells and insulin action in target tissues such as liver, fat and muscle[1-4]. In the development of microvascular complications such as diabetic nephropathy (DN), neuropathy and retinopathy, prolonged hyperglycemia could play a role[2,5]. In addition, high glucose concentration does increase angiotensin gene expression in proximal tubule cells and increase angiotensin II production in primary mesenchymal cells[6].

Angiotensin II shows impact by binding to angiotensin receptor (AT1 receptor) in tissues. While angiotensis-converting enzyme regulates systemic and renal blood flow via angiotensin II, it also inactivates bradykinin. As a result, intraglomerular hypertension occurs, and in the future, it forms the potential for development of glomerular sclerosis[6].

Glucose and its metabolites activate the renin
angiotensin system (RAS). Angiotensin type 1 (AT1) receptors of angiotensin II, which is increased by RAS activation, plays an important role in the development of DN[7].

The roles of RAS in insulin signaling pathway and insulin resistance have been well documented. The blockade of the system has been shown to have beneficial effects in the prevention of T2DM. These findings strongly imply that the variations in RAS might be associated with the onset of T2DM[2,8,9]. The human AT1 (accession number: P30556) gene is composed of five exons and four introns. A polymorphism in the AT1 gene causes an A-to-C substitution at position 1166, located at the 5' end of the 3' untranslated region of the AT1 gene[10-14].

In this study, we propose to examine the association of genetic variations of the Angiotensin II type 1 receptor gene with susceptibility to T2DM.

SUBJECTS AND METHODS

Peripheral blood samples were obtained from T2DM and DN patients and controls that were enrolled at the Department of Internal Medicine, Artvin State Hospital. Controls were those coming for routine health screening at clinics, with no evidence or family history of T2DM. T2DM was diagnosed by qualified clinicians based on fasting blood glucose levels ≥7.0 mmol/L for two consecutive routine screen readings and HbA1c ≥6.5% with normoalbuminuria.

This study included 135 T2DM and DN patients and 124 controls recruited from the Artvin State Hospital’s Department of Internal Medicine.

Ethical statement

This study was approved by the local ethics committee of the Karadeniz Technical University, Turkey. According to the Helsinki Declaration, informed consent was obtained from all patients prior to inclusion in this study.

Genetic analysis

Genomic DNA was extracted using an EZ-10 Spin Colon Blood Genomic DNA Minipreps Kit (Biotechnology Department Bio Basic Inc., Markham, Ontario, Canada). Genotypes for the A1166C polymorphism of AT1 were determined by polymerase chain reaction (PCR) as described previously[10,15], and PCR amplification was performed in a Bio-Rad Thermal Cycler (T100TM, Foster City, CA, USA). The DNA samples were amplified using the primers, PCR mixture (one sample) and PCR conditions described in Table 1.

<table>
<thead>
<tr>
<th>PCR mixture</th>
<th>PCR condition</th>
<th>Step</th>
<th>Time</th>
<th>Temperature (°C)</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primer 1</td>
<td>Sense: 5'-AGAAGCCCTGCACCATGTITTGGAG-3'</td>
<td>Amplification</td>
<td>Denaturation</td>
<td>4 min.</td>
<td>94 °C</td>
</tr>
<tr>
<td>Primer 2</td>
<td>Antisense: 5'-CCTGTTGCTCCTCTAACGATTTA-3'</td>
<td></td>
<td>Annealing</td>
<td>20s</td>
<td>94 °C</td>
</tr>
<tr>
<td>dNTP mix</td>
<td></td>
<td></td>
<td>Extension</td>
<td>30s</td>
<td>62 °C</td>
</tr>
<tr>
<td>PCR buffer</td>
<td></td>
<td></td>
<td>Final extension</td>
<td>30s</td>
<td>72 °C</td>
</tr>
<tr>
<td>Tris-HCl</td>
<td>10 mM</td>
<td>Hold</td>
<td></td>
<td>5 min.</td>
<td>72 °C</td>
</tr>
<tr>
<td>KCI</td>
<td>50 mM</td>
<td></td>
<td></td>
<td>4 °C</td>
<td>-</td>
</tr>
<tr>
<td>Taq pol</td>
<td>2 U</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>H2O (distile)</td>
<td>9 µl</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DNA</td>
<td>0.5-1 µg</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction

Table 2: Distribution of AT1 A1166C genotype and alleles according to control, diabetes and diabetic nephropathy group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Genotypes (n, %)</th>
<th>Alleles (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AA</td>
<td>AC</td>
</tr>
<tr>
<td>Control</td>
<td>124</td>
<td>0 (0)</td>
<td>40 (32.3)</td>
</tr>
<tr>
<td>Diabetes and diabetic nephropathy</td>
<td>135</td>
<td>0 (0)</td>
<td>99 (73)</td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td><em>P</em>=.000</td>
<td></td>
</tr>
</tbody>
</table>

*P* = Independent Two-Sample t Test
(410 bp), AC (410, 219 and 191 bp), and CC (219 and 191 bp).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS v.21) software package. Distribution of genotypes according to controls and total patients were compared using independent two-sample t-test. According to AT1 gene A1166C polymorphism genotypes, clinical parameters of total patient and controls were compared using independent two-sample t-test. Values were given as ±SE and P < 0.05.

RESULTS

AT1 gene A1166C genotype frequencies and allele rates of the control group and all patients group are given in Table 2. AT1 gene A1166C genotype frequencies were 73% AC, 27% CC in the patient group and 32.3% AC, 67.7% CC in the control group (Table 2).

There was no statistically significant difference between the control group and the patient groups in genotype frequencies. Allele frequencies were found to have statistically significant difference between the control group and the patient groups.

Statistically, AT1 A1166C between the control group and the patient group was found to be significantly different in terms of genotype number and percentage (Table 3). On the other hand, AC genotype was significantly higher in the patient group.

DISCUSSION

When we examined every patient and control in our study in terms of AT1 A1166C genotype distribution and allele frequency, A1166C genotype frequency was determined as 32.3% AC and 67.7% CC for controls and as 73% AC and 27% CC for patients. The frequency of occurrence of the 1166A allele was higher among total patients than among the control group. In our study, AT1 A1166C polymorphism genotype number and percentage values was found to be significantly different between the control group and the patient group.

In accordance with our results, Buraczyniska and colleagues examined the AT1 C1166T polymorphism in patients with T2DM and DN and found that this polymorphism could be a useful marker for DN[16].

Lin et al have examined the AT1 gene C1166T polymorphism in patients with T2DM and DN and have reported that this polymorphism is associated with DN[17]. They also reported that among type 2 diabetics, the AT1 1166 C allele is directly associated with kidney dysfunction[17].

Xue et al have also determined that the AT1 gene C1166T polymorphism may be helpful for the prevention of DN[18].

Fradin et al reported that they have observed an interaction of A1166C AT1 polymorphism with diabetes in men. At the same time, they have also said that AT1 polymorphism interacts with diabetes duration for deterioration of nephropathy in type 2 diabetic patients[19].

In the studies of the relationship between the genetic variants of RAS and the prevalence of T2DM, researchers reported that there was no significant association between T2DM and angiotensin-converting enzyme, AGT and AT1 variants[20].

In contrast to our results, in a study conducted in Malaysia, they reported that there were no significant differences in allele frequencies between cases and controls for AT1[2]. In a meta-analysis study, the authors have reported that role of genetic polymorphisms of

Table 3: Clinical variables of patient and control group according to genotypes

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Genotypes</th>
<th>AC</th>
<th>CC</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>6.95±0.12</td>
<td>6.78±0.25</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>8.64±2.59</td>
<td>6.12±0.08</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td>P*=.155</td>
<td>P*=.012</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td>203.33±6.26</td>
<td>195.16±7.62</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>166.00±10.38</td>
<td>186.42±5.67</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>P*=.013</td>
<td>P*=.353</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td></td>
<td>192.90±14.74</td>
<td>165.53±16.75</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>116.00±16.58</td>
<td>143.04±11.20</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>P*=.024</td>
<td>P*=.257</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td></td>
<td>136.46±2.24</td>
<td>135.55±3.59</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>119.00±3.62</td>
<td>121.66±1.07</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>P*=.001</td>
<td>P*=.000</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td></td>
<td>80.00±1.09</td>
<td>82.25±3.12</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>73.00±2.30</td>
<td>69.52±1.12</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>P*=.009</td>
<td>P*=.000</td>
<td></td>
</tr>
</tbody>
</table>

P* = Independent Two-Sample t Test
the RAS were not significantly associated with renal diseases[21]. However, Prasad et al have suggested that there is no association between type 2 diabetic chronic renal failure and AT1 C1166T polymorphism in Asian Indians[22].

CONCLUSION
So far, the association between the AT1 gene A1166C genetic variants and the prevalence of T2DM and DN has been examined in a small number of studies. The obtained results revealed that T2DM and DN associate with the AT1 gene A1166C polymorphism. AC genotype may be considered as a prognostic marker for patients with T2DM and DN.

DN is the most important microvascular complication of T2DM. The gene region we have examined in the diagnosis and treatment of the disease may be an auxiliary parameter to physicians.

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Conflict of interest: No potential conflict of interest was reported by the authors.

Aysegul Bayramoglu, Gokhan Bayramoglu and Halil İ. Guler participated in the study design, statistics, laboratory work method implementation, oriented the data collection and revised the manuscript critically. Güleser Hazar participated in monitoring the patients and collected blood samples. All authors read and approved the final manuscript.

REFERENCES


Original Article

The role of optic nerve sheath diameter and Rotterdam Computerized Tomography scoring in predicting the severity of traumatic brain injury

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ABSTRACT

Objective: To determine the predictive value of the optic nerve sheath diameter (ONSD) at distances 3 mm and 10 mm behind the posterior limit of the eyeball and of the initial Rotterdam CT Scoring (RCTS) scores in determining the severity and mortality in traumatic brain injury (TBI).

Design: Retrospective study

Setting: Department of Emergency Medicine, Health Science University Antalya Training and Research Hospital, Antalya, Turkey

Subjects: One hundred and eighty-two patients were included from January to December, 2017

Intervention: None

Main outcome measure: Demographic and clinical data and computed tomography (CT) scans of the brain were recorded. ONSD for each eye was measured on the initial CT scans. Bilateral ONSD was measured at distances 3 and 10 mm behind the posterior limit of the eyeball and RCTS scores were assessed on the same CT images.

Results: The study included 182 patients [age: 43.68±19.65 years; 79.1% males; mean RCTS: 2.53±1.35; mortality: 14.3% (n=27)]. The median RCTS score was 4(1-6) mm in non-survivors vs. 2(1-6) mm in surviving patients (P<.001). The mortality rate for RCTS score of ≥4 was 40% (18/45). The mean ONSD values measured both at 3 mm and 10 mm distances were higher for lower Glasgow Coma Scale (GCS) scores (P=.001, P=.003, respectively). The mean ONSD values were higher for higher RCTS scores (P<.001). The receiver operating curve analysis calculated the best ONSD cut off value to predict mortality as 5.0 mm (sensitivity: 80%; specificity: 78.46%) with an area under curve of 0.856 (95% CI: 79-92.1%).

Conclusion: ONSD values along with RCTS and GCS scores enhance the prognostic performance and improve sensitivity while maintaining high specificity in predicting severe TBI and mortality.

KEY WORDS: computed tomography, optic nerve sheath, Rotterdam CT Score, traumatic brain injury

INTRODUCTION

Severe traumatic brain injury (TBI) is one of the most important reasons for mortality and disability[1]. In Europe, the incidence of TBI was estimated to be 235 per 100,000, with a mortality rate of about 15.4 per 100,000, mainly due to road traffic injuries[2].

In recent years, neuroimaging techniques have explored radiological markers assessing the severity of TBI, which may be appropriate for prognostication. Rotterdam computed tomography scoring (RCTS) is a computed tomography (CT) classification system that was developed in 2005, in patients with TBI based on multiple CT characteristics. These scores evaluate a combination of individual CT characteristics including any midline shift, the status of the basal cisterns and the types of mass lesions or intracranial hemorrhage[3]. Studies have shown the relationship between mortality rates and increased RCTS scores in pediatric and adult age groups. Mortality rates were found in the range between 26-61% in patients with RCTS scores of 4 and above in the adult age group[4,5].

Intracranial pressure (ICP) is one of the important
indicators of TBI. Elevated ICP is a challenging and potentially fatal complication of TBI in patients who present to the emergency department. Recently, measurement of the diameter of the optic nerve sheath (ONSD) has gained increasing popularity among emergency physicians as a few studies have reported the relationship between ONSD and the prognosis in head trauma patients. It has been demonstrated that ONSD reflects high ICP because the optic nerve sheath is bound to the surrounding dura mater, emphasizing its importance in the proper management of TBI. Increased ONSD has been shown to be as beneficial as invasive methods in detecting ICP. Furthermore, ONSD measurement with neuroimaging is a reliable and convenient way of detecting high ICP[6-8]. Therefore, ONSD is accepted as an indicator of elevated ICP among others. Moreover, several studies have reported a correlation between ONSD and ICP[9-12].

This study aimed to determine the relationship between the RCTS scores and ONSD measurements, showing the severity of TBI and estimating the mortality. To the best our knowledge, there have been no studies in the literature using a combination of RCTS scores and ONSD values in predicting mortality and severity in TBI patients.

SUBJECTS AND METHODS

This retrospective cross-sectional study included patients presenting to a tertiary care university teaching hospital, classified as a level 1 trauma center receiving 300,000 emergency visits annually. We reviewed the records of patients with TBI from January 1, 2017 to December 31, 2017. The ethics committee approved the study protocol. All patients who had undergone CT scanning in this period were included in the study based on convenience consecutive sampling. A total of 182 patients were included in the study regardless of age and gender. The CT images of the patients included in the study were interpreted and optic nerve sheath measurements were performed by a single radiologist with eight years of experience.

Patients fulfilling the following criteria were included in the study: (1) recent history (<24 hours) of TBI; (2) age ≥18 years; (3) initial CT performed within 24 hours after the injury; and (4) moderate (Glasgow Coma Scale (GCS) 9-12) or severe (GCS <8) TBI. Patients with mild TBI (GCS 13-15) were also included if they underwent CT examinations in accordance with the New Orleans criteria and/or the Canadian CT head rule[13,14]. The GCS scores of the patients were calculated at the time of admission to the emergency department by emergency physicians with at least 10 years of experience. We excluded the patients with facial trauma affecting the eyeballs, the patients with pre-existing orbital diseases affecting the orbital nerve, and the patients with exophthalmia, hyperthyroidism, hematologic system diseases (including lymphoma, leukemia and bone marrow malignancies), chronic inflammatory diseases (including tuberculosis, Henoch-Schönlein purpura) or any autoimmune disorders. The patients with incomplete medical records or insufficient data and the patients whose brain CT scans or millimeter-scale sequences were unavailable were also excluded. During the study period, 216 adults were admitted with TBI and 182 (84.2%) patients who met the inclusion criteria were included in the final analysis.

Measurements of ONSD and RCTS

The same physician examined all initial CT scans included in the study. He was blinded to the patient’s medical history and to the circumstances of the TBI. All CTs were found to have been performed preoperatively. Brain CTs of all patients at the time of admission to the emergency service were reviewed using Image Archiving and Communication Software. The individual diameter of each optic nerve sheath exactly at a distance of 3 mm (measure 1) and 10 mm (measure 2) behind the posterior limit of the eyeball was measured on axial 1.5-mm-thick slices. All measurements were made using the same window (WW 60, WL 350), contrast and brightness settings. Optic nerve laxity was also recorded. Diameters of both optic nerves were measured and also an average ONSD value was obtained for each patient (Figure 1). Brain CT scan of each patient was also scored according to RCTS as described by the original authors[4,15].

