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OUR GRATITUDE

The Editorial Board of the Kuwait Medical Journal
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I have been detailing the risks of some medical tests and procedures, for which I was criticised by many. Now, a large body of USA physicians have voiced similar opinions, which were sent to me by a patient.

1. **Avoid inducing labour or C-section before 39 weeks.** Delivery prior to 39 weeks is associated with increased risk of learning disabilities, respiratory problems and other potential risks. While sometimes induction prior to 39 weeks is medically necessary, the recommendation is clear that simply having a mature fetal lung test, in the absence of appropriate clinical criteria, is not an indication for delivery. (American College of Obstetricians and Gynaecologists: American Academy of Family Physicians).

2. **Avoid routine annual pap testing** in average risk women, and routine annual Pep tests (cervical cytology screenings) offer no advantage. (American College of Obstetricians and Gynaecologists).

3. **Avoid CT scans to evaluate minor head injuries.** Approximately 50% of children who visit hospital emergency departments with head injuries are given a CT scan. CT scanning is associated with radiation exposure that may escalate future cancer risk. CT technology exposes patients to approximately 100 times the radiation of a standard chest X-ray, which itself increases the risk of cancer. The recommendation calls for clinical observation prior to making a decision about needing a CT. (American Academy of Paediatrics).

4. **Avoid stress test using echocardiography.** The recommendation states that there is very little information on the benefits of using stress echocardiography in asymptomatic individuals for the purposes of cardiovascular risk assessment, as a stand-alone test or in addition to conventional risk factors. (American Society of Echocardiography).

5. **Avoid prescribing type 2 diabetes medication to achieve tight glycaemic control.** The recommendation states that there is no evidence that using medicine to tightly control blood sugar in older diabetics is beneficial. In fact, using medications to strictly achieve low blood sugar level is associated with harms, including higher mortality rates. (American Geriatrics Society).

6. **Avoid EEGs on patients with recurrent headaches.** Recurrent headache is the most common problem, affecting up to 20% of people. The recommendations state that EEG has no advantage over headache, does not improve outcomes, and increases costs. (American Academy of Neurology).

7. **Avoid routinely treating acid reflux.** Anti Reflux Therapy, which is commonly prescribed in adults, has no demonstrated effect in reducing the symptoms of gastroesophageal reflux disease (GERD) in infants, and there is emerging evidence that it may in fact be harmful in certain situations. (Society of Hospital Medicine).
8. **Avoid lipid profile tests.** Lipid profile test checks various parameters of blood, such as cholesterol (good or high density lipoprotein as well as bad or low density lipoprotein) and triglyceride levels. Several scientific papers have proven that people with high so-called “bad” LDL cholesterol live the longest, and there are now a large number of findings that contradict the lipid hypothesis that cholesterol has to be lowered at all.

9. **Avoid mammograms.** Mammograms and breast screening have had no impact on breast cancer deaths, and have actually been found to increase breast cancer mortality. With tail radiation, mammogram testing compresses sensitive breast tissue causing pain and possible tissue damage. To make matters worse, the false negative and false positive rates of mammography are a troubling 30% and 89% respectively. Another concern is that many breast cancers occur below the armpits; however, mammography completely misses this auxiliary region, viewing only breast tissue compressed between two plates of glass. Considering these drawbacks, breast thermography should be given closer consideration. Thermography is a non-invasive and non-toxic technique which can detect abnormalities before the onset of a malignancy, as early as 10 years before being recognized by mammography. This makes it a much safer and potentially lifesaving health test for women who are unknowingly developing abnormalities, as it can take several years for cancerous tumour to develop and be detected by a mammogram.

10. **Avoid PSA testing.** A PSA blood test looks for prostate specific antigen, a protein produced by the prostate gland. High levels are supposedly associated with prostate cancer. The problems are that association is not always correct, and when it is, the prostate cancer is not necessarily deadly. Nearly 20% of men will be diagnosed with prostate cancer, which sounds scary, but 3% of all men die from it. The PSA test usually leads to over diagnosis - biopsies and treatment in which the side effects are impotence and incontinence. Moreover, there is some evidence which suggests that biopsies and treatment actually aggravate prostate cancer. During a needle biopsy, a tumour may need to be punctured several times to retrieve an amount of tissue that is adequate enough to be screened. It is believed that this repeated penetration may spread cancer cells to the track formed by the needle, or by spilling cancerous cells directly into the bloodstream or lymphatic system.

11. **Avoid routine colorectal cancer screening.** Colorectal cancer screening often results in unnecessary removal of benign polyps which are of no threat to patients and the risks of their treatment or removal far exceed any benefit. The evidence is insufficient to assess the benefits and harms of computed tomographic colonography and faecal DNA testing as screening modalities for colorectal cancer.

12. **Avoid DEXA.** Dual energy X-ray absorptiometry is a technique developed in the 1980s that measures, among many things, bone mineral density. The scans can determine bone strength and signs of osteopenia, a possible precursor to osteoporosis. Limitations abound, though. Measurements vary from scan to scan of the same person, as well as from machine to machine. DEXA does not capture the collagen to mineral ratio, which is more predictive of bone strength than just mineral density. Also, higher bone mineral density does not necessarily mean stronger bones, for someone with more bone mass will have more minerals but could have weaker bones.