The data were analyzed using the Statistical Package for the Social Sciences for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA). The Shapiro-Wilk test was used in order to test whether the distribution of continuous variables was normal or not. Descriptive qualitative data were presented as numbers and...
percentage values, while descriptive quantitative data were presented as mean scores, standard deviations, ranges and medians with minimum-maximum values. The comparison of the qualitative data between the groups was performed with the Chi-square test. The quantitative data with a parametric distribution were compared between two groups with the independent t-test and the quantitative data with a nonparametric distribution was compared with the Mann-Whitney test. In addition, comparisons between more than two

**Table 1:** Comparison of Glasgow coma scale (GCS), Rotterdam computed tomography score (RCTS), optic nerve sheath diameter (ONSD), laboratory findings between patients who were alive versus dead

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=182)</th>
<th>Alive (n=155)</th>
<th>Dead (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>43.6±19.65</td>
<td>43.2±19.07</td>
<td>46.6±18.84</td>
<td>.352</td>
</tr>
<tr>
<td>GCS (median, minimum-maximum)</td>
<td>12(3-15)</td>
<td>13 (3-15)</td>
<td>8(3-13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3-8 (Severe)(n,%)</td>
<td>28(15.4%)</td>
<td>11(7.1%)</td>
<td>17(63%)</td>
<td></td>
</tr>
<tr>
<td>8-13 (Moderate)(n,%)</td>
<td>72(39.6%)</td>
<td>63(40.6%)</td>
<td>9(33.3%)</td>
<td></td>
</tr>
<tr>
<td>13-15 (Mild) (n,%)</td>
<td>82(45.1%)</td>
<td>81(52.3%)</td>
<td>1(3.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rotterdam CT Score (median,minimum:maximum)</td>
<td>2(1-6)</td>
<td>2(1-6)</td>
<td>4(1-6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rotterdam CT Score (n;%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44(24.1%)</td>
<td>44(100%)</td>
<td>0(0%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>68(37.4%)</td>
<td>65(95.5%)</td>
<td>3(4.5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25(13.8%)</td>
<td>20(80%)</td>
<td>5(20%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>25(13.8%)</td>
<td>19(76%)</td>
<td>6(24%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15(8.1%)</td>
<td>6(40%)</td>
<td>9(60%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5(2.7%)</td>
<td>2(40%)</td>
<td>3(60%)</td>
<td></td>
</tr>
<tr>
<td>Mean ONSD 3 mm</td>
<td>4.8±0.84</td>
<td>4.9±0.85</td>
<td>4.6±0.75</td>
<td>.103</td>
</tr>
<tr>
<td>Mean ONSD 10 mm</td>
<td>3.9±0.67</td>
<td>4.0±0.69</td>
<td>3.8±0.52</td>
<td>.150</td>
</tr>
<tr>
<td>Optic nerve laxity</td>
<td>48(26.4%)</td>
<td>44(28.4%)</td>
<td>4(14.8%)</td>
<td>.140</td>
</tr>
<tr>
<td>Clinical biochemical parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>12.7±3.86</td>
<td>13.7±3.12</td>
<td>139.6±5.51</td>
<td>.03</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.6±2.24</td>
<td>12.89±4.43</td>
<td>11.67±2.74</td>
<td>.004</td>
</tr>
<tr>
<td>Neutrophil count (×10^3/mm^3)</td>
<td>11.35±6.77</td>
<td>11.47±5.67</td>
<td>10.96±4.32</td>
<td>.02</td>
</tr>
<tr>
<td>Lymphocyte count (×10^3/mm^3)</td>
<td>2.56±3.67</td>
<td>2.36±1.92</td>
<td>3.84±8.31</td>
<td>.36</td>
</tr>
<tr>
<td>Platelet count (×10^3/mm^3)</td>
<td>244.9±86.80</td>
<td>247.4±85.89</td>
<td>233.2±65.89</td>
<td>.49</td>
</tr>
<tr>
<td>PLR</td>
<td>164.3±133.66</td>
<td>165.6±126.46</td>
<td>197.5±152.53</td>
<td>.19</td>
</tr>
<tr>
<td>NLR</td>
<td>8.8±9.75</td>
<td>8.7±9.28</td>
<td>9.8±9.03</td>
<td>.31</td>
</tr>
<tr>
<td>RDW</td>
<td>14.3±2.01</td>
<td>14.2±1.79</td>
<td>14.7±2.94</td>
<td>.91</td>
</tr>
</tbody>
</table>

PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; RDW: red cell distribution width

Fig 2: Line diagrams depicting mean ONSD 3 mm - 10 mm across GCS and RCTS.
groups regarding quantitative data with parametric distribution were performed by using the one-way analysis of variance test. Depending on the homogeneity of variance and F test, post-hoc tests (TUKEY HSD and Dunnett) were used for the subgroup analysis. Receiver operating characteristic (ROC) curves were plotted to determine the performance of ONSD to predict the severity of TBI. Once the best cut off value had been determined graphically, the sensitivity, specificity, positive and negative predictive values, and the positive and negative likelihood ratios were calculated with their 95% confidence intervals. The correlation of the GCS and RCTS scores with the values of ONSD was evaluated using the Spearman coefficient of correlation formula. The accepted risk of error for statistical tests was 5%.

RESULTS

A total of 182 patients fulfilled the inclusion criteria and were included in the study. Of these, 144 (79.1%) were males and 38 (20.9%) females. The mean age of the patients was 43.68±19.65 years. Road traffic accidents were the most common cause of head injury with 111 (61%) patients, followed by fall from a height with 54 (29.7%) patients, assault with 9 (4.9%), and other causes with 8 (4.4%) patients.

The GCS and RCTS scores, ONSD values, and the laboratory findings of the surviving patients versus the non-survivors were

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Severe injury (n=28)</th>
<th>Moderate injury (n=72)</th>
<th>Mild injury (n=82)</th>
<th>P value 1</th>
<th>P value 2</th>
<th>P value 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.7±17.37</td>
<td>44.97±18.56</td>
<td>41.52±21.19</td>
<td>.916</td>
<td>.451</td>
<td>.524</td>
</tr>
<tr>
<td>Gender (Female vs Male)</td>
<td>13(32.5%) vs 27(67.5%)</td>
<td>13(10.6%) vs 50 (79.4%)</td>
<td>12(15.2%) vs 67 (84.8%)</td>
<td>.317</td>
<td>.073</td>
<td>.705</td>
</tr>
<tr>
<td>Mean ONSD (3mm)</td>
<td>5.73±0.13</td>
<td>4.82±0.08</td>
<td>4.48±0.08</td>
<td>.907</td>
<td>.079</td>
<td>.002</td>
</tr>
<tr>
<td>Mean ONSD (10mm)</td>
<td>4.58±0.08</td>
<td>3.92±0.07</td>
<td>3.68±0.07</td>
<td>.848</td>
<td>.032</td>
<td>.021</td>
</tr>
</tbody>
</table>

P value 1: comparison between severe and moderate traumatic injury; P value 2: comparison between severe and mild traumatic injury; P value 3: comparison between moderate and mild traumatic injury; ONSD: optic nerve sheath diameter

Fig 3: Correlation of ONSD 3 mm and 10 mm was demonstrated.
presented in Table 1. The mortality rate for a RCTS score of 4 and higher was 40% (18/45).

The mean values for ONSD-at-3mm and ONSD-at-10 mm were statistically different in the mild, moderate, and severe head injury patients by RCTS levels. The comparison between mean ONSD at 3 mm and 10 mm values by the TBI groups and RCTS levels were shown in Tables 2 and 3 and Fig 2 a-b. Subgroup analyses of both the severity of TBI and RCTS scores were evaluated. Table 4 demonstrated the statistically significant and non-significant differences between the subgroups. The ONSD-at-3mm and 10 mm values showed a strong correlation (r=0.845, \(P <.001\)) (Fig 3).

There were no statistically significant differences in the optic nerve laxity in the patients in relation to the mortality rates and RCTS scores (\(P =.18; P =.373\), respectively).

The statistical correlations between the GCS scores, mean ONSD values and the RCTS scores in the patient group were shown in Table 5. The mean ONSD value was higher for higher RCTS scores (\(P <.001\)). The mean ONSD value was higher for higher RCTS scores (\(P <.001\)).

The cut off value for ONSD for the prediction of mortality was calculated with ROC analysis; which showed that the area under curve was 0.856 (\(P <.001\), 95% CI: 79-92.1%) and the best cut off value for ONSD was 5.0 mm (sensitivity 80%; specificity 78.46%) (Table 6, Fig 4).

Table 4: Post hoc analysis (*Dunnett) for optic nerve sheath diameter measurements (ONSD) 3 mm and 10 mm between Rotterdam computed tomography scores (RCTS) subgroup. Rotterdam CTS 1 was accepted as a control and compared all other scores against it.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ONSD(3mm)</th>
<th>Mean ONSD(10mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam CTS 1</td>
<td>4.51±0.76</td>
<td>3.72±0.66</td>
</tr>
<tr>
<td>Rotterdam CTS 2</td>
<td>4.86±0.78</td>
<td>3.96±0.65</td>
</tr>
<tr>
<td>Rotterdam CTS 3</td>
<td>5.13±1.03</td>
<td>4.05±0.76</td>
</tr>
<tr>
<td>Rotterdam CTS 4</td>
<td>5.05±0.76</td>
<td>4.15±0.63</td>
</tr>
<tr>
<td>Rotterdam CTS 5</td>
<td>5.20±0.88</td>
<td>4.23±0.47</td>
</tr>
<tr>
<td>Rotterdam CTS 6</td>
<td>4.99±0.35</td>
<td>4.11±0.70</td>
</tr>
<tr>
<td>(P) value</td>
<td>.013</td>
<td>.05</td>
</tr>
</tbody>
</table>

Table 5: Correlation analysis of parameters (GCS, mean ONSD 3 mm and 10 mm, RCTS) of the patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r-value</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS &amp; Mean ONSD(3mm)</td>
<td>-.254</td>
<td>.001</td>
</tr>
<tr>
<td>GCS &amp; Mean ONSD(10mm)</td>
<td>-.217</td>
<td>.003</td>
</tr>
<tr>
<td>Rotterdam CT score &amp; Mean ONSD (3 mm)</td>
<td>0.287</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rotterdam CT score &amp; Mean ONSD (10 mm)</td>
<td>0.257</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GCS &amp; Rotterdam CT score</td>
<td>-.822</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

GCS : Glasgow coma scale; RCTS: Rotterdam computed tomography score; ONSD: optic nerve sheath diameter

DISCUSSION

The advent of routine direct monitoring of ICP in the ventricles in 1960 resulted in its implementation in clinical practice[16]. However, the gold standard for diagnosis of elevated ICP is to use an external ventricular device, which is too invasive to be used for an initial evaluation. Measurement of ONSD has recently been introduced as an alternative non-invasive method of monitoring ICP[10,17]. The diagnostic accuracy of the use of ONSD values measured in CT scans and their correlation with ICP have been demonstrated in many studies. Sekhon et al looked at ONSD to determine its correlation with ICP in severe TBI. Based on the results of that study, the authors found a cut-off ONSD value of 6 mm with an area under the curve value of 0.83 (95% confidence interval: 0.73-0.94), with a positive predictive value of 67% and a negative predictive value of 92%. They concluded that the ONSD measurement in CT scans...
was a much stronger predictor compared to other CT features\[6,18\]. Tayal et al found that an ONSD of 5.0 mm or higher correlated with the CT findings of a shift, edema or effacement suggestive of elevated ICP\[10\]. Karakitsos et al looked at ONSD in patients with severe head injury. According to this study, an ONSD larger than 5 mm indicated a 96% probability of raised ICP, while the probability was only 9% when the diameter was smaller than 5 mm\[19\].

ONSD is measured by different radiological methods in the literature, but there have been no generally accepted protocols to standardize the use of the technique. Vaiman et al compared different points of location away from the globe for the eye for ONSD measurements and they found that the most stable results were obtained when the diameter was measured at a distance of 10 mm from the globe\[20\]. They also emphasized that a distance of 3 mm from the globe affected the measured ONSD values most. In our opinion, ONSD measurements on thin-slice brain CT scans provide more objective and repeatable results compared to ultrasonographic ONSD measurements. ONSD-at-3 mm and ONSD-at-10 mm values showed a strong correlation (r=0.845, P<.001) in our study. Furthermore, in ROC analysis performed to analyze the predictive value of the measurements for mortality, the diagnostic accuracy of the ONSD-at-3 mm value was slightly higher than the result found for the ONSD-at-10 mm. Currently, the scores of GCS and RCTS, and ONSD values are considered as independent predictors of outcome in patients with TBI. Higher RCTS and lower GCS scores, as well as an increased ONSD, were identified as independent predictors of poor outcome\[22\]. This present study attempted to find the correlations of patient characteristics and different ONSD values with the RCTS scores and mortality. In our study population, higher RCTS scores were consistent with an incremental increase in ONSD values, excluding the patients with RCTS of 6. In our study population, the number of patients with RCTS scores of ‘6’ was quite low as they died at the time of admission. We thought that the reason why lower ONSD values were found in those patients with RCTS scores of ‘6’ could be related to the low number of patients. Das et al showed the nearly linear association between the RCTS scores and ONSD, which was consistent with our study results\[22\]. However, in their study, they did not perform any subgroup analyses. In an overall assessment, we thought that an ONSD value >5.0 mm in correlation with higher RCTS scores could indicate a critical severity of TBI and risk of mortality. In our study, the cut off value of an ONSD-at-3 mm for the prediction of mortality was calculated with ROC analysis and it was found that the area under curve was 0.856 (P<.001, 95% CI: 79-92.1%) and the best cut off value of ONSD was 5.0 mm (sensitivity 80%; specificity 78.46%).

Waqas et al analyzed the RCTS scores and ONSD as predictors of outcome in patients requiring decompressive craniectomy. Bilateral mean ONSD values as a predictor of mortality were not found to be significantly different between survivors and non-survivors and the RCTS score was a significant predictor of 30-day mortality\[20\]. In addition, Flint et al found that the severity of an initial RCTS score was associated with both mortality and poor 6-month Glasgow outcome scores as determined by multivariable logistic regression analysis, although they did not assess the presence of a direct association between RCTS scores and prognosis\[24\]. In our single-center study, we found a mortality rate of 14.8% with moderate and severe TBI, similar to a large multicenter trial in pediatric TBI, where the overall mortality was 16%. Several other single-center studies on severe TBI reported the mortality rates in a range from 14% to 22%\[25-27\]. Furthermore, RCTS scores of 4 and over were associated with mortality rates of 40%.

Intracranial hypertension may be accompanied by optic nerve laxity at frequencies of approximately 40%\[20,28\]. In our study, 26.4% of our patients had optic nerve laxity. However, there was no correlation of optic nerve laxity to RCTS scores and mortality.

Our study has some limitations. First, data were collected retrospectively from a single center, so only the data recorded in the patient charts were included in the analyses. Secondly, we did not include another group in our study for comparison purposes or a control group for the estimation of normal ONSD.

Table 6: Receiver operating characteristics analysis of mean ONSD for the prediction of the mortality

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Criterion</th>
<th>AUC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV(%) (95% CI)</th>
<th>NPV(%) (95% CI)</th>
<th>DA(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ONSD(3mm)</td>
<td>&gt;5.00</td>
<td>0.856 (0.79-0.921)</td>
<td>80.00 (70.82-87.33)</td>
<td>78.46 (68.61-87.63)</td>
<td>78.43 (71.28-84.20)</td>
<td>79.59 (72.22-85.40)</td>
<td>79</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>Mean ONSD(10mm)</td>
<td>&gt;4.12</td>
<td>0.847 (0.783-0.911)</td>
<td>78.12 (67.63-85.67)</td>
<td>74.56 (64.27-82.26)</td>
<td>75.24 (67.96-80.93)</td>
<td>77.08 (69.55-83.29)</td>
<td>76</td>
<td>P&lt;.001</td>
</tr>
</tbody>
</table>

AUC: area under the receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy; ONSD: optic nerve sheath diameter.
values. Third, inter- and intra-observer variability of the method could not be assessed since all measurements were performed by the same co-investigator. Finally, the number of patients with a RCTS score of ‘6’ was low. Despite these limitations, we believe that the study provides useful information in understanding the prognostic role of radiological features in traumatic brain injury.

CONCLUSION

ONSD-at-3mm measurements via CT combined with the RCTS and GCS scores enhance the prognostic performance and improve the sensitivity while maintaining high specificity in predicting the severity of TBI and mortality.

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Conflict of interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Patient consent: It is a retrospective study with Ethical Committee approval, hence there was no need for the informed consent.

Ethical approval: University of Health Science Antalya Training and Research Hospital ethical approval committee permission date 28 December 2017, number: 2017-252.

Human Rights: Our study was not a clinical study that involves clinical intervention. We only retrospectively reviewed with data collected in the surveillance system

REFERENCES


Anesthesia in a patient with a rare disease: Von Hippel-Lindau syndrome

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Kuwait Medical Journal 2020; 52 (4): 439 - 442

ABSTRACT

Von Hippel-Lindau disease is a rare autosomal dominant disorder characterized by capillary hemangioblastoma of the central nervous system or retina. Renal and pancreatic cysts as well as pheochromocytoma may accompany this disease. Tumors may be either cancerous or noncancerous and the signs and the symptoms of the disease can occur throughout life. Non-specific findings and wide age range makes differential diagnosis a complicated issue. The diagnosis of von Hippel-Lindau disease depends on the combination of clinical, radiological, pathological and genetic data. The anesthetic concern during operation for this disease is a huge challenge, usually requiring detailed preoperative evaluation. Here, we presented the surgical resection of a spinal hemangioblastoma in a patient with von Hippel-Lindau disease and discussed the significance of this syndrome.

KEY WORDS: anesthesia, hemangioblastoma, von Hippel-Lindau disease

INTRODUCTION

Von Hippel-Lindau disease (OMIM number 193300) is a cancer syndrome with characteristics of the central nervous system and retinal tumors, clear cell renal carcinomas, pheochromocytoma, pancreatic islet cell tumors, endolymphatic sac tumors and benign cystic lesions in multiple organs[1]. The causative gene is a tumor suppressor gene that plays a role in the regulation of angiogenesis and cell division[2]. The most common manifestations of this disease include benign hemangioblastomas typically developed in the cerebellum, spinal cord and retina. The chromosome 3p25-26 is responsible for central nervous system hemangioblastomas[3].

The disease is often overlooked in diagnosis and has a reported prevalence of one in 39-91 people across different populations[4-7]. The related data for our country, Turkey, is limited, with unknown disease incidence.

This report describes the anesthetic management of a unique case of von Hippel- Lindau disease, wherein the patient presented with spinal hemangioblastoma.