If only people had listened to me in the last three decades, they could have saved their health and precious money.
Hysterosalpingography in the assessment of uterine cavity: A wide spectrum of acquired structural pathology

Firoozeh Ahmadi, Fatemeh Zafarani, Gholam Shahrzad
Department of Reproductive Imaging at Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran

ABSTRACT

Hysterosalpingography (HSG) has been used for various indications in clinical gynecology for many years. Despite recent developments in reproductive imaging and various diagnostic options such as magnetic resonance imaging, ultrasonography, laparoscopy and hysteroscopy, HSG is still a quick and minimally invasive method in the early evaluation of infertility. This method provides valuable diagnostic information about the inner surface of the uterine cavity, fallopian tubes and endocervical canal. The technical quality of the HSG is important to avoid misinterpretations.

The teamwork between the gynecologist and radiologist should be presented at HSG for appropriate evaluation and diagnostic workup of infertile couple. This review describes the normal variants and a spectrum of acquired structural pathology involving uterus along with their imaging features on HSG. The radiographic appearances of technical artifacts, normal variants, benign and malignant endometrial neoplasm, intrauterine synechiae, retained products of conception and foreign bodies within the uterine cavity will be discussed.

INTRODUCTION

Uterine abnormalities account for about 10 - 15% of the cases of infertility and abnormal uterine findings are reported in approximately in 50% of women with infertility[1]. Abnormalities of the uterus can be described as either congenital or acquired. Acquired uterine abnormalities may interfere with uterine structure or function and affect endometrial receptivity that leads to subinfertility, recurrent implantation failures or preterm delivery. As a result, investigation of the uterine cavity is one of the initial steps in female infertility workup. Clinical imaging is essential in stratification of the different abnormalities of the uterus. Despite recent developments in reproductive imaging and various diagnostic options such as magnetic resonance imaging (MRI), ultrasound, laparoscopy and hysteroscopy, hysterosalpingography (HSG) is still a fast and minimally invasive method in the early evaluation of infertility. This method is the radiographic study of the uterine cavity and fallopian tubes after introduction of a radio-opaque contrast through the cervical canal. Although HSG is limited to evaluate the external uterine contour adequately[2], it provides valuable diagnostic information about the uterine cavity and allows clinicians to observe any filling defects or irregularities, and define the general configuration of the cavity[3,4]. In comparison with hysteroscopy, HSG has been reported to have high sensitivity (79 - 81%) and specificity (80 - 82%) in the detection of intrauterine abnormalities[3,4].

We retrospectively reviewed 41,407 HSGs performed over a 31-year period (January 1985 – December 2015) by one author (GS). The indications for HSG were infertility, abnormal uterine bleeding, lost IUD and symptoms related to uterine fibroids.

LITERATURE REVIEW

The present article intends to review the normal variants and pathological conditions involving uterus along with their imaging features on HSG. These findings should be considered by all radiologists and gynecologists for precise diagnosis and optimal management.

The cases with structural lesions, such as...
endometrial polyp, leiomyoma, endometrial hyperplasia and carcinoma, adenomyosis, intrauterine synechiae, early pregnancy, and retained products of conception were confirmed by other diagnostic tools such as hysteroscopy with directed biopsy, ultrasound and/or cytological results.

Embryology of female genital tract

Around the 6th week of development, the female embryo’s reproductive system begins growth from the paired Müllerian (paramesonephric) ducts, fusing to create the uterus, cervix, and upper two-thirds of the vagina. The process involves three main stages including the development of both Mullerian ducts, fusion, and septal absorption that form the fallopian tube, uterus, cervix and upper two thirds of the vagina. At week 12, the uterus presents its triangular configuration. Mesonephric or Wolffian ducts play an important role as inductors for development of Müllerian ducts. There is controversy over formation of the vagina. The results of most studies have demonstrated that the vagina forms from both mesonephric ducts and Mullerian tubercle[5].

By week 20, the vagina is completely canalized and the process of development is completed.

Radiographic anatomy of the uterus

The uterine cavity is variable in shape and size. In the normally anteflexed uterus, the uterine cavity is observed as inverted triangular. The contour of the fundus may be straight, convex or slightly concave. Mild fundic concavity is normal and differentiated from a malformed arcuate uterus. An arcuate uterus should be characterized when the ratio between the height of the fundal indentation and the distance between the lateral apices of the horns is less than 10%[6].

The convexity of the fundal outline is moderate unless the whole uterine cavity is overestimated by a large amount of contrast material introduced under high pressure or extreme antero-posterior flexion is present. The lateral margins of the uterine cavity may be straight, concave or (rarely) convex.

The normal radiographic appearance of the cornual lumen is pear-shaped and may be separated from the uterine cavity by a short lucent line. This linear lucency is owing to the localized muscular contraction corresponding to the tubal sphincter.