CASE REPORT

A 52-year-old woman was admitted to the emergency unit with complaints of back pain, progressive weakness of the lower extremities for two months, bilateral paresthesia and difficulty in walking. Her physical examination revealed she had 2/5 and 3/5 motor strength in the right and left lower limbs respectively, with tenderness in the lumbar spine as well as paraspinal muscle spasm. Routine laboratory evaluation revealed mild hyperglycemia (140 g/dL). Electrocardiogram showed normal sinus rhythm and chest radiograph was normal. Ophthalmic examination revealed retinal micro hemangiomas and minimal papilloedema. A diagnosis of von Hippel-Lindau disease was confirmed 10 years ago with multiple cystic lesions occurring in the kidney and pancreas. Magnetic resonance imaging demonstrated a cystic lesion with syringomyelia at the T1 level and accordingly the patient was scheduled for surgery.

Preoperatively, the patient showed mild hypertension (150/100 mmHg), which was treated with β-blocker. An ultrasound scan of the abdomen and
levels of serum metanephrine and normetanephrine were considered to rule out the possibility of an adrenal mass.

Following premedication with 0.03 mg/kg midazolam, general anesthesia was induced with fentanyl (1 µg/kg) and propofol (3mg/kg). Rocuronium (0.6 mg/kg) was administered to facilitate endotracheal intubation. Anesthesia was maintained with the infusion of remifentanil (0.8µg/kg/min) and propofol (30-50 µg/kg/min). The depth of anesthesia was monitored with bispectral index targeted between 40 and 60 values through an electrode placed on the patients’ forehead. Since the maintenance of smooth hemodynamics was another treatment objective, infusion of the remifentanil was also adjusted to sustain the mean arterial pressure at 80-90 mmHg. Mechanical ventilation with intermittent positive pressure was initiated at a tidal volume of 7 ml/kg of an ideal body weight, and the respiratory rate was adjusted to maintain end-tidal CO₂ concentration at 30-35 mmHg in a semi-closed-circuit with 4 mL/min of fresh gas flow.

Intraoperative monitoring included continuous electrocardiogram of 3-leads electrocardiogram, as well as monitoring of central venous pressure by catheterization of the right internal jugular vein, invasive blood pressure by right radial artery cannulation, heart rate, peripheral O₂ saturation, end-tidal CO₂, esophageal temperature and urine output. The measurement of somatosensory-evoked potentials recorded from the tibial nerve (P37) was used to monitor the functions of the spinal cord throughout the operation. The use of any neuromuscular blocker was avoided after intubation. The intraoperative normothermia was maintained with the use of a forced air-warming blanket.

The patient was placed in the prone position to avoid compression over the pressure points. The surgery lasted for six hours, wherein an encapsulated mass was totally excised (Figure 1). The estimated blood loss during the operation was 500 mL. Approximately 4 L of crystalloid and 500 mL of colloid were transfused throughout the surgery. Intraoperative arterial blood gas analysis and laboratory findings were within the acceptable limits. Analgesia was provided toward the end of the procedure with the intravenous administration tramadol and paracetamol in conventional doses. Metoclopramide 20 mg was intravenously administered to prevent postoperative nausea and vomiting. The patient was reversed with 0.02 mg/kg neostigmine and 0.5 mg atropine and extubated on the operation table.

The patients’ postoperative course was uneventful and she was discharged with advice for review after two weeks. Histopathological examination of the surgical specimen showed well-circumscribed hemangioblastoma. An improvement was noted in the motor and sensorial deficits. Periodic follow-up of the patient is ongoing, and no recurrence has been noted to date.

Informed consent was obtained from the patient for this case report, and the ethical principles outlined in the Declaration of Helsinki were followed.

**DISCUSSION**

This case presents a unique anesthetic challenge in a patient with von Hippel-Lindau disease. The literature includes case presentations and case series including a few with von Hippel- Lindau disease. Kanno et al[8] presented 48 spinal cord hemangioblastoma cases, of which 47.9% manifested more than one lesion in the spinal cord. The tumor was accompanied by a syrinx in 64 patients from a total of 74 tumors. Spinal cord hemangioblastomas are slow-growing tumors that become symptomatic after the syrinx associated with the tumor enlarges. Earlier features are mostly retinal and cerebellar hemangioblastomas, whereas it is relatively rare in spinal cord hemangioblastoma[9]. When the manifestation of von Hippel- Lindau disease aside from spinal cord hemangioblastoma occurs early, the prediction of spinal cord hemangioblastoma takes approximately five years[8]. The concurrence on the optimal timing for surgical intervention in spinal hemangioblastomas without symptoms remains debatable. One study has suggested that small hemangioblastomas must be closely followed-up radiologically and surgery is recommended in significantly large tumors or tumors combined with an extensive syrinx to prevent the development of any neurological deficit[8,9].

Reportedly, when the neurological condition was evaluated before and after the condition, the presence of a syrinx was not a predictor of the outcome and 83% of the surgical cases showed improvement[8,9]. Our patient also demonstrated dramatic improvement with respect to sensorial and motor weakness.

A strong association has been reported between pheochromocytoma and the clinical classification of von Hippel-Lindau disease. For instance, a study has suggested that approximately 35% of patients are asymptomatic[11]. Undiagnosed pheochromocytoma carries a high risk during the perioperative period and it may result in increased morbidity and mortality. In particular, in the prone position, the potential for abdominal compression leads to excessive endocrine discharges from the adrenal glands, resulting in uneventful outcomes[12]. The possible presence of pheochromocytoma must be considered in patients during preoperative assessment, and we accordingly eliminated the presence of pheochromocytoma in our
patient during preoperative screening based on the laboratory and imaging findings.

CONCLUSION

A patient with von Hippel-Lindau disease requires adequate preoperative evaluation to diagnose the various associated organ system pathologies. These patients may require anesthesia for several surgical procedures, and the type of anesthesia depends on the nature of surgery. The patients’ clinical condition is the major factor in determining the best anesthetic approach. Thus, based on our experience, an interdisciplinary approach is helpful in the management of patients with von Hippel-Lindau disease.
ACKNOWLEDGMENT

Author’s contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: BC, OS

Drafting the work or revising it critically for important intellectual content: BC

Final approval of the version to be published: BC, OS

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: BC

The authors declare that they have no competing interest.

REFERENCES

Case Report

Emergency caesarean section with severe thrombocytopenia (8000/mm$^3$)

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ABSTRACT

Thrombocytopenia is defined as a blood platelet count below 150,000/mm$^3$. It is the most common hemostatic abnormality in pregnancy. The risk of thrombocytopenia during pregnancy is 6-15%. The most common causes of thrombocytopenia are benign gestational thrombocytopenia (79.5%), pre-eclampsia (16%), HELLP syndrome (2.5%), immune thrombocytopenia (1%), and hepatitis C (1%).

In this case report, we present a 37-week pregnant woman diagnosed as immune thrombocytopenic purpura (ITP), in whom emergency caesarean was performed due to fetal distress despite platelet levels as low as 8000/mm$^3$. A single liveborn male infant of 2560g weight and 40 cm length with an Apgar score of 8/10 was delivered. No complications were encountered during the operation. Her platelet count returned to normal levels after steroid treatment (methylprednisolone: 2 mg/kg for three weeks and then 1 mg/kg for three weeks). The case was diagnosed with ITP. The etiology should be determined and treatment should be planned in pregnant women with thrombocytopenia. With failure to act promptly and accurately, maternal and/or fetal morbidity, even mortality, may occur. In the literature, it is rare to perform caesaean, even any surgery, in cases with a platelet count below 10,000/mm$^3$. In this study, we aimed to show that a caesarean can be performed in cases with a platelet level of 8,000/mm$^3$ when the life of the fetus is at risk.

KEY WORDS: cesarean section, gestational thrombocytopenia, immune thrombocytopenic purpura

INTRODUCTION

Thrombocytopenia is defined as a blood platelet count below 150,000/mm$^3$. Normal pregnancy is characterized by a left shift in platelet distribution in addition to a physiologic drop in platelet count associated with increased breakdown, reduced platelet synthesis or dilutional causes. The risk of thrombocytopenia during pregnancy is 6-15%. Many thrombocytopenia cases during pregnancy present with mild-to-moderate decreases in thrombocytopenia levels. If the cutoff point for thrombocytopenia is considered as a platelet count below 100,000/m$^3$, this rate may decline to about 1%[12].

The most common causes of thrombocytopenia are benign gestational thrombocytopenia (79.5%), pre-eclampsia (16%), HELLP syndrome (2.5%), immune thrombocytopenic purpura (ITP) (1%), and hepatitis C (1%)[3].

The presence of thrombocytopenia during emergencies in pregnancy may be a serious problem. In emergency surgical patients with thrombocytopenia, the underlying cause should be determined and treated accordingly. Spontaneous hemorrhage is rarely seen in patients with platelet levels above 10,000/mm$^3$. Surgical hemorrhage at platelet levels above 50,000/mm$^3$ often does not pose a threat. When emergency surgery is planned, platelet transfusion is recommended to elevate the platelet count above 50,000/mm$^3$[4].

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In this case report, we present a 37-week pregnant woman in whom emergency caesarean was performed due to fetal distress, despite platelet levels as low as 8000/mm³.

CASE REPORT

The 20-year-old, primigravid patient with 37-week pregnancy presented to a healthcare center because of pain and she was referred to our hospital due to thrombocytopenia (19,000/mm³). The history revealed no hemorrhage.

Based on the date of last menstruation, she was 36 weeks and 5 days pregnant. Ultrasound examination demonstrated a living, single, 35/36 week pregnancy in a headfirst position. Vaginal examination showed a 60% effaced and 3 cm dilated cervix. According to the blood workup, hemoglobin was 12.3 g/dl, white blood cell count was 2500/mm³ and platelet count was 8000/mm³. The patient was hospitalized due to a prediagnosis of pain and thrombocytopenia.

Although preparations for platelet suspension transfusion were planned, since the non stress test of the patient revealed severe late decelerations, emergency caesarean was performed under general anesthesia due to a diagnosis of fetal distress before transfusion was initiated. A single liveborn male infant of 2560g weight and 40 cm length with an Apgar score of 8/10 was delivered. No complications were encountered during the operation.

The first platelet suspension transfusion was performed after the sixth hour from operation due to difficulties in providing and provision. The patient received six units of platelet suspension because the complete blood count performed at postoperative 2-hours showed the following results: Hb, 9.9g/dl; WBC, 3100/mm³; and platelets, 8000/mm³. Based on the follow-up test results (Hb, 10.3g/dl; WBC, 2800/mm³; platelets, 9000/mm³), the patient was referred to the Hematology Clinic. Bone marrow biopsy and peripheral blood smear that included schistocytes were compatible with ITP. Her platelet count returned to normal levels (137,000-167,000/mm³) after six weeks of steroid treatment. Following discharge, follow-up assessments indicated no postoperative problem and she was retrospectively evaluated as a case of ITP.

The American Society of Hematology and the British Society for Haematology recommend treatment of pregnant women with severe thrombocytopenia or mild thrombocytopenia coupled with spontaneous hemorrhage. Treatment is recommended when the platelet level is below 10,000/mm³ at any time of pregnancy or when the platelet level drops below 30,000/mm³ during the second or third trimester of pregnancy. However, in our case, thrombocytopenia was determined incidentally in emergency settings and caesarean section had to be performed without having the chance to apply any treatment beforehand.

For emergency surgical patients with thrombocytopenia, the underlying cause should be determined and the proper treatment should be started. Spontaneous bleeding is uncommon at platelet levels above 10,000/mm³. Surgical bleeding at platelet levels above 50,000/mm³ often do not pose a serious problem. Platelet transfusion is recommended to increase the platelet level above 50,000/mm³ in patients scheduled for emergency surgical intervention.

In one case reflecting the general approach in such cases, Wood et al performed a successful caesarean in...
a pregnant ITP patient with a platelet level of 21,000/mm³, following a 5×10¹¹ allogeneic platelet transfusion elevating the platelet level to 97,000/mm³ [9].

In the literature, the number of patients receiving surgical treatment because of serious thrombocytopenia is limited due to a common perception aiming to avoid possible complications. However, successful outcomes achieved in patients with severe thrombocytopenia show that surgical intervention is also an option in emergency cases. Ashoub et al successfully performed a coronary artery bypass grafting in a patient with a platelet count of 19,000/mm³ [10].

Incebiyik et al conducted a successful vaginal birth in a pregnant woman with gestational thrombocytopenia reflected by a platelet count of 7916/mm³ [11]. Harde et al performed a successful caesarean section by intraoperatively delivering 10 units of platelets in a pregnant woman with hypocellular bone marrow and pancytopenia characterized by a platelet count of 7000/mm³ [12].

CONCLUSION

In conclusion, the etiology should be determined and treatment should be planned in pregnant women with thrombocytopenia. With failure to act promptly and accurately, maternal and/or fetal morbidity, even mortality, may occur. If emergency surgical intervention is planned, platelet transfusion aiming to elevate the platelet count above 50,000/mm³ is recommended. In the literature, it is rare to perform caesarean, even any surgery, in cases with a platelet count below 10,000/mm³. In this study, we aimed to show that a caesarean can be performed in cases with a platelet level of 8,000/mm³ when the life of the fetus is at risk.

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None

Authors Contribution
Buğra Çoşkun and Selçuk Erklinç conceived, designed and editing of manuscript.
Buğra Çoşkun, did data collection and manuscript writing.
Selçuk Erklinç and A.Seval Özgü-Erdinç did review.

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REFERENCES

Learning beyond standard practice during awake craniotomy: Integrated Pulmonary Index (IPI™)

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ABSTRACT

Integrated Pulmonary Index (IPI™) is an index that integrates the values of respiratory rate, oxygen saturation (SpO₂), capnography and pulse rate in a single value. This system provides an early warning system of respiratory compromise in spontaneously breathing patients. The predictive role of IPI™ during procedural sedation in a 36-year-old male patient undergoing awake craniotomy was assessed. IPI™ scores dropped to critical levels while the real-time SpO₂ was 98%. IPI provided an early recognition of apnea episode and prevented the progress of clinical deterioration. This tool may be a valuable adjunct to the standard monitoring during awake craniotomy.

KEY WORDS: integrated pulmonary index, respiratory monitoring, sedation

INTRODUCTION

Due to the lesions located in the functional areas of the brain, awareness of the patient is preferred during some intracranial procedures. The management of anesthesia in an awake patient requires skilled practice and the maintenance of adequate sedation, analgesia, respiratory and hemodynamic stability in a cooperative, responsive patient for intraoperative neurologic testing[1].

In awake craniotomy, different techniques such as asleep-awake-asleep, monitored anesthesia care and awake-awake-awake technique has been recommended. The superiority of one technique over another has not been proved yet[2].

In awake craniotomy, monitoring is the most important point of view during the procedure. The respiratory monitoring during anesthesia includes end-tidal CO₂, respiratory rate, oxygen saturation (SpO₂) and pulse rate. The Integrated Pulmonary Index (IPI™) is a new smart monitoring which is an index score based on the integrating of real-time interaction of four parameters resulting in a single value showing the respiratory status from a scale of 1 (critical insufficiency) to 10 (optimal status) (Table 1). IPI™ provides early warning of altered respiratory patterns and alerts the physicians to the need for further clinical assessment and intervention[3].

In the literature review, IPI™ is mostly preferred in outpatient anesthesia in both pediatric and adult patients[4-6]. We present a unique case of awake craniotomy for intracranial tumor excision using IPI™ during conscious sedation and discuss the role of this tool in perioperative monitored anesthesia care.

CASE REPORT

A 36-year-old male patient was admitted to the hospital with a complaint of headache and left-sided hypoesthesia on his face. Patient history revealed there was an operation approximately one year ago due to an intracranial mass on the right frontal superior gyrus which was histopathologically diagnosed as diffuse astrocytoma Grade 2. Brain magnetic resonance imaging revealed a repeated solid lesion on the frontal lobe and because of the location of tumor close to the eloquent regions of the brain, he was scheduled as awake craniotomy for tumor excision.
According to institution protocol, the patient was evaluated by an anesthetist in respect of laboratory findings, chest x-ray and electrocardiogram for preoperative risk assessment and the patient was considered American Society of Anesthesiology physical status II. The patient and his family were informed about the surgical procedure and explained that he would be awake during the operation in a painless and cooperative condition. The patient was kept fasting for eight hours prior to surgery. Once the patient was shifted to the operating room, standard monitoring was applied including 3-lead electrocardiogram with continuous ST segment analysis, non-invasive blood pressure and pulse oximetry (SpO₂). He was calm, oriented and cooperative with a Glasgow Coma Scale of 15/15. The patient was advised to raise his hand during the procedure in case of pain, discomfort or any uneventful situation. An 18-G intravenous cannula was inserted on the dorsum of the left hand and 0.9% sodium chloride infusion was initiated.

A BIS Quarto sensor (Aspect Medical Systems, Newton, MA, USA) was placed on his forehead connected to a BIS Vista monitor (Aspect Medical Systems, Newton, MA, USA) to define the optimal depth of anesthesia throughout the surgical procedure. The depth of anesthesia was adjusted to maintain the BIS values higher than 60.

A cerebral oximeter probe (Invos™, Cerebral/Somatic Oximeter 5100C, Somanetics Cooperation, Troy, MI, USA) was attached to the forehead for monitoring the real-time regional oxygen saturation (rSO₂) of the frontal cortex. The initial rSO₂ levels were 62% on the left and 72% on the right side.