Lateral displacement of the uterus is considered a common normal variant, unless the other evidence of a pathologic process causes uterine displacement.

The uterine isthmus is the transition between the cervix and the uterine body. Its length and width are approximately 1.5 cm and 0.05 cm respectively[6]. Some patients show a well-defined, narrow internal os and others show virtually no definition of the internal os, having a gradual, funnel-shaped internal os. The diameter of internal os ranges from 1 - 10 mm. The diameter of the internal os varies in the same patient during different phases of the menstrual cycle.

Patient preparation

Specific patient preparation is not required for HSG. The patient should be instructed to abstain from sexual intercourse from the time menstrual bleeding ends until the day of the study to avoid a potential pregnancy. Most patients can tolerate the procedure with minimal discomfort.

However, in cases suspicious for tubal occlusion, the patients may have more pelvic pain, thus requiring a slower medium injection. Prior to the procedure, a patient may be given a mild sedative or a pain relief medication to minimize any potential discomfort. Administration of one of the prostaglandin synthesizer inhibitors 30 minutes before the procedure reduces the patient’s discomfort and diminishes errors associated with HSG[7]. Some physicians prescribe an antibiotic prior to and/or after the procedure. The choice antibiotic is doxycycline, 100 mg twice daily, starting the day before HSG and continuing for 3 to 5 days[7].

Indications and contraindications

HSG is recommended for any condition that requires morphological demonstration of the endocervical canal, uterine cavity and uterine tubes for clinical decisions. It is indicated in early evaluation of the infertile couple. Potentially serious causes contributing to infertility, such as tubal occlusion, intrauterine synechiae or uterine anomalies are diagnosed readily[7]. The procedure is often used to examine the reasons that may be associated with repeated miscarriages[8]. Recently, HSG has become important prior to using assisted reproductive methods, such as gamete and zygote intrafallopian transfer and in vitro fertilization and is an integral part of transcervical tubal recanalization techniques[9]. The other advantage of HSG for infertile couples is the therapeutic effect of the procedure. It has been recognized that, after a normal HSG finding, the infertile patient has a 30% chance to conceive spontaneously within the first 3 months[9].

Contraindications for HSG are acute pelvic inflammatory disease with abdominal tenderness or palpable mass, recent uterine and tubal surgery, active uterine bleeding, pregnancy and allergic reaction to the contrast medium[7].

Normal variants and non pathological findings

The radiographic appearance of the uterine cavity and tubes is affected by various factors such
as technique of HSG, type of contrast medium used, and the amount and pressure of the contrast material injected. The technical quality of the HSG is important to provide sufficient information for proper interpretation. Variation in the position of the normal uterus or cyclic changes in the endometrium may cause a different normal appearance.

**Technical artifact**

**Air bubble**

Air bubbles may be inadvertently injected into the uterine cavity during HSG and sometimes mistaken for other intratubular filling defects such as polyps, submucosal myomas, or endometrial hyperplasia. Air bubbles manifest as transient solitary or multiple rounds, well-circumscribed lucencies which are usually identified by their mobility (Fig 1a)[10,11]. Another indication to prove its true nature is that they collect in the non-dependent portion of the uterus when the patient turns.

Introduction of air bubbles can be prevented by introducing the instrument into contrast medium prior to initiation of the procedure. Air bubble is usually removed by additional injection of contrast material to the uterine cavity.

**Cervical mucus and blood clots**

Sometimes cervical mucus is retrogradely pushed through the uterine cavity and produces an unusual filling defect. On HSG, an amorphous mass often appears in linear shape without obvious rounded contour (Fig 1b). The subsequent image represents disappearing of this mobile filling defect.

Blood clots owing to either pre-existing bleeding or trauma of the instrumentation are another cause of such mobile filling artifacts, which should be differentiated from a polyp or submucosal myoma. Usually, blood clots are mobile and displaced by more injection of contrast into the uterine cavity. Transvaginal ultrasound is useful in the assessment of blood clots. A thin endometrial lining with echogenic material within the endometrial cavity separating from uterus is suggestive of adherent blood clots.

**Venous or lymphatic intravasation**

Intravasation of contrast media into the venous plexus or lymphatic system can occur in up to 6% of patients undergoing HSG[12]. The contrast transits from the uterine cavity directly to myometrial vessels, subsequently entering the pelvic veins.

The most common causative factor is excessive pressure within the uterine cavity during injection[12]. Other predisposing factors are recent endometrial instrumentation (surgery, biopsy, endometritis, dilatation and curratage), acute endometritis, tubal occlusion and synechiae; especially when intrauterine pressure is markedly elevated.
Intravasation of contrast is diagnosed by HSG. The radiographic appearance of early intravasation is represented as filling of multiple thin beaded channels following an ascendant course (Fig 2). When vascular channels are outlined by contrast, their appearances are transitory and become clear in seconds as a reflection of normal blood flow. Contrast in thin delicate lymphatics is differentiated from blood vessels by their thinner caliber and slower emptying.