A Capnostream 20 monitor (Medtronic, Israel) was connected to the patient alongside the Smart CapnoLine™ Microstream CO₂ sampling line (Medtronic, Israel) for delivering supplemental oxygen to non-intubated patients (Figure 1). Integrated pulmonary scores were recorded every five minutes.

To avoid discomfort, shoulders, arms and lower extremities were supported by pillows keeping the head slightly elevated in order not to compress jugular venous flow. The preparations to convert to general anesthesia was also completed.

The patient was premedicated with 2 mg intravenous midazolam. Oxygen was delivered via a nasal cannula. Following intravenous administration of 1µgr/kg fentanyl (Talinat; Vem İlaç Sanayi, Tekirdağ, Turkey), propofol (Fresenius Kabi, Bad Homburg vor der Höhe, Germany) injection was started to titrate to an endpoint where the patient appeared drowsy but cooperation was maintained (Figure 2). We used Ramsey sedation score to assess the level of sedation and a score between 4 and 6 was targeted. After 10 minutes of anesthesia induction, the bilateral scalp block with bupivacaine 0.05% was applied. The patient was deeply sedated during scalp incision, bone flap removal and dural opening. Lidocaine 2% soaked pads were also placed over dura mater before incision. During this period, IPI scores dropped to 5 and 3 within an interval of a few minutes while the real-time SpO₂ was 98%. The patient was in an episode of apnea, so we lifted the chin and called to take a deep

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**Table 1: IPI Patient Status Descriptors³⁹**

<table>
<thead>
<tr>
<th>IPI</th>
<th>Patient Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Normal</td>
</tr>
<tr>
<td>8-9</td>
<td>Within normal range</td>
</tr>
<tr>
<td>7</td>
<td>Close to normal range; requires attention</td>
</tr>
<tr>
<td>5-6</td>
<td>Requires attention and may require intervention</td>
</tr>
<tr>
<td>3-4</td>
<td>Requires intervention</td>
</tr>
<tr>
<td>1-2</td>
<td>Requires immediate intervention</td>
</tr>
</tbody>
</table>

---

**Fig 1:** Monitoring of the patient during procedure. **A)** IPI monitoring showing the integrated single index (8) of EtCO₂ (40), SpO₂ (96%), RR (13/min) and PR (83 beats/min); **B)** Cerebral oxymetry showing the right and left brain; **C)** BIS showing the sedation level as 86.

**Fig 2:** The prepared patient before surgery.
breath. The score returned to 8 within 30 seconds and operation was continued. The duration of operation was 90 minutes and uneventful. 

 Totally 100µgr fentanyl and 440 mg propofol was used during operation and the patient was cooperative, breathing spontaneously without the necessity of an airway device. The real-time SpO2 levels ranged from 75-90% on the right and from 81-95% on the left throughout the surgical procedure.

 The patient remained in the post-anesthesia care unit for 60 minutes for the follow-up of any clinical changes during the postoperative period. He was discharged to neurosurgery clinic and following five days of hospital stay, he was discharged to go home without any complication.

 We obtained informed consent from the patient for this case presentation and his photograph. The ethical principles outlined in the Declaration of Helsinki and guideline of Good Clinical Practice was followed.

**DISCUSSION**

The success of an awake craniotomy starts with good preoperative evaluation and explanation of the procedure to the patient with all details. Premedication is a debatable issue and the main goal is to provide anxiolysis with the adequate level of sedation. The decision varies according to the patient’s clinical condition[7]. We preferred premedication to relieve anxiety and to provide sedation before surgery.

Propofol is a widely used hypnotic agent because of easy dose titration and rapid recovery. Its antiemetic, anti-convulsive properties and the reducing effect on intracranial pressure without interference with the electrocorticographic recordings make the drug popular during awake craniotomy[8].

Standard monitors including the electrocardiogram, non-invasive blood pressure, pulse oximeter, respiratory rate and body temperature are inevitable during awake craniotomy procedures. On the other hand, the use of additional equipment to provide the adequate infusion of intravenous sedatives will improve the patient care. Bispectral index or spectral entropy is recommended for this purpose[7]. Capnography monitoring is also recommended by the American Society of Anesthesiologists in sedated patients[9] but it’s usually underestimated by healthcare professionals in spontaneously breathing patients. IPI™ is a simple and objective monitoring tool in which the ventilation and oxygenation cooperate in a single respiratory index. This tool is easy to use in clinical practice and does not require prolonged training[10].

Based on a review of the literature, experiences with IPI™ are mostly reported in outpatient procedures and usage in other anesthetic applications are limited. The use of this device during a few electrical cardioversion cases, tooth extraction and dental implantation are attractive[10-11]. We first used this tool during awake craniotomy and it was an easy method for respiratory monitoring. Early warning of apnea period during the procedure provided an early intervention before deterioration of patient status. IPI™ seems a feasible method of monitoring in patients undergoing procedural sedation and has a potential of being a widely used tool in the future.

**CONCLUSION**

The management of awake craniotomy is a challenge and carries risks of intraoperative adverse events concerning both anesthesiologist and surgeon. The important key points are appropriate patient selection, adequate preoperative preparation of the patient, advanced intraoperative monitoring and close interrelationship between surgeon and anesthesiologist. The use of the new technological equipment may greatly facilitate early recognition of preventable adverse events.

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Drafting the work or revising it critically for important intellectual content: Banu Cevik
Final approval of the version to be published: Ozlem Sezen, Banu Cevik
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Ozlem Sezen, Banu Cevik

**REFERENCES**


Case Report

Rhabdomyosarcoma in a patient with germline TP53 gene mutations: A case report

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ABSTRACT

We herein report the case of a patient with germline TP53 gene mutations who developed rhabdomyosarcoma (RMS). A 29-month-old female patient with a family history of early-onset malignancies was diagnosed with RMS, and her final pathological diagnosis was embryonal RMS. In this patient, two constitutional mutations at codon 215 in exon 4 (c.215C>G) and codon 844 in exon 8 (c.844C>T) of the TP53 gene were identified in the peripheral blood, and Li-Fraumeni syndrome (LFS) was suspected. These mutations cause missense mutations, and TP53 gene mutations were also found in her family members. Moreover, the TP53 mutation sites were similar in her family members. This is the first case of RMS in a patient with LFS and family hereditary TP53 gene mutations.

KEY WORDS: Li-Fraumeni syndrome, P53 gene, rhabdomyosarcoma

INTRODUCTION

The TP53 gene is a tumor suppressor, and the germline TP53 gene is located on chromosome 17p13.1 and consists of 11 exons and 10 introns[1]. Many scientists have studied this gene and its functions, since it was discovered in 1979 by Lane et al[2]. p53 is a nuclear transcription factor that transactivates numerous target genes involved in the induction of cell cycle arrest and/or apoptosis. There is an important restriction fragment length polymorphism in codon 72 of exon 4 of the TP53 gene, coding for proline or arginine[3]. Germline pathogenic TP53 mutations may result in a predisposition to multiple cancers and are associated with a markedly increased risk of cancer-related morbidity and mortality[4], but penetrance and cancer patterns remain incompletely documented[5].

Since Li-Fraumeni syndrome (LFS) was described by Li and Fraumeni over 40 years ago, it remains one of the most striking familial cancer predisposition syndromes[6] and is characterized by a high frequency of early-onset and diverse tumor types and an increased frequency of multiple primary tumors[7]. Sarcoma and breast cancer are the most common presentations, although other malignancies can develop[8]. The only gene that has been consistently associated with LFS is TP53[9]. While some studies have described rhabdomyosarcoma (RMS) as a malignant tumor of striated muscle origin, with overall 5-year survival >70%[10], others hypothesize that RMS represents another sentinel cancer of LFS, in addition to adrenocortical carcinomas and choroid plexus tumor[11]. We herein report a patient with germline TP53 gene mutations who presented with RMS and discuss the carcinogenesis of these lesions.

CASE REPORT

A 35-month-old female patient with a family history of early-onset malignancies visited our hospital for a medical examination, because of diagnosis of RMS when she was 29 months of age. She suffered from swallowing difficulties at the beginning of her illness, and her mother found that her left mandible block was reddened and warm (Figure 1). The patient was hospitalized in the local hospital and presented no obvious improvements under anti-inflammatory treatment. The mass became enlarged and caused breathing problems. A computed tomography (CT) scan indicated that the lesion occupying the left
Pharyngeal space (Figure 2a) potentially originated from a tonsil or lymph node tumor source. The pathological result of the CT scan was embryonal RMS. After two cycles of chemotherapy, the CT revealed that the mass was significantly smaller than before. As the tumor location was too dangerous to allow surgical treatment, which may cause substantial changes to her facial features, 125I radiotherapy and chemotherapy were chosen to control tumor progression (Figure 2b). Currently, the patient still undergoes chemotherapy, and we have achieved relatively stable tumor control (Figure 2c).

In the patient’s family, her brother was diagnosed with RMS of the abdomen when he was two years of age and died, and her grandmother was diagnosed with breast cancer at the age of 40 years and currently remains alive. First-degree relatives of the proband and portions of the extended family are shown in Figure 3. Because of the patient’s family history, we performed a mutation analysis of the TP53 gene from genomic DNA that we prepared from isolated peripheral blood lymphocytes. After polymerase chain reaction amplification, a direct sequencing analysis was performed for exons 2-11 of the TP53 gene, which encode the DNA-binding domain of the p53 protein. These exons are a known open region for the TP53 somatic mutations that are associated with oncogenesis and malignancy. The nucleotide sequence of the sample revealed a heterozygous pattern at codon 215 in exon 4, which had a single nucleotide polymorphism, and codon 844 in exon 8, which encoded a missense mutation in the TP53 gene (Table 1). This study was conducted in accordance with the declaration of Helsinki. Approval was received from the Ethics Committee of Tongren Hospital Capital Medical University. Written informed consent was obtained from all participants’ guardians.

DISCUSSION

RMS is the most common soft tissue sarcoma of children. Morbidity from RMS is observed in about 6% of malignant solid tumors of children and approximately 53% of soft tissue sarcomas, most of which occur before the age of five years[12]. It is the third most common extracranial solid tumor in children, after neuroblastoma and Wilms tumors[13]. RMS in children can derive from any part of the body, and studies have shown that the most common primary site of childhood RMS is the head and neck[14]. In the 2013 World Health Organization classification of soft tissues and bone tumors, RMS was divided into embryonal, alveolar, pleomorphic and spindle cell/sclerosing RMS. Embryonal RMS is the most common, accounting for 50%–60% of RMS incidences, and the histological characteristics, genetic characteristics, pathogeneses, age ranges and prognoses vary among the different RMS subtypes[15]. Chromosomal abnormalities and changes in molecular pathways are often the main causes of RMS and have important
Mutations in the TP53 gene are the most common tumor-specific genetic alternation in human neoplasms and have been identified in more than 50% of human cancers, across many different types. Many children with anaplastic RMS (anRMS) carry TP53 germline mutations\(^\text{[16]}\). Since the 1990s, the TP53 gene has been screened across large RMS samples and has shown a mutation rate of 30%. The TP53 mutations that were observed in our case were single-nucleotide variants in the coding sequences of exons 4 and 8 of the human TP53 gene that resulted in missense mutations.

Aberrations of both mutation sites within the TP53 coding sequence have been previously reported in the UMD TP53 database\(^\text{[17]}\). anRMS often presents at a young age in children with TP53 germline mutations\(^\text{[14]}\). In our case, the patient and her brother presented with TP53 germline mutations and were diagnosed with anRMS before three years of age, and the TP53 gene mutations were simultaneously detected. At the same time, similar sites of TP53 gene mutations were found in the patient’s sister and parents; however, no tumors have been identified in their bodies. Due to the cancer history and high cancer incidence of the patient’s family, we advised regular body checks and

### Table 1: TP53 germline mutations in some family members

<table>
<thead>
<tr>
<th>Case ID</th>
<th>anRMS</th>
<th>TP53 germline mutation</th>
<th>Exon</th>
<th>Mutation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-5</td>
<td>-</td>
<td>c.215C&gt;G</td>
<td>4</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>II-6</td>
<td>-</td>
<td>c.215C&gt;G</td>
<td>4</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>III-1</td>
<td>-</td>
<td>c.215C&gt;G</td>
<td>4</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>III-2</td>
<td>+</td>
<td>c.215C&gt;G</td>
<td>4</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>III-3</td>
<td>+</td>
<td>c.215C&gt;G c.844C&gt;T</td>
<td>4,8</td>
<td>Single nucleotide polymorphism</td>
</tr>
</tbody>
</table>

\(\text{anRMS: anaplastic rhabdomyosarcoma}\)

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**Fig. 3:** Pedigrees of the families.
close follow-ups. Neither the child nor her family has carried out relevant prenatal testing for TP53 germline mutations. If her mother is pregnant again or her sister becomes pregnant in the future, prenatal testing for TP53 germline mutations can be recommended.

LFS is an inherited cancer predisposition syndrome that is characterized by the early onset of cancers, which include, but are not limited to, soft tissue sarcomas, sarcomas, adrenocortical carcinomas, brain tumors and breast carcinomas[18]. In addition, LFS occurs over a wide age range, is usually diagnosed in patients under 45 years of age, is responsible for some childhood cancers, and has an over-represented tumor distribution in the general population[19]. TP53 is the only gene that has been consistently associated with LFS. Adrenocortical carcinoma is considered to be a sentinel cancer in TP53 germline mutation carriers, and the frequency of TP53 germline mutations in a cohort of 21 children with adrenocortical carcinoma was found to be 67%[9]. More recently, Simone et al investigated anRMS in TP53 germline mutation carriers and found that 11 of 15 children with anRMS had TP53 germline mutations. This suggests that anRMS represents another sentinel cancer of LFS[11]; however, this finding needs to be confirmed in larger RMS cohorts.

In our case, the child and her brother were diagnosed with RMS accompanied by TP53 gene mutations, which is consistent with the relevant literature reports and supports RMS as an LFS outpost carcinoma. For various tumors in patients with LFS, including RMS, multidisciplinary treatment approaches including chemotherapy and surgery are recommended[20]. In the present patient, repeated chemotherapy and radiotherapy were performed for the tumor, and good results have been achieved. However, it is generally assumed tumors in germline p53 mutation carriers may be relatively radiation-resistant[21]. The patient has not been cured at present. She developed tumor metastasis after eight months of stable disease control and cessation of chemotherapy, suggesting a poor long-term prognosis, consistent with relevant literature reports. However, the tumor of this child was very sensitive to chemotherapy, which was of great help to the improvement of survival rate. Patients with LFS also display abnormal sensitivities to radiogenic carcinogenesis and show high risks of secondary malignancies in areas that are exposed to the radiation field[22]. In addition, p53 mutations may predispose some children to therapy-related leukemia and myelodysplastic syndrome[23]. Since local radiotherapy was used for the child in this case, it is necessary to pay attention to the possibility of cancer and other blood system diseases. Recent data revealed that mutant p53 is not just one protein, but rather a multitude of proteins that can contribute to a wide range of oncogenic processes[24]. While drugs that are designed to target mutant p53 tumors can provide a new treatment for patients, p53 mutants present highly challenging targets, and we require a deeper understanding of p53 degradation pathways, interaction partners and downstream signaling pathways in cells with p53 mutations.

CONCLUSION
Our results demonstrate that the familial embryonic TP53 gene mutations were closely related to RMS and LFS incidences. For the treatment of patients with these diseases, drugs targeting TP53 gene mutations should be studied on the basis of traditional discharge, chemotherapy and surgical treatment, to provide new research directions for the treatment of these tumors.

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The authors declare no conflict of interest.

D.S, Hang contributed design of the study. W.L, Zhang and L.P, Chen performed the statistical analysis. L.P, Chen wrote the first draft of the manuscript. All authors discussed, commented and improved the manuscript.

REFERENCES
2. Lane DP, Crawford LV. T antigen is bound to a host protein in SY40-transformed cells. Nature 1979; 278(5701):261-263.


Laparoscopic radical nephrectomy of a pelvic kidney mass

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ABSTRACT
Renal cell carcinoma (RCC) in pelvic kidney (PK) is very rare. Using computed tomography, we detected a 60x46 mm solid mass in right PK of a 47-year-old man. Laparoscopic radical nephrectomy (LRN) was done. No complications occurred and patient was discharged after 36 hours. Pathology revealed multicystic RCC. During the two year follow-up period, no local recurrence or metastasis was observed. LRN for a PK mass has been reported rarely in literature. It can be safely performed in centres experienced in laparoscopy, after delineating the vascular anatomy and surrounding structures with adequate pre-operative screening.

KEY WORDS: computed tomography angiography, laparoscopy, pelvic kidney, renal cell carcinoma

INTRODUCTION
The development of pelvic kidney (PK) is contingent on the non-completion of anatomic ascent of the kidney in the sixth to ninth weeks of the gestation period, and its incidence is 1 in 2000–3000[1]. Masses in PKs are extremely rare, with an incidence estimated at 1 in 22,000,000[2]. Most cases of PK with renal mass have been managed with open radical nephrectomy. We present a case in which we performed laparoscopic radical nephrectomy (LRN) for a mass in the pelvic right kidney.