**Tubal spasm**

Fallopian tube spasm is a temporary tubal muscle contraction which mimics a true proximal tubal obstruction. At radiography, tubal spasm cannot be distinguished from a tubal occlusion. Tubal spasm usually occurs in patients with high levels of stress and anxiety. Cornual spasm should be differentiated from true organic obstruction of the proximal fallopian tube. Many drugs such as analgesia and antispasmodic agents have been administered to reduce lower abdominal pain and to prevent tubal muscular spasms.

Rotation of the patient toward the non-filling side or placing her prone while introducing more contrast often reveals previously non-visualized tubes.

**Normal variants**

**Myometrial folds**

Normal myometrial folds are multiple longitudinal linear filling defects parallel to the long axis of the uterine cavity and appear in 0.6% of HSGs. They are usually observed at 5 - 10 mm linear defects in early stages of HSG (Fig 3). Although the exact etiology is unknown, it is probably the result of undulations on the inner surface of the myometrium or the remnants of mullerian duct fusion during fetal development. These folds are not associated with endometrial abnormalities and are diagnosed by HSG.

**Double-outlined uterine cavity**

HSG should be scheduled during the proliferative phase, 2 - 5 days after cessation of menstrual flow. The procedure should be avoided during an early pregnancy. If HSG is performed during the late secretory phase or if it is accidentally done on an early pregnancy patient, a double uterine contour may be seen as a thin line of contrast that surrounds the uterine cavity (Fig 4). This rare normal variation

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Fig 2: Intravasation of contrast medium into the venous and lymphatic channels (arrows) secondary to bilateral tubal occlusion.

Fig 3: Longitudinal myometrial uterine folds parallel to the long axis of the uterine cavity (arrows) owing to undulation of the inner surface of the myometrium.

Fig 4: Double outlined uterine cavity (DOUC). Hysterographic double outline uterine cavity following contrast penetrating endometrial gland in secretory phase (arrow).
occurs in about 1% of HSGs and is not associated with infertility or obstetric complications\textsuperscript{[15]}.

**Spiculated uterine cavity**

Fine spiculation of the uterine cavity is occasionally visible on HSGs by using water-soluble contrast material. The cause of these spiculations is not clear. This spiculation may be associated with a thin, inactive endometrial and atrophic uterus, caused by lack of hormonal stimulation (both pre- and postmenopausal), exogenous hormonal suppression and sometimes other pathologic conditions such as tuberculosis\textsuperscript{[16]}. Occasionally, the contrast medium may have entered mucosal glands, possibly due to pressure of the injection and the impairing of endometrial surface, and produce spiculated uterine appearance (Fig 5). Available method for its diagnosis is HSG\textsuperscript{[3]}. HSG shows uterus with diffuse irregularities and spiculated aspects.

**Polypoid defects in uterine cavity**

Sometimes, normal endometrium shows polypoid filling defects ranging from 5 mm to 10 mm in diameter without any clinical importance\textsuperscript{[17]}.

This normal variation should not be confused with endometrial hyperplasia producing a shaggy and irregular contour in the contrast medium, found in patients with a history of amenorrhea and menstrual irregularities. Hysterosalpingographic features of the polypoid filling defects are similar to small submucous leiomyomas or endometrial polyps (Fig 6).

![Fig 5](image1.png)  
**Fig 5**: Fine spiculation in a pre-menopausal uterine cavity (long arrow). Hysterosalpingography of a woman with a history of abnormal uterine bleeding showed entrance of contrast into the mucosal glands. The biopsy showed atrophic endometrium. Note the filling defect observed in cervical canal was owing to rapid evacuation of contrast medium. It is not pathologically significant (short arrow).

![Fig 6](image2.png)  
**Fig 6**: Multiple filling defects in a septate uterus (arrows). The patient had a history of oligomenorrhoea. Note the normal contour and size of the uterine cavity. This normal variation should not be confused with endometrial hyperplasia which produces a shaggy and irregular contour.

On transvaginal sonography, the endometrium is asymmetrically thickened and irregular. In doppler evaluation, the presence of color flow within the lesion, excludes polypoid defects from a blood clot.

Moreover, further hysteroscopic investigation provides a more precise analysis of this normal endometrial variation from submucous leiomyomas and polyps.

**Acquired structural abnormalities of the uterus**

The uterine cavity shows various imaging manifestations in addition to the normal manifestation such as reactive, inflammatory, benign and malignant neoplasm. Intrauterine abnormalities can be found only if they are of sufficient size, distort the uterine cavity or present as a mass with displacement of the contrast medium. Acquired uterine abnormalities are an important cause of infertility. Intrauterine
abnormalities often present as filling defects, outpouchings or uterine wall irregularities. Abnormalities of the uterine cavity which can be diagnosed by HSG are endometrial lesions such as benign/malignant endometrial neoplasms, intrauterine synechiae; abnormalities of the myometrium include submucous and intramural leiomyomas as well as foreign bodies in the uterine cavity.

**Uterine neoplasms**

**Endometrial polyp**

Endometrial polyps are common benign localized endometrial tumors, which are usually found in women between 40 and 50 years of age[18].

The prevalence of endometrial polyps ranges from 10%[18] in symptomatic women to 33%[19] in symptomatic patients, but polyps is much higher in postmenopausal women[20]. Clinically endometrial polyp can cause abnormal uterine bleeding, infertility, recurrent abortion, infection endometritis or pain.

Abnormal bleeding mostly results from vascular fragility, chronic inflammatory changes and surface erosions. Endometrial polyps may occur in the setting of endometrial hyperplasia or less commonly, carcinoma[21]. Hormonal factors in patients taking hormone replacement therapy[22] or tamoxifen treated women[23] may be associated with endometrial abnormalities such as polyp.

Endometrial polyps can be single or multiple, small or large, pedunculated or sessile. Recognition of endometrial polyps is very important to avoid unnecessary operation.

On HSG, the endometrial polyp appears as a persistent round filling defect which is regular and sharply outlined (Fig 7). The uterine cavity has normal size and shape. The lateral borders of the uterine cavity may represent some irregularities produced by the attachment of the sessile type of polyps. Endometrial polyps are better visualized when small amounts of contrast medium is introduced into the uterine cavity, since large amounts of medium may obscure the defect. The polyps must be distinguished from air bubbles, submucous leiomyomas, synechiae, adenomyosis and normal functional variants by their fixed position, oval shape and more rounded and regular appearance.

Polyps may appear as a thickened area of endometrium with a transvaginal sonography. Although polyps can be seen by ultrasound in the follicular phase, they are more accurately visualized by hysterosonography during the periovulatory phase, when surrounded by anechoic fluid. On HSG, they look like an echogenic mass with smooth edges. Polyps are infrequently illustrated as an irregular marginated echogenic endometrial mass.

**Leiomyoma**

Leiomyomas or fibroids are the most common benign uterine tumor that may occur in more than 30% of women of reproductive age[24]. This monoclonal tumor consists of uterine smooth muscle and large amounts of extracellular matrix including collagen, fibronectin, and proteoglycan. The target risk factors include obesity, nulliparity, diabetes, polycystic ovary, familial history, black race and hypertension[2]. Cytogenetic abnormalities, particularly deletions of chromosome 7 have been identified in up to 50% of leiomyoma specimens[25].

Uterine leiomyoma are often asymptomatic, but they may be associated with abnormal uterine bleeding, urinary incontinence or retention, pelvic pain and reproductive dysfunction such as infertility, recurrent miscarriage and premature labor[26]. As a neoplasm, small percentages of leiomyomas undergo malignant transformation[27].

They vary in size from buds to massive uterine tumors. They may be single or multiple, and are classified into three types depending on the location: submucosal (least common), intramural (most common), and subserosal. Most leiomyomas are hybrids and have more than one anatomical location.

Leiomyomas show a broad spectrum of radiographic appearances, depending on their number, size and location relative to the uterine cavity[28].
Hysteroscopy is considered the gold standard for identification of a submucosal leiomyoma[29]. A submucosal leiomyoma must be differentiated from air bubbles, endometrial polyps, blood clots, and retained products of conception. Large masses may cause generalized enlargement of the uterine cavity. Submucosal leiomyoma usually distort the uterine contour and size (Fig 8a and b). Polyps are smaller and more sharply outlined than submucosal fibroids, while blood clots and retained placenta have more angular outlines. Intramural leiomyomas may enlarge, distort, displace and rotate the uterine cavity. Asymmetric enlargement of the uterus produced by large intramural or subserosal myoma gives the uterus a crescenting appearance (Fig 8c).

Smooth and symmetric fundal myomas may simulate a subseptate or bicornuate uterus (Fig 8a).

Subserosal myomas will not be apparent on hysterograms unless they are large enough to cause obvious displacement of the uterus. Subserosal leiomyomas may also be pedunculated and they are attached to the uterus by a narrow stalk (Figs 8d and e). Subserosal leiomyomas should be differentiated from solid ovarian and pelvic tumors. Since leiomyomas are responsive to estrogen, they tend to regress after menopause.

Endometrial hyperplasia
Endometrial hyperplasia is characterized by a proliferation of endometrial glands of irregular size
and shape with an increase in gland/stroma ratio compared to normal proliferative endometrium\(^{30}\). It is caused by endometrial stimulation by unopposed estrogen and is a common cause of dysfunctional bleeding in pre-and postmenopausal women\(^{31}\).

The World Health Organization classifies endometrial hyperplasia into two broad categories: hyperplasia without cytologic atypia and hyperplasia with cytologic atypia\(^{32}\). These two main categories are further subdivided into simple or complex, based on the extent of glandular texture\(^{32}\).

Several imaging tools including HSG, ultrasound, hysterosonography, and MRI can be applied to evaluate suspected endometrial hyperplasia, but hysteroscopy with directed biopsy is considered the gold standard in the differential diagnosis of hyperplasia and different subtypes\(^{33}\).