CASE REPORT
We report a 47-year-old male patient with a right pelvic kidney mass. The patient had attended the internal diseases polyclinic with diarrhoea and weight loss. The mass was detected by abdominal ultrasound. In computed tomography, there was a 60x46 mm exophytic mass in the upper pole which was heterogeneous (Fig. 1A, 1B, 1C). We evaluated the kidney’s vascular anatomy, position and dimensions of mass and pathological lymph nodes by performing triphasic abdominal computed tomography angiography (CTA). Three renal arteries and three renal veins were observed. The first artery originated from mid-section of abdominal aorta and continued to tumour location. The second artery originated from right anterolateral aspect of the bifurcation of distal abdominal aorta. This artery reached the renal hilus. The third artery originated from the proximal right common iliac artery and supplied the posterior surface of the kidney (Fig. 2A). The first vein originated from inferior vena cava and drained the upper pole of right kidney. The second vein originated from left anterior wall of inferior vena cava and drained the mid pole of right kidney. The third vein originated from anterior surface of left common iliac vein and drained the lower pole and hilum of right kidney (Fig. 2B).

Surgical technique
Once patient was under anaesthesia, we moved him into a modified left lateral position at 45-degree angle. We entered peritoneal cavity from right side of umbilicus with Veress needle and inflated the
abdominal cavity with CO₂ gas at 12 mm Hg. We placed three trocars in abdominal wall. The camera trocar was positioned in the same place as the Veress needle, trocar for right was placed on right hand side about 5 cm laterally from the umbilicus, and trocar for left hand was placed about 3 cm above symphysis pubis (Fig 3). Thirty degree telescope was used (Karl Storz, Tuttlingen, Germany).

Using the transperitoneal approach, right Toldt line was incised and caecum and ascending colon were dissected. We identified and dissected the three arteries, three veins and ureter of PK. We used XL size Hem-o-lock clips (Hem-o-lock, Weck Closure Systems, Research Triangle Park, NC, USA) and 45 mm laparoscopic linear stapler (EndoGIA, Ethicon, Cincinnati, OH, USA) to clamp and cut vascular structures and ureter. We extracted the specimen from 3 cm vertical incision between right hand trocar and subcostal area. A drainage catheter was placed. Operation time was 145 minutes, bleeding was 30 cc and there were no intraoperative or postoperative complication. We removed the catheter after 24 hours and the patient was discharged after 36 hours. Pathology revealed multicystic renal cell carcinoma. No recurrence was detected in follow-up of the patient on the 3rd, 6th, 12th, 18th and 24th months.

**DISCUSSION**

Laparoscopic surgery (LS) provides shorter hospitalization, less requirement for analgesia and better cosmetic appearance\(^3\). As surgeons have increased their laparoscopic experience, they have started to perform laparoscopic surgery in compelling cases who have anatomical variations\(^1\). LS for PK is different from standard surgery. To prevent a
limited working area, camera port and ports for other working trocars should not be close to each other. As transperitoneal approach provides better working area for PK than the retroperitoneal approach, it should be preferred initially. For interventions to right PK, dissecting caecum and ascending colon from the Toldt line without opening the perirenal tissues allows retroperitoneal area to be reached and the main vascular structures in the iliac region to be revealed. We reached kidney safely by transperitoneal approach guided by the preoperative CTA, which revealed neighboring and vascular structures.

LRN for renal cell carcinoma in PK has been rarely reported[1,4,5]. There are only a few reports of minimally invasive surgical approaches on tumors in PKs[6-10]. Gill et al and Chung et al performed LRN for PK mass (4.8 cm and 2.6 cm, respectively)[8,10]. They reported that LRN for PK mass is safe and efficacious. Ellen et al performed robotic partial nephrectomy on a mass of 2 cm in a PK and they stated that robotic surgery is ideal for this kind of cases[7]. Goel et al reported a case of mass in a PK evaluated by preoperative CTA, for which they successfully completed transperitoneal LRN surgery[6]. The current study also found preoperative CTA was useful and transperitoneal LRN was possible in these cases.

LS of a PK must be performed with care[11]. In order to reduce risks, the patient’s renal vascular structure and its relationship with neighbor organs must be delineated by preoperative CTA or magnetic resonance imaging angiography. Pre-operative detailed screening provides major benefits for this kind of surgeries, as it allows the establishment of dissection plan and enables tissue and vascular structures to be identified more easily during dissection. Accurate placement of trocar ports is an important part of the procedure with regards to ease of dissection during LS. In PK surgery, there is no standardized way of placing trocars. This should be performed entirely according to anatomic position of kidney and mass. Preoperative computed tomography or magnetic resonance imaging angiography methods are vital for this reason also[4,6,11,12].
CONCLUSION

LRN for a PK mass has been reported rarely in literature. Surgery for a PK is difficult due to anatomical and vascular variations. However, transperitoneal LRN can be performed safely in experienced centres, provided that vascular anatomy and surrounding structures are delineated with adequate preoperative screening methods.

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Author Contribution

Dr. Erkan Olcucuoglu performed the surgery and evaluated the patient. He also wrote the manuscript. Dr. Mahmut Taha Olcucu helped to research the literature and writing. Dr. Mustafa Ozdemir provided the imaging of the case.

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Informed Consent: Written informed consent was obtained from the patient.

REFERENCES

Case Report

Hemoperitoneum resulting from spontaneous splenic rupture

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ABSTRACT

Splenic rupture is commonly encountered after a history of blunt abdominal trauma, and the patient with this diagnosis underwent emergency laparotomy splenectomy to reduce the risk of hemorrhagic shock. In this report, we describe non-traumatic splenic rupture with previously chronic myelo-monocytic leukemia. We reported a 64-year-old female patient who suffered from left upper abdominal pain and general weakness for three days. This patient subsequently had hemorrhagic shock and received transarterial embolization intervention.

KEY WORDS: chronic myelo-monocytic leukemia, non-traumatic splenic rupture, transarterial embolization

INTRODUCTION

Splenic rupture is commonly encountered in patients experiencing blunt abdominal trauma resulting from athletic injury or motor vehicle accidents¹¹. When such patient’s present hypotension and extravasation of contrast medium of the spleen and hemoperitoneum on computed tomography (CT), emergency department (ED) physicians and the surgeon-on-call will arrange emergency splenectomy. We describe a patient with non-traumatic splenic rupture (NTSR) having a history of chronic myelo-monocytic leukemia (CMML) who received transarterial embolization (TAE) intervention. NTSR or pathological splenic rupture is extremely rare and is associated with hematological malignancies. Thus, awareness about this rare condition and timely diagnosis are required. The present case illustrates NTSR as the presenting symptom in a patient with a history of CMML. Our case report allows ED physicians to become cognizant of the diagnosis and management of this potential life-threatening condition, as well as reviews the potential clinical and radiographic indications of splenic rupture in a patient experiencing no trauma.

CASE REPORT

A 64-year-old woman presented to our ED with a chief complaint of left upper abdominal pain and general weakness for three days. On further questioning, she said that she had been feeling weak and had a poor appetite for the past week, yet she continued with her normal activities. She denied any contusion to the abdomen or chest wall in the recent two weeks. A review of her system was only positive for the aforementioned findings; she did not experience chest pain, diarrhea, shortness of breath, tarry stool, nausea/vomiting or consumed alcohol. She had a past medical history of CMML for which she was treated with Vidaza 110 mg once daily, the fifth cycle. She had not undergone any surgeries previously. Her vital
signs at triage were blood pressure, 100/58 mm Hg; heart rate, 59 beats/min; temperature, 36.4 °C; respiratory rate, 18 breaths/min; and oxygen saturation on room air was 99%. The patient was alert and oriented at the time of examination and in no apparent distress. Her skin was cold and diaphoretic. Her abdominal examination findings were as follows: the abdomen was soft and distended in the lower quadrants, with mild muscle guarding; no palpable liver or spleen, no masses, and no hernias were noted. The rest of her physical examination was nonspecific. Her initial laboratory examination results were significant for elevated white blood cells of $35.77 \times 10^3 / \mu L$, hemoglobin of 11.3 g/dL, platelet of $14 \times 10^3 / \mu L$, and
activated partial thromboplastin time >180 sec, international normalized ratio: 1.66 and creatinine of 0.7 mg/dL. CT with contrast medium of the abdomen was performed; findings revealed marked splenomegaly with multifocal infarcts and splenic rupture with ascites and hemoperitoneum (Fig 1). The patient was subsequently diagnosed with grade III hemorrhagic shock (blood pressure, 100/68 mm Hg; heart rate, 122 beats/min, respiratory rate, 24 breaths/min) from a spontaneous splenic rupture with laboratory abnormalities for acute leukemia. A surgeon was then consulted for operation evaluation, and TAE intervention was suggested first for suspected acute hemorrhage and abnormal coagulopathy (Fig 2). The intervention was performed smoothly and partial splenic embolization with 5% non-embolized splenic parenchyma at upper portion of the spleen was done. Hemostasis was achieved and the patient was transferred to intensive care unit for close monitor. Due to the concern of re-bleeding with unstable vital signs (hypotension and tachycardia) and drop of hemoglobin level (9.3 g/dL) despite blood transfusion, splenectomy was arranged two days after correction of coagulopathy. This patient was transferred to general ward after 41 days of intensive care unit admission. However, she contracted pneumonia and urine tract infection with septic shock after 12 days in general ward. Her family then requested for hospice care and the patient expired two months after admission.

**DISCUSSION**

CMML is a clonal hematopoietic stem cell disorder that is classified as myelodysplastic/myeloproliferative neoplasm by the 2008 World Health Organization classification of hematopoietic tumors[2]. Presenting symptoms of CMML are varied, including anemia, infection, bleeding, weight loss, night sweats and abdominal discomfort from splenomegaly.

Spleen is one of the most frequently injured organs during blunt or penetrating injury to the abdomen in traumatic cases. Ruptured spleen or laceration can cause serious life-threatening internal bleeding in a relatively short time. ED physicians and traumatic surgeons are cognizant of potential splenic impaction, and injuries are often discovered or ruled out early in the course of the patient’s emergent survey in traumatic commonality.

Carl von Rokitansky, a Bohemian physician and pathologist, first described a correlation between NTSR and leukemia in 1861; however, very few articles have been published. A case series study from 2007 mentioned that only 40 cases of splenic rupture associated with leukemia have been reported in the English literature[3]. However, when a patient with no traumatic injury or significant medical history, but only leukemia, presents to the ED with general complaints of malaise and abdominal pain, the differential diagnosis is extensive. The diagnosis of NTSR secondary to leukemia is extremely rare, and the potential for a delay or miss in diagnosis is high. Due to its rarity, we present this unique case as an opportunity to review the potential clinical, laboratory, physical and radiographic signs that may indicate NTSR and to discuss the management of NTSR.
A patient would suspect that splenic rupture usually results in hemorrhagic shock. Symptoms comprise tachycardia, hypotension and decreased perfusion to the extremities leading to pale, cool and clammy skin[4]. The patient in the present case initially exhibited both tachycardia and cold sweating. However, initial vital signs indicated that the patient was primarily able to compensate without hypotension. During physical examination, splenic injury often leads to left upper abdominal pain because this area overlies the spleen. A study noted this pain to only be present in approximately 14% of patients with splenic injury[5]. Physical examination of our patient revealed a soft and slightly distended lower abdomen, with mild muscle guarding. Physical examination for splenic pathology can vary widely and is difficult to confirm or rule out a diagnosis. Laboratory results unique to NTSR secondary to leukemia are consistent with those for hematomic malignancy. The results include monocytosis, leukocytosis, modest thrombocytopenia (although thrombocytosis may also be seen) and mild anemia. In this case, the patient’s initial laboratory results were consistent with these findings, including leukocytosis and thrombocytopenia.

As discussed above, patient’s initial appearance, physical examination, serum laboratory tests and initial vital signs are limited in their ability to confirm or rule out the diagnosis of NTSR. NTSR is on the list of the ED physician’s differential diagnosis at the time of presentation. Unfortunately, time is never an ED physician’s friend in case of splenic rupture, and the more expedient a diagnosis is made, the sooner emergent interventions can be performed. Although CT remains the gold standard, focused assessment with sonography in trauma has become a common adjunct to the ED physician’s repertoire when evaluating patients with traumatic abdominal injury and those with hemodynamic instability even without traumatic history[6]. CT scan findings consistent with splenic infarction and rupture include multifocal wedge-shaped hypo-enhanced areas at the periphery of the spleen with irregular splenic parenchyma, subcapsular fluid collection, ascites and hemoperitoneum, as observed in this patient[6].

Traditionally, most patients with splenic injury underwent emergency laparotomy splenectomy to reduce the risk of hemorrhagic shock. For this patient, she had grade III hemorrhagic shock despite her initial hemoglobin level of 11.3 g/dL. Ongoing hemorrhage of spleen was suspected due to unstable vital signs and surgical intervention was indicated. This surgery has associated morbidity and mortality risk, including hypotension after the induction of general anesthesia, overwhelming post-splenectomy infection and lifelong antibiotic prophylaxis. The development of advanced endovascular interventional techniques has led to a greater consideration of non-operative management for hemodynamically stable patients. Lin et al in their series of 13 patients showed that splenic TAE is safe and effective even in hemodynamically unstable patients[7]. Splenic TAE intervention for active hemorrhage, utilized to reduce risk of delayed hemorrhage, can be used[8]. Wahl et al in their series compared embolization to surgery and demonstrated a significantly lower number of complications in the TAE group (13%) than the surgical group (29%)[9]. A majority of trauma centers now opt for non-operative management in hemodynamically stable patients with splenic injury[10]. Splenic TAE intervention is increasingly being performed recently in comparison to surgical splenectomy, which has a higher risk of complication.

CONCLUSION

NTSR is extremely rare with a high morbidity and mortality rate. This unique case report provides an additional differential diagnosis for patients with the aforementioned symptoms and signs, indicating the risk of pathologic splenic infarction with rupture in patients with leukemia. Awareness about this rare condition and timely diagnosis are required.

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Author Contribution in the Manuscript
Ping-Yen Chung wrote the manuscript, Sen-Kuang Hou edited the references and Chun-Chieh Chao wrote and revised the manuscript.

Conflict of interest: The authors confirm that there is no conflict of interest.

REFERENCES
6. Miller LA, Mirvis SE, Shanmuganathan K, Ohson AS.


Dear Editor,

The never-ending multifaceted evolution of the third millennium has grasped the attention of many. The ones influenced by the internet, having excessive screen exposure, seem to be especially impressed by the famous quote “Any sufficiently advanced technology is indistinguishable from magic- Arthur C. Clarke”. Yet others, less impressed by this enchantment and utilizing it effectively, must be having strong self-control and might practice a more substantially disciplined life. The spectrum of problems due to this disguised opportunity may be as subtle as insomnia to as pathological as Internet Addiction Disorder or Problematic Internet Use[1].

The millennials were already used to a torpid lifestyle, nevertheless, the unwelcome coronavirus disease (COVID-19) in 2020 followed by lockdown, quarantines and home isolations have supplemented the sedentary situation[2]. Watching television is probably the most common recreation of the current time. Internet applications, chiefly Netflix, providing skillful streaming facility has literally left the impressionable spell bound[3]. There is no limit to this, and people can actually complete a season watching episodes back to back for hours. Similarly, the abundance of online gaming during this crisis has caused vulnerabilities to be exploited by authorities to promote their products in order to engage the youth confined to their houses[4]. Hence, due to the long-lasting impact of the COVID-19 pandemic, there is an increasing number of masses addicted to binge watching of television and excessive use of electronic gadgets, leading to psychological disorders on the solid ground.

There has been lack of physical activity; social distancing practice might have been perceived incorrectly. Lack of physical socialism has contributed to anxiety and depression amid the COVID-19 pandemic. Social distancing also reduces the possibility of peer pressure expected for technology misuse. Hence, there is a sheer chance of loss of self-control and over-indulgence in virtual reality. This leads not only to chronic mental, but inevitable physical deterioration of serious consequences[5]. In the long run, one can easily expect adults having mentally and physically challenged health states to either contribute least in their society or to add to socioeconomic burden[6]. The above factors convey that the social restriction and locked down states in most parts of the world can be a risky affair, especially if there is lack of guidance regarding efficient utilization of electronic gadgets.

There is an urgent need to make the concept of social distancing clear, as confusing it with avoiding or neglecting the social and cultural responsibilities by effective utilization of technology is unfair. Especially in an eastern culture like ours, where people are used to turning to each other when times get rough, this distancing might be perceived as disturbing in social context. The lack of this might be one reason for technology binging. The term spatial distance sounds more appropriate as it means to keep a physical distance only[7]. Hence, it is prima facie that it is the imprudent use of the internet which in reality may incur numerous life problems.
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Author’s Contribution

SK: Conception, design of published data and article drafting.

NN: Conception, design, acquisition of published data and proof reading the final draft.

REFERENCES


Brief Communication

Safe airway management of critically ill COVID-19 patients

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ABSTRACT

As the COVID-19 pandemic evolves, health care workers (HCWs) are facing lots of challenges due to the highly contagious nature of the virus. Undoubtedly, one of the most crucial and substantial steps of patient care is airway management, which represents a major risk of infection spread to HCWs and others. Safe airway management of critically ill patients is always challenging and primarily depends on staff training, simulation drills, pre-defined management protocols, and the availability of appropriate equipment. We present a COVID-19 airway management algorithm that we developed in our institution in order to provide our service in a timely manner, as well as ensure HCWs and other patients safety.