Radiographic feature of endometrial hyperplasia depends on the gross appearance of endometrial hyperplasia and is variable. In cases with normal endometrial thickness, the outline of the uterine cavity is regular and smooth; however, in patients with moderately thickened hyperplastic endometrium, some irregularity in the inner surface of the uterine wall is present (Fig 9a). When the endometrium is polypoid, the uterine shadow shows variations in density and projections of lesions may be seen as well (Figs 9b and c). In such cases, the border of defects is usually smoother than in cases of carcinoma, but a certain diagnosis is made after histological examination.

Hysterosalpingograms performed during the secretory phase of the menstrual cycle demonstrate a very prominent mucosal pattern, which should not be confused with endometrial hyperplasia. Other sources of misinterpretation include mucus secretions and blood clots within the uterine cavity and endometrial polyps. Endometrial hyperplasia should be differentiated from tuberculosis endometritis.

In endometrial tuberculosis, uterine tubes are often involved and irregularity in the uterine borders which mimic heterogeneous thickening are observed.

**Endometrial carcinoma**

Uterine cancer is the fourth most common malignancy in women and most commonly affects postmenopausal women, particularly in the sixth and seventh decades, while less than 5% occurs in women under 40 years of age\(^{34}\).

Several risk factors have been identified for the development of endometrial cancer. Nulliparity, unopposed estrogen replacement therapy, adenomatous endometrial hyperplasia, polycystic ovary syndrome, diabetes mellitus, hypertension and obesity are associated with an increased risk of developing endometrial cancer\(^{35}\).

The presenting symptom in 75 - 90% of patients is postmenopausal or intermenstrual bleeding or spotting, which often has been investigated by endometrial biopsy or dilation and curettage\(^{35}\).

HSG is not routinely used for the investigation of uterine malignancy, but it may occasionally reveal an endometrial carcinoma. In the past, HSG has been used in patients with suspected endometrial carcinoma and the technique was useful to predict the volume and distribution of the tumor, to differentiate between benign and malignant lesions, and to diagnose the point of maximum invasion of tumor to modify patient management\(^{36,37}\).

Radiographic findings of endometrial carcinoma vary from case to case\(^{36}\). The malignancy may be detected as a solitary growth, often in the uterine

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**Fig 9:** Spectrum of radiographic finding of endometrial hyperplasia depending on the gross appearance of lesion in two different patients. (a) Thickened endometrial mucosa with a diffusely irregular outline. The endometrial biopsy confirmed endometrial hyperplasia. (b) Early filling view of uterine cavity shows polypoid filling defect secondary to endometrial hyperplasia (arrows). (c) This pattern was hidden completely with further filling. The diagnosis was confirmed by biopsy.
fundus, as a multiple circumscribed tumor, a diffuse spreading lesion, or as a process filling defect in the uterine cavity. In cases with well-defined extensive tumor, HSG represents a smooth and localized filling defect, whereas in patients with slightly exophytic, ill-defined and widely extensive lesion, an irregularity in the outline of uterine contour is present (Fig 10).

The differential diagnosis includes large polyps for the smooth masses and severe endometrial hyperplasia for infiltrate tumors. Both polyps and hyperplasia usually have a less aggressive appearance than that of carcinoma.

**Adenomyosis**

Adenomyosis is a benign condition of the uterus characterized by the infiltration of endometrial stroma and glands into the myometrium.

The etiology is unclear, but it is generally accepted that adenomyosis occurs when the normal boundary between the basal layer of endometrium and the myometrium is damaged and the endometrium is exposed to direct contact with the myometrium. Adenomyosis has been found in 10 - 50% of uteri examined at autopsy and in 5.6% to 61.5% of surgical specimens.

Adenomyosis is characterized by the ingrowing of the endometrial tissue into the myometrium with adjacent smooth muscle hyperplasia. The degree of invasion is variable and can involve the whole uterine wall up to the serosa.

Adenomyosis is usually asymptomatic, but it may be presented by uterine bleeding, dysmenorrhea, dyspareunia, metrorrhagia, and infertility. These symptoms are non-specific and can occur as part of many other gynecological disorders.

HSG was the first imaging tool utilized for the diagnosis of adenomyosis. The characteristic findings on HSG are mild to moderate enlargement of the uterine cavity and the presence of small rounded or oval diverticulum-like structures (1 - 2mm) that extend from the border of the uterine cavity into the walls of the uterus presenting a honeycomb appearance. The diverticuli may be localized to one area or involve the uterine wall diffusely (Fig 11).

The ultrasound features of adenomyosis are often subtle and extremely variable. The most common findings on transvaginal sonography in the patient with adenomyosis are poorly marginated hypoechoic and heterogeneous areas (Swiss cheese appearance). In about 50% of the cases, small (1 - 6 mm) myometrial cysts are present.

The differential diagnosis includes localized intravasation of contrast into myometrial vascular channels and endometrial hyperplasia. Intravasated contrast medium is rapidly vanished from the veins.
whereas it persists within adenomyotic diverticula or sinuses. Endometrial hyperplasia is characterized on HSG by irregularities of the contours of the uterine cavity and variations in density of the uterine shadow.

When adenomyosis and endometrial hyperplasia coexist, precise diagnosis may be difficult. Confusion may sometimes occur with the diverticula seen in HSGs after cesarean sections, which are different in character from those of adenomyosis. They are large and usually single in comparison to the small and usually multiple sinuses found in adenomyosis.

**Intrauterine adhesion**

Intrauterine adhesion, known as an acquired uterine condition, is characterized by the destruction of endometrium which may produce subsequent scar in endometrium and expansion of scar tissue band within the uterine cavity. Asherman described the association of intrauterine adhesions both with menstrual dysfunction, especially hypomenorrhea, and with infertility. Uterine synechiae is caused by trauma to the basal layer of the endometrium, generally following curettage. However, any uterine surgery (myomectomy, cesarean section, or repair of Müllerian anomalies) or endometrial infection owing to schistosomiasis, genital tuberculosis and intrauterine devices may lead to intrauterine synechiae. The main symptoms are infertility (43%) and menstrual disorders (62%), followed by amenorrhea.

Scarring may range from minor filmy synechiae that affects a small area of the uterine wall with no reproductive consequences to severe diffuse involvement of the uterine cavity that affects menstrual function and fertility due to extensive obliteration and destruction of the endometrial cavity.

According to severity stages of synechiae diagnosed by both hysterosalpingographic and hysteroscopic criteria and menstrual pattern, intrauterine adhesion is classified into three categories: mild (involvement of 1/4), moderate (involvement of 1/2), and severe (involvement of 3/4 or more) (Figs 12 a-c).

HSG can show both extent and the location of the synechiae. The radiographic feature of intrauterine adhesions varies with the sites and the degree of involvement. Synechiae appear as filling defects that distort the contour of the uterine cavity; they typically have an irregular, angulated shape and are immobile. They are readily defined because the uterine walls are adhered and contrast material does not completely surround the filling defects. Occasionally, synechiae may obliterate the whole endometrial cavity or obstruct the lower uterine segment and allow contrast opacification of only a short segment of the blunt-ending to cervical canal giving Glove’s finger appearance (Netter syndrome) (Fig 13).

In cases with extensive symmetrical obliteration of the uterine cavity, sometimes the cavity is smaller than its normal size and gives the appearance of an infantile uterus. A history of previous endometrial trauma or disease, as well as clinical and sonographic signs can be useful in this particular situation. On ultrasound, adhesions are observed as endometrial irregularities or hypoechoic bridges within the endometrial cavity. Intrauterine synechiae do not present with increased vascularity on color Doppler examination. Three-dimensional ultrasound demonstrates a significant reduction of the endometrial cavity volume in all reformed sections.

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**Fig 12:** The categories of intrauterine adhesion classified by both hysterosalpingographic and hysteroscopic criteria and menstrual pattern, which is diagnosed by HSG (a) Mild intrauterine adhesion; if adhesions involve one-fourth of the uterine cavity (arrows). Large filling defect in the lower segment of the uterus (open arrow) is owing to introduction of an air bubble into the uterine cavity during hysterosalpingography, (b) Moderate intrauterine adhesion, if adhesions involve one-half of the uterine cavity (arrow), (c) Severe intrauterine adhesion, if adhesions involve three-fourths of the uterine cavity (open arrow).
Retained products of conception

Inadvertently, retained products of conception following spontaneous pregnancy loss may be detected within the endometrial cavity on HSG. The symptoms include irregular bleeding, dysmenorrhea, dyspareunia, chronic pelvic pain and a high risk of secondary infertility[45].

It may be completely asymptomatic and found only during a preliminary pelvic ultrasound as part of a routine infertility workup. Although HSG is useful in outlining the endometrial cavity and in determination the state of fallopian tubes; its utility in the diagnosis of retained fetal products is limited. Hysterosalpingographic features are asymmetrical enlargement, irregularity in the border of the uterus and filling defects (Fig 14).

Intrauterine device

Intrauterine device (IUD) as a contraceptive device was firstly introduced by Richard Richter in 1909 and now it is a common form of birth control[46]. These small devices fit into the uterus and provide long-term contraception. In rare cases, the IUD can be pushed through the wall of the uterus and uterine perforation
into the peritoneal cavity or uterine musculature, but both perforations are usually asymptomatic. HSG should be performed to check the relationship between the uterus and the site of the IUD (Fig. 15). Lost IUDs may tear into or through uterine wall or through cervix into the vagina.

CONCLUSION

Morphological evaluation of the intrauterine cavity and tubal patency is indicated for many clinical conditions in gynecology clinic and infertility workup. Although HSG is limited to evaluate the external uterine contour adequately, it potentially allows clinicians to diagnose any filling defects or irregularities contributing to infertility.

Modern radiographic equipment by using a fluoroscopic control system provides an ability to observe sequential filling of the uterine cavity and fallopian tubes. An accurate interpretation of the HSG is essential to prevent unnecessary and aggressive treatment.