KEY WORDS: airway management, COVID-19, intubation, health workers

REPORT

The novel coronavirus continues to infect people globally. It is highly contagious and transmits predominantly by droplet, contact with a patient or contaminated surface, and airborne spread[]. Up to 70% of critically ill COVID-19 patients require mechanical ventilation, which is related to higher mortality rates[]. Intubation and other procedures during airway management may generate aerosols, which will result in risk of COVID-19 spread among health care workers (HCWs) and other patients[]. Nosocomial amplification is a common cause of spread among HCWs[]. HCWs who perform airway management are at high risk of exposure to the virus and might be associated with increased severity of illness[]. Aerosol-generating procedures, such as non-invasive ventilation, a high-flow nasal cannula, bag-mask ventilation, and intubation are of particularly high risk[]. Thus, one of the most crucial and substantial points in patient care is safety during airway management. To overcome the challenge, we developed an airway management algorithm for COVID-19 patients in our institution (Table 1) which we have implemented after providing regular simulation drills and training sessions on airway management of the COVID-19 patients in order to ensure staff awareness and familiarity of this challenging situation prior to dealing with COVID-19 patients.

The key step in airway management is organizing a dedicated COVID-19 airway rapid response team, which includes a physician that is experienced in airway management such as from anesthesia or intensive care background. In addition, there should be an experienced assistant such as anesthesia technician or ICU nurse as well as a third member who can assist with patient management such as drug administration and patient monitoring. There should also be a fourth member which is the runner, who should wait outside the patient room and assist in any tasks or supply of any necessary materials.

To minimize the task for the team and allow them adequate time for personal protective equipment (PPE) donning, we suggest using pre-prepared basic intubation and medication kits[]. These kits can be prepared in advance according to departmental preferences and availability of items, to ensure fast and safe practice. The most critical step in safely managing...
COVID-19 patients is to practice PPE donning in a prompt manner. The use of the unified sequence of PPE donning and doffing helps to ensure staff safety and to speed up the response time. The sequence of PPE donning and doffing may vary according to institutional infection control policy, but the critical steps are universal and important to follow (Table 2).

We have used UK guidelines along with new American Heart Association resuscitation guidelines to accumulate the proper safety tips and design our policy. To avoid delay in an emergency, we found it useful to wear disposable overall bodysuit all the time during the shift. This became a routine in our institution, as the physician is ready to attend the patient immediately if any emergency situation arises. The other point in doffing is to perform hand hygiene between each step and to remove respirator outside the patient room as the last step. The inadvertent self-contamination is important to keep in mind while doffing PPEs.

### Table 1: COVID-19 Airway management algorithm

| Planning | • Intervene early  
| • Early documented airway assessment  |
|---|---|
| Prepare & Communicate | • Anesthetist covering the area to activate COVID crash team  
| • Team members roles:  
| * Team leader (COVID anesthetist)  
| * 2nd Airway member (anesthetist of the assign area)  
| * COVID Technician (airway and medication assistant)  
| * Bed side nurse (if available)  
| * Runner (outside the room).  |
| • Communicate with your team intubation plan before entering the room  
| • Intubation plan by Team leader:  
| * COVID Technician to collect intubation kit and Ambu bag with HME filter.  
| * Disposable video-laryngoscope (VL) or VL with disposable blade & reusable screen (if available).  
| * Additional equipment (if needed).  |
| • Medications: (to be prepared by anesthetist covering the area, outside the room)  
| • Rapid sequence induction:  
| * IV hypnotic agent (Midazolam/Ketamine/Propofol)  
| * Muscle relaxant (Succinylcholine or Rocuronium 1.2 mg/kg)  
| * Sugammadex, Atropine, Ephedrine, Phenylephrine, Adrenaline  
| * Additional Medications (if needed)  |
| Preoxygenation | • Cover the patient face and upper body with plastic cover  
| • Keep patient 45° head up position  
| • Assemble Ambu bag or MAP C circuit, connect oxygen tubing and (Heat and Moisture Exchangers) HME filter  
| • Preoxygenation with low flow O2 by bag or Mapleson C circuit (preferred hands out of drapes) with two hands technique, avoid any positive pressure breaths  
| • 2nd airway member prepare endotracheal tube (ETT), lubricate and connect viral filter (if available) + 10 ml syringe connected to ETT cuff  |
| Intubation | • Give medications as advice by team leader.  
| • Ensure full muscle relaxation before intubation (no coughing and bucking)  
| • Remove plastic cover, roll it with Ambu bag and face mask inside, keep Ambu bag and disposable laryngoscope in the plastic bag till transfer to ICU and then discard in biohazard bag  
| • Intubate, inflate cuff, connect circuit with capnography and closed suction, start the ventilator, 2nd airway member to review ventilator settings.  
| • Perform all required procedures before leaving the room, like nasogastric intubation (NGT), Foleys catheter, invasive lines, bronchoalveolar lavage (BAL) or deep tracheal aspirate for investigations  |
| Extubation | • Full PPE gear till patient shifted to ICU  
| • Do closed suction and put plastic drape over the patient face and upper body  
| • Do oral suction and put large gauze or towel on the mouth near ETT  
| • Put the ventilator standby  
| • Deflate ETT cuff, extubate, wrap the ETT tube with the towel and discard immediately in the biohazard bin  
| • Disconnect circuit with HME filter toward the ventilator  
| • Remove plastic drape while the assistant is putting NRM  |

COVID emergency medication kit with the content list

- One each of the following medications: pre-filled Adrenaline syringe, pre-filled Atropine syringe, Ephedrine ampoule, Ketamine 500 mg, Propofol 200 mg, Rocuronium 50 mg.
- Other items with quantities: pre-filled flush syringe (2), water for injections 10 ml (2), needles 18G (2), syringes 5 ml (4), syringes 10 ml (4), alcohol swabs (2), cannula 18 and 20 G (one each), extension line (1). COVID intubation kit with the content list
  - Endotracheal tubes size 7.0/7.5/8.0/8.5 one each, oropharyngeal airway sizes 4.5 one each, one tube tie, lubricant, one scalpel, one HME filter, disposable laryngoscope sizes 3, 4 one each, one 10 ml syringe, and one bougie.
During preoxygenation, the technician/nurse should prepare endotracheal tube (ETT), lubricate with gel, connected to heat and moisture exchanger/viral filter (if available) and a 10 ml syringe for ETT with gel, connected to heat and moisture exchanger/should prepare endotracheal tube (ETT), lubricate Foley’s catheter, bronchoalveolar lavage, or tracheal leaving the room like invasive lines, nasogastric tube, virus spread. To limit staff exposure and to conserve the ventilator should be on stand-by mode, to avoid inadvertent circuit disconnection with a running during the procedure. Close observation is needed to avoid inadvertent circuit disconnection with a running ventilator. However, in case airway maneuver is needed and disconnection required, all members inside the patient room should be alarmed and tube clamps should be applied. Before the tube removal, the ventilator should be on stand-by mode, to avoid virus spread. To limit staff exposure and to conserve PPE, perform all the required procedures before leaving the room like invasive lines, nasogastric tube, Foley’s catheter, bronchoalveolar lavage, or tracheal aspirate for investigations.

New respiratory viruses are emerging each year, posing new challenges to the health care community. We aimed to highlight the key element in managing COVID airway emergencies and to develop a simple airway algorithm to encourage safe, accurate and swift performance. The suggested algorithm is based on available consensus at the time of writing and one should be aware that practice may differ in other countries. In this period of global crisis, we hope our suggestions will be of great value and may help others in optimizing safety practices in COVID airway emergencies.

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REFERENCES
Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Surgical site infection following cesarean section in a general hospital in Kuwait: trends and risk factors

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Surgical site infections (SSI) are a significant cause of post-surgical morbidity and mortality. The objectives of this study were to determine the prevalence of SSI and identify risk factors for infections following cesarean section (CS). A prospective study of SSI after CS was carried out from January 2014 to December 2016 using the methodology of the American National Nosocomial Infection Surveillance System. Suspected SSIs were confirmed clinically by the surgeon, and or, by culture. Seven thousand two hundred thirty five CS were performed with an overall SSI prevalence of 2.1%, increasing from 1.7% in 2014 to 2.95% in 2016 (P = 0.010). Of 152 cases of SSI, the prevalence of infection was 46.7% in women ⩽ 30 years and 53.3% in women >30 years (P = 0.119). Of 148 culture samples from as many women, 112 (75.7%) yielded growth of microorganisms with 42 (37.5%) of isolates being multi-drug resistant (MDR). Women who did not receive prophylactic antibiotics (35.5%) developed SSI more often than those who did (P < 0.0001). These findings suggest that emergency CS and inappropriate antibiotic prophylaxis are risk factors for developing SSI. In the light of the emergence of MDR bacteria there is a need to implement revised prophylactic antibiotic policy as part of antimicrobial stewardship to decrease SSI rates.

Prevalence of Primary Headache Disorders in Kuwait

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BACKGROUND
Only an insignificant quantum of data exists on the prevalence of primary headaches among those living in Kuwait. We aimed to determine the prevalence of primary headaches among the Kuwaiti population.

METHODS
This community-based study included Kuwaiti population aged 18-65 years. Using systematic random sampling, data was collected by the Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation questionnaire. Responses to the diagnostic questions were transformed into diagnoses algorithmically to confirm the diagnosis of primary headache.
RESULTS
A total of 15,523 patients were identified of whom 9,527 (61%) were diagnosed with primary headache disorder; a female predominance of 62.2% was observed. The mean age was 34.84 ± 10.19. Tension-type headache (TTH) was the most prevalent at 29% followed by episodic migraine (23.11%), chronic migraine (5.4%), and medication overuse headache (2.4%). Primary headache prevalence declined steadily from 71% in those aged 18-30 years to 23% in those over 50 (p < 0.037). The female:Male ratio was 1.7:1. Frequency and severity of primary headache were correlated significantly with lost work days (r = 0.611, p < 0.001 and r = 0.102, p = 0.001, respectively).

CONCLUSIONS
In Kuwait, primary headache disorder is more frequent in young adults and females. TTH followed by episodic migraine were the more prevalent types of headache. Higher frequency and severe headaches were associated with increasing social and work-related burden.

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**Period prevalence and factors associated with road traffic crashes among young adults in Kuwait**

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OBJECTIVES
This cross-sectional study assessed one-year period prevalence of road traffic crashes (RTC\(s\)) and examined the factors associated with RTC\(s\) among young adults in Kuwait.

DESIGN AND SETTINGS
During December 2016, 1500 students enrolled in 15 colleges of Kuwait University were invited to participate in the study. Students 18 years old or older and who drive by themselves were eligible. Data were collected using a structured self-administered questionnaire. One-year period prevalence of RTC\(s\) (\(\geq\)1 vs. none) was computed. Multivariable log-binomial regression model was used to identify the risk factors associated with one-year period prevalence of RTC\(s\).

RESULTS
Of 1500 invited individuals, 1465 (97.7%) participated, of which 71.4% (1046/1465) were female, 56.4% (804/1426) were aged between 21 and 25 years, and 67.1% (980/1460) were Kuwaitis. One-year period prevalence of RTC was 38.9%. The final multivariable log-binomial regression model showed that after adjusting for the influences of other variables in the model, participants were more likely to have had at least one RTC during the past year, if they habitually sped over limit (adjusted PR = 1.19; 95% confidence interval (CI): 1.04-1.36), crossed a red light (adjusted PR = 1.33; 95% CI: 1.16-1.52), or if they have had three or more speeding tickets (adjusted PR = 1.40; 95% CI: 1.13-1.73) compared to those who reportedly had no RTC during the same period.

CONCLUSION
One-year period prevalence of RTC\(s\) among university students in Kuwait, though relatively lower than the reported figures in similar populations elsewhere in the region, is yet high enough to warrant diligent attention. Habitual speeding, having had three or more speeding tickets, and the practice of crossing a red light were significantly and independently associated with at least one RTC during the past year. Targeted education and enforcement of existing traffic laws may reduce the RTC\(s\) frequency in this relatively young population. Future studies may look at impact of such interventions.
The place of death of patients with cancer in Kuwait

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BACKGROUND
The place of death (PoD) has a significant effect on end-of-life care for patients dying of cancer. Little is known about the place of cancer deaths in our region.

METHODS
To identify the PoD of patients with cancer in Kuwait, we reviewed the death certificates submitted to the Kuwait Cancer Registry in 2009.

RESULTS
Of 611 cancer deaths, 603 (98.7%) died in hospitals and only 6 (1%) patients died at home. More than half (57.3%) of inhospital deaths were in the Kuwait Cancer Control Center. Among those for whom the exact PoD within the hospital was identified (484 patients), 116 (24%) patients died in intensive care units and 12 (2.5%) patients died in emergency rooms.

CONCLUSIONS
This almost exclusive inhospital death of patients with cancer in Kuwait is the highest ever reported. Research is needed to identify the reasons behind this pattern of PoD and to explore interventions promoting out-of-hospital death among terminally ill cancer patients in Kuwait.

Prevalence of food allergy among schoolchildren in Kuwait and its association with the coexistence and severity of asthma, rhinitis, and eczema: A cross-sectional study

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BACKGROUND
Food allergy (FA) is a common public health problem that affects both children and adults. Empirical knowledge of the burden of FA in Kuwait is limited. This study sought to estimate the prevalence of FA among schoolchildren in Kuwait and assess associations between FA and the coexistence and severity of asthma, rhinitis, and eczema.

METHODS
Schoolchildren aged 11-14 years (n = 3,864) were enrolled in a cross-sectional study. Parents completed questionnaires regarding their children’s early life exposures and clinical history of FA and allergic diseases. Study-defined FA was ascertained by a convincing clinical history. Associations were assessed
using Poisson regression with robust variance estimation, and adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) were estimated.

RESULTS
The 12-month prevalence of study-defined FA was estimated to be 4.1% (154/3,738), with more girls being affected than boys (aPR = 1.44, 95% CI: 1.04-1.99). Egg (2.7%), fish (1.6%), shellfish (1.3%), peanut (1.3%), and tree nut (1.2%) were the most reported offending food allergens. Underweight and adiposity, cesarean section delivery, exposure to household dogs during infancy, and parental history of doctor-diagnosed FA were associated with an increased prevalence of study-defined FA. However, later birth order was associated with a reduced prevalence of study-defined FA. The prevalence of eczema only was higher in children with study-defined FA than in those without study-defined FA (aPR = 3.49, 95% CI: 2.37-5.14). In contrast, this association was not pronounced for children who had asthma only (aPR = 1.56, 95% CI: 0.94-2.57) or rhinitis only (aPR = 1.40, 95% CI: 0.86-2.28). Study-defined FA was associated with a 9.20-fold (95% CI: 4.50-18.78) higher prevalence of coexisting asthma, rhinitis, and eczema. Moreover, study-defined FA was associated with increased severity of symptoms of asthma, rhinitis, and eczema.

CONCLUSIONS
FA affects a considerable proportion of schoolchildren in Kuwait, and the most reported offending food allergens are similar to those reported in Western countries. Study-defined FA was associated with the coexistence and increased severity of asthma, rhinitis, and eczema, indicating that FA may link the comanifestations of allergic diseases and contribute to their chronicity and severity.
Forthcoming Conferences and Meetings

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International Conference and Expo on Drug Discovery, Designing and Development
Dec 02, 2020
Dominican Republic, Santo Domingo
Contact: Universal Research Cluster
Email: info@universal-conference.com

International Conference on Advances in Health and Medical Science (ICAHMS)
Dec 04, 2020
United Kingdom, Glasgow
Contact: SAARD
Email: info.saard.org@gmail.com

988th International Conference on Recent Advances in Medical Science (ICRAMS)
Dec 05, 2020
Sweden, Stockholm
Contact: Theier
Email: info@theier.org

International Conference on Healthcare and Clinical Gerontology (ICHCG)
Dec 05, 2020
South Korea, Incheon
Contact: Sciencefora
Email: info.sciencefora@gmail.com

962nd International Conference on Medical and Health Sciences (ICMHS)
Dec 06, 2020
New Zealand, Hamilton
Contact: ISERD
Email: info@iserd.co

International Conference on Biological and Medical Sciences
Dec 08, 2020
United Kingdom, London
Contact: ARSSS
Email: info.arssss@gmail.com

965th International Conference on Medical, Biological and Pharmaceutical Sciences (ICMBPS)
Dec 09, 2020
Japan, Kyoto
Contact: IASTEM
Email: info@iastem.org

817th International Conference on Pharma and Food (ICPAF)
Dec 12, 2020
France, Paris
Contact: Academicsera
Email: info@academicsera.com

International Conference on Recent Advancement in Medical Education, Nursing, and Health Sciences
Dec 17, 2020
Australia, Sydney
Contact: IRFconference
Email: info.irfconference@gmail.com

971st International Conference on Medical and Health Sciences (ICMHS)
Dec 19, 2020
Italy, Florence
Contact: ISERD
Email: info@iserd.co

International Conference on Medical and Health Sciences
Dec 21, 2020
United States, Oakland
Contact: Scienceplus
Email: papers.scienceplus@gmail.com

World Congress on Medical and Health Informatics
Dec 23, 2020
Cyprus, Larnaca
Contact: Conference Fora
Email: info@conferencefora.org

International Conference on Science, Health and Medicine (ICSHM)
Dec 25, 2020
Canada, Regina
Contact: ISER
Email: info@iser.co

International Conference on Recent Advances in Medical, Medicine and Health Sciences
Dec 26, 2020
Italy, Rome
Contact: WRFER
Email: contact.wrfer@gmail.com
International Virtual Conference on COVID-19 and its Effect (IVCCE)  
Dec 29, 2020  
Russian Federation, Moscow  
Contact: Conference Online  
Email: info@conferenceonline.net

International Conference on Medical Health Science, Pharmacology & Bio Technology (ICMPB)  
Dec 30, 2020  
Canada, Ottawa  
Contact: ISSRD  
Email: papers.issrd@gmail.com

International Conference on Oncology & Cancer Research (ICOCR)  
Dec 31, 2020  
India, Erode, Tamil Nadu  
Contact: Scienceplus  
Email: papers.scienceplus@gmail.com

World Conference on Cancer Research and Drug Development  
Jan 01, 2021  
Mali, Bamako  
Contact: World Research Society  
Email: info@worldresearchsociety.com

International Conference on Science, Health and Medicine (ICSHM)  
Jan 02, 2021  
Germany, Berlin  
Contact: ISER  
Email: info@iser.co

Global Conference on Pharma Industry and Medical Devices  
Jan 03, 2021  
Singapore, Singapore  
Contact: Inter Globe Research Network  
Email: info@igrnet.org

World Congress on Medical and Biological Engineering  
Jan 06, 2021  
Scotland, Glasgow  
Contact: Eurasia Web  
Email: info@eurasiaweb.com

831st International Conference on Sports Nutrition and Supplements (ICSNS)  
Jan 06, 2021  
Australia, Melbourne  
Contact: Academicsera  
Email: info@academicsera.com

International Conference on Tissue Science and Regenerative Medicine  
Jan 10, 2021  
Cyprus, Limassol  
Contact: Eurasia Web  
Email: info@eurasiaweb.com

879th International Conference on Food Microbiology and Food Safety (ICFMFS)  
Jan 13, 2021  
France, Cannes  
Contact: Theiier  
Email: info@theiier.org

838th International Conference on Pharma and Food (ICPAF)  
Jan 16, 2021  
United States, Boston  
Contact: Academicsera  
Email: info@academicsera.com

International Conference on Recent Advances in Medical Science (ICRAMS)  
Jan 17, 2021  
United States, Orlando  
Contact: Theiier  
Email: info@theiier.org

International Conference on Medical and Biosciences (ICMBS)  
Jan 17, 2021  
United States, Denver  
Contact: Researchworld  
Email: info@researchworld.org

839th International Conference on Sports Nutrition and Supplements (ICSNS)  
Jan 18, 2021  
United Kingdom, London  
Contact: Academicsera  
Email: info@academicsera.com

International Conference on Recent Advances in Medical and Health Sciences (ICRAMHS)  
Jan 18, 2021  
United Kingdom, Manchester  
Contact: Academicsworld  
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World Congress on Medical and Health Informatics  
Jan 21, 2021  
Scotland, Dundee  
Contact: Conference Fora  
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International Conference on Recent Advances in Medical and Health Sciences (ICRAMHS)
Jan 26, 2021
Italy, Milan
Contact: Academicsworld
Email: info@academicsworld.org

International Conference on Medical, Biological and Pharmaceutical Sciences (ICMBPS)
Jan 27, 2021
Canada, Ottawa
Contact: IASTEM
Email: info@iastem.org

International Conference on Medical and Health Sciences (ICMHS)
Jan 28, 2021
Kuwait, Kuwait City
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International Conference on Tissue Science and Regenerative Medicine
Jan 29, 2021
Belarus, Gomel
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World Conference on Cancer Research and Drug Development
Feb 04, 2021
Maldives, Male
Contact: World Research Society
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International Conference and Expo on Drug Discovery, Designing and Development
Feb 05, 2021
Jordan, Amman
Contact: Universal Research Cluster
Email: info@universal-conference.com

International Conference on Cell and Tissue Science
Feb 06, 2021
Scotland, Glasgow
Contact: Conference Fora
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International Conference on Cell and Tissue Science
Feb 10, 2021
Cyprus, Limassol
Contact: Conference Fora
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International Conference on Cell and Tissue Science
Feb 19, 2021
Kenya, Kisumu
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International Conference on Cell and Tissue Science
Feb 20, 2021
Iraq, Baghdad
Contact: Conference Fora
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International Conference on Science, Health and Medicine (ICSHM)
Feb 22, 2021
Canada, Vancouver
Contact: ISER
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International Conference on Tissue Science and Regenerative Medicine
Feb 23, 2021
Jamaica, Montego Bay
Contact: Eurasia Web
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International Conference on Medical and Biosciences (ICMBS)
Feb 25, 2021
South Africa, Johannesburg
Contact: Researchworld
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International Conference on Medical and Biosciences (ICMBS)
Feb 26, 2021
Mexico, Mexico City
Contact: Researchworld
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International Conference on Science, Health and Medicine (ICSHM)
Feb 26, 2021
United Arab Emirates, Dubai
Contact: ISER
Email: info@iser.co
World Conference on Cancer Research and Drug Development  
Feb 27, 2021  
Armenia, Vanadzor  
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International Conference on Medical, Biological and Pharmaceutical Sciences (ICMBPWS)  
Mar 01, 2021  
Ireland, Dublin  
Contact: IASTEM  
Email: info@iastem.org

International Conference on Recent Advances in Medical Science (ICRAMS)  
Mar 01, 2021  
United Arab Emirates, Dubai  
Contact: Theiier  
Email: info@theiier.org

International Conference and Expo on Drug Discovery, Designing and Development  
Mar 02, 2021  
Slovakia, Kosice  
Contact: Universal Research Cluster  
Email: info@universal-conference.com

International Conference on Recent Advances in Medical Science (ICRAMS)  
Mar 03, 2021  
Germany, Munich  
Contact: Theiier  
Email: info@theiier.org

International Conference on Cancer Research and Drug Development  
Mar 05, 2021  
Jordan, Amman  
Contact: Universal Research Cluster  
Email: info@universal-conference.com

International Conference on Science, Health and Medicine (ICSHM)  
Mar 05, 2021  
Australia, Sydney  
Contact: ISER  
Email: info@iser.co

International Conference on Tissue Science and Regenerative Medicine  
Mar 06, 2021  
Scotland, Glasgow  
Contact: Eurasia Web  
Email: info@eurasiaweb.com

International Conference on Sports Nutrition and Supplements (ICSNS)  
Mar 07, 2021  
United Kingdom, London  
Contact: Academicsera  
Email: info@academicsera.com

International Conference on Medical and Biosciences (ICMBS)  
Mar 08, 2021  
Japan, Osaka  
Contact: Researchworld  
Email: info@researchworld.org

Dubai International Pharmaceutical & Technology Conference & Exhibition  
Mar 09, 2021  
United Arab Emirates, Dubai  
Contact: INDEX® Conferences & Exhibitions Organisation Est.  
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International Conference on Sports Nutrition and Supplements (ICSNS)  
Mar 10, 2021  
Qatar, Doha  
Contact: Academicsera  
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International Conference on Recent Advances in Medical Science (ICRAMS)  
Mar 12, 2021  
France, Paris  
Contact: Theiier  
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World Conference on Cancer Research and Drug Development  
Mar 18, 2021  
Georgia, Atlanta  
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World Conference on Cancer Research and Drug Development  
Mar 19, 2021  
Slovakia, Bratislava  
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International Conference on Science, Health and Medicine (ICSHM)  
Mar 20, 2021  
United States, San Diego  
Contact: ISER  
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International Conference on Recent Advances in Medical Science (ICRAMS)
Mar 21, 2021
Italy, Venice
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International Conference on Food Microbiology and Food Safety (ICFMFS)
Mar 22, 2021
Spain, Madrid
Contact: Theires
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International Conference on Medical, Biological and Pharmaceutical Sciences (ICMBPS)
Mar 28, 2021
Kuwait, Kuwait City
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Euro Cardiology Summit 2021
Apr 15, 2021
United Kingdom, London
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1059th International Conference on Medical and Biosciences (ICMBS)
May 22, 2021
Spain, Madrid
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WHO-Facts Sheet

1. Heat and health
2. Infertility
3. Lymphatic filariasis
4. Mental health: Strengthening our response

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1. HEAT AND HEALTH

KEY FACTS

• Population exposure to heat is increasing due to climate change, and this trend will continue. Globally, extreme temperature events are observed to be increasing in their frequency, duration, and magnitude. Between 2000 and 2016, the number of people exposed to heat waves increased by around 125 million. In 2015 alone, 175 million additional people were exposed to heat waves compared to average years.

• Single events can last weeks, occur consecutively, and result in significant excess mortality. In 2003, 70,000 people in Europe died as a result of the June-August event, in 2010, 56,000 excess deaths occurred during a 44-day heatwave in the Russian Federation.

• Exposure to excessive heat has wide ranging physiological impacts for all humans, often amplifying existing conditions and resulting in premature death and disability.

• The negative health impacts of heat are predictable and largely preventable with specific public health actions. WHO has issued public health guidance for the general public and medical professionals on coping with extreme heat.

Overview

Global temperatures and the frequency and intensity of heatwaves will rise in the 21st century as a result of climate change. Extended periods of high day and nighttime temperatures create cumulative physiological stress on the human body which exacerbates the top causes of death globally, including respiratory and cardiovascular diseases, diabetes mellitus and renal disease. Heatwaves can acutely impact large populations for short periods of time, often trigger public health emergencies, and result in excess mortality, and cascading socioeconomic impacts (e.g. lost work capacity and labor productivity). They can also cause loss of health service delivery capacity, where power-shortages which often accompany heatwaves disrupt health facilities, transport, and water infrastructure.

Awareness remains insufficient of the health risks posed by heatwaves and prolonged exposure to increased temperatures. Health professionals must adjust their planning and interventions to account for increasing temperatures and heatwaves. Practical, feasible, and often low-cost interventions at the individual, community, organizational, governmental and societal levels, can save lives

Who is affected?

Rising global ambient temperatures affect all populations. However, some populations are more exposed to, or more physiologically or socio-economically vulnerable to physiological stress, exacerbated illness, and an increased risk of death from exposure to excess heat. These include the elderly, infants and children, pregnant women, outdoor and manual workers, athletes, and the poor. Gender can play an important role in determining heat exposure

How does heat impact health?

Heat gain in the human body can be caused by a combination of external heat from the environment and internal body heat generated from metabolic processes. Rapid rises in heat gain due to exposure to hotter than average conditions compromises the body’s ability to regulate temperature and can result in a cascade of illnesses, including heat cramps, heat exhaustion, heatstroke, and hyperthermia.
Deaths and hospitalizations from heat can occur extremely rapidly (same day), or have a lagged effect (several days later) and result in accelerating death or illness in the already frail, particularly observed in the first days of heatwaves. Even small differences from seasonal average temperatures are associated with increased illness and death. Temperature extremes can also worsen chronic conditions, including cardiovascular, respiratory, and cerebrovascular disease and diabetes-related conditions.

Heat also has important indirect health effects. Heat conditions can alter human behavior, the transmission of diseases, health service delivery, air quality, and critical social infrastructure such as energy, transport, and water. The scale and nature of the health impacts of heat depend on the timing, intensity and duration of a temperature event, the level of acclimatization, and the adaptability of the local population, infrastructure and institutions to the prevailing climate. The precise threshold at which temperature represents a hazardous condition varies by region, other factors such as humidity and wind, local levels of human acclimatization and preparedness for heat conditions.

What actions should the public take?

Keep your home cool
- Aim to keep your living space cool. Check the room temperature between 08:00 and 10:00, at 13:00 and at night after 22:00. Ideally, the room temperature should be kept below 32 °C during the day and 24 °C during the night. This is especially important for infants or people who are over 60 years of age or have chronic health conditions.
- Use the night air to cool down your home. Open all windows and shutters during the night and the early morning, when the outside temperature is lower (if safe to do so).
- Reduce the heat load inside the apartment or house. Close windows and shutters (if available) especially those facing the sun during the day. Turn off artificial lighting and as many electrical devices as possible.
- Hang shades, draperies, awnings or louvers on windows that receive morning or afternoon sun.
- Hang wet towels to cool down the room air. Note that the humidity of the air increases at the same time.
- If your residence is air conditioned, close the doors and windows and conserve electricity not needed to keep you cool, to ensure that power remains available and reduce the chance of a community-wide outage.
- Electric fans may provide relief, but when the temperature is above 35 °C, may not prevent heat-related illness. It is important to drink fluids.

Keep out of the heat
- Move to the coolest room in the home, especially at night.
- If it is not possible to keep your home cool, spend 2–3 hours of the day in a cool place (such as an airconditioned public building).
- Avoid going outside during the hottest time of the day.
- Avoid strenuous physical activity if you can. If you must do strenuous activity, do it during the coolest part of the day, which is usually in the morning between 4:00 and 7:00.
- Stay in the shade.
- Do not leave children or animals in parked vehicles.

Keep the body cool and hydrated
- Take cool showers or baths. Alternatives include cold packs and wraps, towels, sponging, foot baths, etc.
- Wear light, loose-fitting clothes of natural materials. If you go outside, wear a wide-brimmed hat or cap and sunglasses.
- Use light bed linen and sheets, and no cushions, to avoid heat accumulation.
- Drink regularly, but avoid alcohol and too much caffeine and sugar.
- Eat small meals and eat more often. Avoid foods that are high in protein

Help others
- Plan to check on family, friends, and neighbours who spend much of their time alone. Vulnerable people might need assistance on hot days.
- Discuss extreme heat-waves with your family. Everyone should know what to do in the places where they spend time.
- If anyone you know is at risk, help him or her to get advice and support. Elderly or sick people living alone should be visited at least daily.
- If a person is taking medication, ask the treating doctor how it can influence thermoregulation and the fluid balance.
- Get training. Take a first-aid course to learn how to treat heat emergencies and other emergencies. Everyone should know how to respond.

If you have health problems
- Keep medicines below 25 °C or in the refrigerator (read the storage instructions on the packaging).
- Seek medical advice if you are suffering from a chronic medical condition or taking multiple medications.
If you or others feel unwell

- Try to get help if you feel dizzy, weak, anxious or have intense thirst and headache; move to a cool place as soon as possible and measure your body temperature.
- Drink some water or fruit juice to rehydrate.
- Rest immediately in a cool place if you have painful muscular spasms (particularly in the legs, arms or abdomen, in many cases after sustained exercise during very hot weather), and drink oral rehydration solutions containing electrolytes. Medical attention is needed if heat cramps last more than one hour.
- Consult your doctor if you feel unusual symptoms or if symptoms persist. If one of your family members or people you assist presents hot dry skin and delirium, convulsions and/or unconsciousness, call a doctor/ambulance immediately. While waiting for help, move the person to a cool place, put him or her in a horizontal position and elevate legs and hips, remove clothing and initiate external cooling, for example, by placing cold packs on the neck, axillae and groin, fanning continuously and spraying the skin with water at 25–30 °C. Measure the body temperature. Do not give acetylsalicylic acid or paracetamol. Position an unconscious person on his or her side.

2. INFERTILITY

KEY FACTS

- Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.(1)

- Infertility affects millions of people of reproductive age worldwide – and has an impact on their families and communities. Estimates suggest that between 48 million couples and 186 million individuals live with infertility globally. (2, 3, 4)

- In the male reproductive system, infertility is most commonly caused by problems in the ejection of semen (1), absence or low levels of sperm, or abnormal shape (morphology) and movement (motility) of the sperm.

- In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others.

- Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved.

- Fertility care encompasses the prevention, diagnosis and treatment of infertility. Equal and equitable access to fertility care remains a challenge in most countries; particularly in low and middle-income countries. Fertility care is rarely prioritized in national universal health coverage benefit packages.

What causes infertility?

Infertility may be caused by a number of different factors, in either the male or female reproductive systems. However, it is sometimes not possible to explain the causes of infertility.

In the female reproductive system, infertility may be caused by:

- tubal disorders such as blocked fallopian tubes, which are in turn caused by untreated sexually transmitted infections (STIs) or complications of unsafe abortion, postpartum sepsis or abdominal/pelvic surgery;
- uterine disorders which could be inflammatory in nature (such as such endometriosis), congenital in nature (such as septate uterus), or benign in nature (such as fibroids);
- disorders of the ovaries, such as polycystic ovarian syndrome and other follicular disorders;
- disorders of the endocrine system causing imbalances of reproductive hormones. The endocrine system includes hypothalamus and the pituitary glands. Examples of common disorders affecting this system include pituitary cancers and hypopituitarism.

The relative importance of these causes of female infertility may differ from country to country, for example due to differences in the background prevalence of STIs, or differing ages of populations studied.4

In the male reproductive system, infertility may be caused by:

- obstruction of the reproductive tract causing dysfunctionalities in the ejection of semen. This blockage can occur in the tubes that carry semen (such as ejaculatory ducts and seminal vesicles). Blockages are commonly due to injuries or infections of the genital tract.
- hormonal disorders leading to abnormalities in hormones produced by the pituitary gland, hypothalamus and testicles. Hormones such as testosterone regulate sperm production. Example of disorders that result in hormonal imbalance include pituitary or testicular cancers.
- testicular failure to produce sperm, for example
due to varicoceles or medical treatments that impair sperm-producing cells (such as chemotherapy).
• abnormal sperm function and quality. Conditions or situations that cause abnormal shape (morphology) and movement (motility) of the sperm negatively affect fertility. For example, the use of anabolic steroids can cause abnormal semen parameters such as sperm count and shape. Environmental and lifestyle factors such as smoking, excessive alcohol intake and obesity can affect fertility. In addition, exposure to environmental pollutants and toxins can be directly toxic to gametes (eggs and sperm), resulting in their decreased numbers and poor quality, leading to infertility.5 6

**Why addressing infertility is important?**

Every human being has a right to the enjoyment of the highest attainable standard of physical and mental health. Individuals and couples have the right to decide the number, timing and spacing of their children. Infertility can negate the realisation of these essential human rights. Addressing infertility is therefore an important part of realizing the right of individuals and couples to found a family.7

A wide variety of people, including heterosexual couples, same-sex partners, older persons, individuals who are not in sexual relationships and those with certain medical conditions, such as some HIV sero-discordant couples and cancer survivors, may require infertility management and fertility care services. Inequities and disparities in access to fertility care services adversely affect the poor, unmarried, uneducated, unemployed and other marginalised populations.

Addressing infertility can also mitigate gender inequality. Although both women and men can experience infertility, women in a relationship with a man are often perceived to suffer from infertility, regardless of whether they are infertile or not. Infertility has significant negative social impacts on the lives of infertile couples and particularly women, who frequently experience violence, divorce, social stigma, emotional stress, depression, anxiety and low self-esteem.

In some settings, fear of infertility can deter women and men from using contraception if they feel socially pressured to prove their fertility at an early age because of a high social value of childbearing. In such situations, education and awareness-raising interventions to address understanding of the prevalence and determinants of fertility and infertility is essential.

**Addressing challenges**

Availability, access, and quality of interventions to address infertility remain a challenge in most countries. Diagnosis and treatment of infertility is often not prioritized in national population and development policies and reproductive health strategies and are rarely covered through public health financing. Moreover, a lack of trained personnel and the necessary equipment and infrastructure, and the currently high costs of treatment medicines, are major barriers even for countries that are actively addressing the needs of people with infertility.

While assisted reproduction technologies (ART) have been available for more than three decades, with more than 5 million children born worldwide from ART interventions such as in vitro fertilization (IVF), these technologies are still largely unavailable, inaccessible and unaffordable in many parts of the world, particularly in low and middle-income countries (LMIC).

Government policies could mitigate the many inequities in access to safe and effective fertility care. To effectively address infertility, health policies need to recognize that infertility is a disease that can often be prevented, thereby mitigating the need for costly and poorly accessible treatments. Incorporating fertility awareness in national comprehensive sexuality education programmes, promoting healthy lifestyles to reduce behavioural risks, including prevention, diagnosis and early treatment of STIs, preventing complications of unsafe abortion, postpartum sepsis and abdominal/pelvic surgery, and addressing environmental toxins associated with infertility, are policy and programmatic interventions that all governments can implement.

In addition, enabling laws and policies that regulate third party reproduction and ART are essential to ensure universal access without discrimination and to protect and promote the human rights of all parties involved. Once fertility policies are in place, it is essential to ensure that their implementation is monitored, and the quality of services is continually improved.

**WHO response**

WHO recognizes that the provision of high-quality services for family-planning, including fertility care services, is one of the core elements of reproductive health. Recognizing the importance and impact of infertility on people’s quality of life and well-being, WHO is committed to addressing infertility and fertility care by:
• Collaborating with partners to conduct global epidemiological and etiological research into infertility.

• Engaging and facilitating policy dialogue with countries worldwide to frame infertility within an enabling legal and policy environment.

• Supporting the generation of data on the burden of infertility to inform resource allocation and provision of services.

• Developing guidelines on the prevention, diagnosis and treatment of male and female infertility, as part of the global norms and standards of quality care related to fertility care.

• Continually revising and updating other normative products, including the WHO laboratory manual for the examination and processing of human semen.

• Collaborating with relevant stakeholders including academic centres, ministries of health, other UN organizations, non-state actors (NSAs) and other partners to strengthen political commitment, availability and health system capacity to deliver fertility care globally.

• Providing country-level technical support to member states to develop or strengthen implementation of national fertility policies and services.

REFERENCES


3. LYMPHATIC FILARIASIS

KEY FACTS

• Lymphatic filariasis impairs the lymphatic system and can lead to the abnormal enlargement of body parts, causing pain, severe disability and social stigma.

• 893 million people in 49 countries worldwide remain threatened by lymphatic filariasis and require preventive chemotherapy to stop the spread of this parasitic infection.

• In 2000 over 120 million people were infected, with about 40 million disfigured and incapacitated by the disease.

• Lymphatic filariasis can be eliminated by stopping the spread of infection through preventive chemotherapy with safe medicine combinations repeated annually. More than 7.7 billion treatments have been delivered to stop the spread of infection since 2000.

• 597 million people no longer require preventive chemotherapy due to successful implementation of WHO strategies.

• A basic, recommended package of care can alleviate suffering and prevent further disability among people living with disease caused by lymphatic filariasis.

Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. Infection occurs when filarial parasites are transmitted to humans through mosquitoes. Infection is usually acquired in childhood causing hidden damage to the lymphatic system.

The painful and profoundly disfiguring visible manifestations of the disease, lymphoedema, elephantiasis and scrotal swelling occur later in life and can lead to permanent disability. These patients are not only physically disabled, but suffer mental, social and financial losses contributing to stigma and poverty.

In 2018, 893 million people in 49 countries were living in areas that require preventive chemotherapy to stop the spread of infection.

The global baseline estimate of people affected by lymphatic filariasis was 25 million men with hydrocele and over 15 million people with lymphoedema. At least 36 million people remain with these chronic disease manifestations. Eliminating lymphatic filariasis can prevent
unnecessary suffering and contribute to the reduction of poverty.

**Cause and transmission**

Lymphatic filariasis is caused by infection with parasites classified as nematodes (roundworms) of the family Filarioidea. There are 3 types of these thread-like filarial worms:

- *Wuchereria bancrofti*, which is responsible for 90% of the cases
- *Brugia malayi*, which causes most of the remainder of the cases
- *Brugia timori*, which also causes the disease.

Adult worms nest in the lymphatic vessels and disrupt the normal function of the lymphatic system. The worms can live for approximately 6–8 years and, during their life time, produce millions of microfilariae (immature larvae) that circulate in the blood.

Mosquitoes are infected with microfilariae by ingesting blood when biting an infected host. Microfilariae mature into infective larvae within the mosquito. When infected mosquitoes bite people, mature parasite larvae are deposited on the skin from where they can enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms, thus continuing a cycle of transmission.

Lymphatic filariasis is transmitted by different types of mosquitoes for example by the Culex mosquito, widespread across urban and semi-urban areas, *Anopheles*, mainly found in rural areas, and *Aedes*, mainly in endemic islands in the Pacific.

**Symptoms**

Lymphatic filariasis infection involves asymptomatic, acute, and chronic conditions. The majority of infections are asymptomatic, showing no external signs of infection while contributing to transmission of the parasite. These asymptomatic infections still cause damage to the lymphatic system and the kidneys, and alter the body’s immune system.

When lymphatic filariasis develops into chronic conditions it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele (scrotal swelling). Involvement of breasts and genital organs is common. Such body deformities often lead to social stigma and sub-optimal mental health, loss of income-earning opportunities and increased medical expenses for patients and their caretakers. The socioeconomic burdens of isolation and poverty are immense.

Acute episodes of local inflammation involving skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema or elephantiasis. Some of these episodes are caused by the body’s immune response to the parasite. Most are the result of secondary bacterial skin infection where normal defences have been partially lost due to underlying lymphatic damage. These acute attacks are debilitating, may last for weeks and are the primary cause of lost wages among people suffering with lymphatic filariasis.

**WHO response**

World Health Assembly resolution WHA50.29 encourages Member States to eliminate lymphatic filariasis as a public health problem. In response, WHO launched its Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000. In 2012, the WHO neglected tropical diseases roadmap reconfirmed the target date for achieving elimination by 2020.

WHO’s strategy is based on 2 key components:

- stopping the spread of infection through large-scale annual treatment of all eligible people in an area or region where infection is present; and
- alleviating the suffering caused by lymphatic filariasis through provision of the recommended basic package of care.

**Large-scale treatment (preventive chemotherapy)**

Elimination of lymphatic filariasis is possible by stopping the spread of the infection through preventive chemotherapy. The WHO recommended preventive chemotherapy strategy for lymphatic filariasis elimination is mass drug administration (MDA). MDA involves administering an annual dose of medicines to the entire at-risk population. The medicines used have a limited effect on adult parasites but effectively reduce the density of microfilariae in the bloodstream and prevent the spread of parasites to mosquitoes.

The MDA regimen recommended depends on the co-endemicity of lymphatic filariasis with other filarial diseases. WHO recommends the following MDA regimens:

- albendazole (400 mg) alone twice per year for areas co-endemic with loiasis
- ivermectin (200 mcg/kg) with albendazole (400 mg) in countries with onchocerciasis
- diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in countries without onchocerciasis

Recent evidence indicates that the combination of all three medicines can safely clear almost all microfilariae from the blood of infected people within a few weeks, as opposed to years using the routine two-medicine combination.

WHO now recommends the following MDA regimen in countries without onchocerciasis:

- ivermectin (200 mcg/kg) together with diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in certain settings
The impact of MDA depends on the efficacy of the regimen and the coverage (proportion of total population ingesting the medicines). MDA with the two-medicine regimens have interrupted the transmission cycle when conducted annually for 4–6 years with effective coverage of the total population at risk. Salt fortified with DEC has also been used in a few unique settings to interrupt the transmission cycle.

At the start of GPELF, 81 countries were considered endemic for lymphatic filariasis. Further epidemiological data reviewed since, indicate that preventive chemotherapy was not required in 10 countries. From 2000 to 2018, 7.7 billion treatments were delivered to more than 910 million people at least once in 68 countries, considerably reducing transmission in many places. The overall economic benefit of the programme during 2000-2007 is conservatively estimated at US$ 24 billion. Treatments until 2015 are estimated to have averted at least US$ 100.5 billion of economic loss expected to have occurred over the lifetime of cohorts who have benefited from treatment.

Sixteen countries and territory (Cambodia, The Cook Islands, Egypt, Kiribati, Maldives, Marshall Islands, Niue, Palau, Sri Lanka, Thailand, Togo, Tonga, Vanuatu, Viet Nam, Wallis and Futuna, and Yemen) are now acknowledged as achieving elimination of lymphatic filariasis as a public health problem. Seven additional countries have successfully implemented recommended strategies, stopped large-scale treatment and are under surveillance to demonstrate that elimination has been achieved. Preventive chemotherapy is still required in 49 countries and within 15 of these countries MDA has not yet been delivered to all endemic areas as of the end of 2018.

Morbidity management

Morbidity management and disability prevention are vital for improving public health and are essential services that should be provided by the health care system to ensure sustainability. Surgery can alleviate most cases of hydrocele. Clinical severity and progression of the disease, including acute inflammatory episodes, can be reduced and prevented with simple measures of hygiene, skin care, exercises, and elevation of affected limbs. People with lymphoedema must have access to continuing care throughout their lives, both to manage the disease and to prevent progression to more advanced stages.

The GPELF aims to provide access to a minimum package of care for every person with associated chronic manifestations of lymphatic filariasis in all areas where the disease is present, thus alleviating suffering and promoting improvement in their quality of life.

Success in 2020 will be achieved if patients have access to the following minimum package of care:

- treatment for episodes of adenolymphangitis (ADL);
- guidance in applying simple measures to manage lymphoedema to prevent progression of disease and debilitating, inflammatory episodes of ADL;
- surgery for hydrocele;
- treatment of infected people with antifilarial medicines

Vector control

Mosquito control is a supplemental strategy supported by WHO. It is used to reduce transmission of lymphatic filariasis and other mosquito-borne infections. Depending on the parasite-vector species, measures such as insecticide-treated nets, indoor residual spraying or personal protection measures may help protect people from infection. The use of insecticide-treated nets in areas where Anopheles is the primary vector for filariasis enhances the impact on transmission during and after MDA. Historically, vector control has in select settings contributed to the elimination of lymphatic filariasis in the absence of large-scale preventive chemotherapy.

4. MENTAL HEALTH: STRENGTHENING OUR RESPONSE

KEY FACTS

- Mental health is more than the absence of mental disorders.
- Mental health is an integral part of health; indeed, there is no health without mental health.
- Mental health is determined by a range of socioeconomic, biological and environmental factors.
- Cost-effective public health and intersectoral strategies and interventions exist to promote, protect and restore mental health.

Mental health is an integral and essential component of health. The WHO constitution states: “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” An important implication of this definition is that mental health is more than just the absence of mental disorders or disabilities.

Mental health is a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community.
Mental health is fundamental to our collective and individual ability as humans to think, emote, interact with each other, earn a living and enjoy life. On this basis, the promotion, protection and restoration of mental health can be regarded as a vital concern of individuals, communities and societies throughout the world.

**Determinants of mental health**

Multiple social, psychological, and biological factors determine the level of mental health of a person at any point of time. For example, violence and persistent socio-economic pressures are recognized risks to mental health. The clearest evidence is associated with sexual violence.

Poor mental health is also associated with rapid social change, stressful work conditions, gender discrimination, social exclusion, unhealthy lifestyle, physical ill-health and human rights violations.

There are specific psychological and personality factors that make people vulnerable to mental health problems. Biological risks include genetic factors.

**Mental health promotion and protection**

Mental health promotion involves actions that improve psychological well-being. This may involve creating an environment that supports mental health.

An environment that respects and protects basic civil, political, socio-economic and cultural rights is fundamental to mental health. Without the security and freedom provided by these rights, it is difficult to maintain a high level of mental health.

National mental health policies should be concerned both with mental disorders and, with broader issues that promote mental health. Mental health promotion should be mainstreamed into governmental and nongovernmental policies and programmes. In addition to the health sector, it is essential to involve the education, labour, justice, transport, environment, housing, and welfare sectors.

**Specific ways to promote mental health include:**

- early childhood interventions (e.g. providing a stable environment that is sensitive to children’s health and nutritional needs, with protection from threats, opportunities for early learning, and interactions that are responsive, emotionally supportive and developmentally stimulating);
- support to children (e.g. life skills programmes, child and youth development programmes);
- socio-economic empowerment of women (e.g. improving access to education and microcredit schemes);
- social support for elderly populations (e.g. befriending initiatives, community and day centres for the aged);
- programmes targeted at vulnerable people, including minorities, indigenous people, migrants and people affected by conflicts and disasters (e.g. psycho-social interventions after disasters);
- mental health promotional activities in schools (e.g. programmes involving supportive ecological changes in schools);
- mental health interventions at work (e.g. stress prevention programmes);
- housing policies (e.g. housing improvement);
- violence prevention programmes (e.g. reducing availability of alcohol and access to arms);
- community development programmes (e.g. integrated rural development);
- poverty reduction and social protection for the poor;
- anti-discrimination laws and campaigns;
- promotion of the rights, opportunities and care of individuals with mental disorders.

**Mental health care and treatment**

In the context of national efforts to develop and implement mental health policy, it is vital to not only protect and promote the mental well-being of its citizens, but also address the needs of persons with defined mental disorders.

Knowledge of what to do about the escalating burden of mental disorders has improved substantially over the past decade. There is a growing body of evidence demonstrating both the efficacy and cost-effectiveness of key interventions for priority mental disorders in countries at different levels of economic development. Examples of interventions that are cost-effective, feasible, and affordable include:

- treatment of depression with psychological treatment and, for moderate to severe cases, antidepressant medicines;
- treatment of psychosis with antipsychotic medicines and psychosocial support;
- taxation of alcoholic beverages and restriction of their availability and marketing.

A range of effective measures also exists for the prevention of suicide, prevention and treatment of mental disorders in children, prevention and treatment of dementia, and treatment of substance-use disorders. The mental health Gap Action Programme (mhGAP) has produced evidence based guidance for non-specialists to enable them to better identify and manage a range of priority mental health conditions.

**WHO response**

WHO supports governments in the goal of strengthening and promoting mental health. WHO has evaluated evidence for promoting mental health and is working with governments to disseminate this
information and to integrate effective strategies into policies and plans.

In 2013, the World Health Assembly approved a “Comprehensive Mental Health Action Plan for 2013-2020”. The Plan is a commitment by all WHO’s Member States to take specific actions to improve mental health and to contribute to the attainment of a set of global targets.

The Action Plan’s overall goal is to promote mental well-being, prevent mental disorders, provide care, enhance recovery, promote human rights and reduce the mortality, morbidity and disability for persons with mental disorders. It focuses on 4 key objectives to:

- strengthen effective leadership and governance for mental health;
- provide comprehensive, integrated and responsive mental health and social care services in community-based settings;
- implement strategies for promotion and prevention in mental health; and
- strengthen information systems, evidence and research for mental health.

Particular emphasis is given in the Action Plan to the protection and promotion of human rights, the strengthening and empowering of civil society and to the central place of community-based care.

In order to achieve its objectives, the Action Plan proposes and requires clear actions for governments, international partners and for WHO. Ministries of Health will need to take a leadership role, and WHO will work with them and with international and national partners, including civil society, to implement the plan. As there is no action that fits all countries, each government will need to adapt the Action Plan to its specific national circumstances.
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