ACKNOWLEDGMENTS

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Original Article

Impact of body mass index in malondialdehyde, antioxidant vitamins A, E, C and plasma zinc among type 2 diabetic patients

Abd Elgadir A Altoum, Ahmed L Osman, Asaad MA Babker
Department of Medical Laboratory Sciences, College of Health Sciences, Gulf Medical University, Ajman, UAE

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ABSTRACT

Objective: To evaluate the impact of body mass index (BMI) in malondialdehyde (MDA), antioxidant vitamins A, E, C and zinc plasma among Sudanese patients with type 2 diabetes mellitus

Design: A cross sectional study

Setting: Advanced diagnostic center for routine follow up, which is a specialized center for diabetes mellitus, in Khartoum, Sudan

Subjects: Three hundred patients with type 2 diabetes were compared to 100 healthy subjects (non-diabetic) as control group.

Intervention: The study group data was collected using structure questionnaire. Blood specimens were collected from both groups and plasma levels of zinc and antioxidant vitamins (A, E, C) were determined. Statistical Package for Social Science SPSS (version 13) computer software was used for data analysis.

The means and standard deviations of variable were calculated and T-test was used for comparison (significant level was set at p ≤0.05).

Main outcome measure(s): The relationship between BMI and serum MDA, antioxidant vitamins A, E, C and zinc.

Results: A significantly strong positive correlation between BMI and plasma MDA in the test group (p = 0.001), while plasma zinc, vitamins A, and E had a significantly weak negative correlation between BMI and plasma vitamin as follows (p = 0.01, p = 0.001, p = 0.03 respectively). There is also a significantly weak negative correlation between BMI and plasma vitamin C of the test group (p = 0.1).

Conclusion: A positive correlation between MDA and BMI and a moderate negative correlation with vitamins (A, E, C) and zinc were found.

KEYWORDS: anti-oxidants, obesity, type 2 diabetes

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. The current global prevalence of 415 million diabetic subjects is projected to increase to 642 million by 2040 if preventive measures are not put in place[2]. Diabetes mellitus (DM) is characterized by chronic hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism due to deficiencies in insulin secretion and insulin action. Diabetic patients have defects in the antioxidant defense mechanism; free radicals and oxidative stress may be responsible for diabetes itself, and its complications[3-5]. Malondialdehyde (MDA) is an organic compound and is one of the final products of polyunsaturated fatty acid peroxidation in cells. An increase in free radicals causes overproduction of MDA. MDA level is commonly known as a marker of oxidative stress and antioxidant status in cancerous patients[6]. Antioxidants are molecules involved in scavenging of free radicals; this defence mechanism involves both enzymatic and non-enzymatic strategies. Antioxidant enzymes include superoxide dismutase (SOD), catalase and glutathione peroxidase,
whereas non-enzymatic include small molecules such as uric acid, vitamins E, C and A [7,8]. Obesity is one of the most important modifiable risk factors for the prevention of type 2 diabetes. An increase in body fat is generally associated with an increase in the risk of metabolic diseases such as type 2 DM, hypertension and dyslipidemia [9]. Several studies have reported that obesity may induce systemic oxidative stress and, in turn, oxidative stress is associated with an irregular production of adipokines, which contributes to the development of the metabolic syndrome [10,11]. Zinc plays a relevant role in antioxidant defense in patients with type 2 DM. This mineral may act by different protection mechanisms by notably being an essential cofactor for more than 300 enzymes, such as SOD. This mineral also facilitates reduction and neutralization of free radicals [12,13]. In this study, we investigated for the first time the effect of BMI on MDA, antioxidant vitamins A, E, C and plasma zinc among Sudanese type 2 diabetic subjects.

SUBJECTS AND METHODS

This cross sectional study was conducted in Khartoum State, the capital and centre of Sudan. Patients that came to the referral clinic Advanced Diagnostic Centre in Bahri, a specialized center for diabetes mellitus, from May 2013 to September 2015 were enrolled in this study. The study group included 300 patients with type 2 DM, aged between 30 and 75 years (mean age: 50.2 years). One hundred healthy subjects with mean fasting blood sugar of 5.61 mmol/l and ages ranging from 22 - 75 years (mean age: 50.1 years) formed the control group. MDA serum was mixed with 20% trichloroacetic acid and allowed to stand for 10 minutes. After that, 0.05M H$_2$SO$_4$ and thiobarbituric acid were added. The mixture was mixed and place in 70 °C water bath for 30 minutes. The resulting chromogen was extracted with n-butanol and centrifuged at 2000 rpm/min, and measured against butanol blank at 532 nm excitation and 553 nm emissions by spectrophotometer [14]. Zinc present in the sample is chelated by 2-(5-bromo-2-pyridylazo)-5-(N-n-propyl-N-3-sulfopropylamino) phenol in the reagent. The formation of this complex is measured at a wavelength of 560 nm [15]. Vitamin A, E and C antioxidants were assayed by chromatography measurements using Hewlett-Packard (Waldborn, Germany) model 1050 pump system, water 717 plus Auto Sampler (Mil Ford, MA, USA), a UV-vis detector, SPD-10 AV VP (Shimadzu Kyoto, Japan) and an HP-3365 series II ChemStation. The body mass index (BMI) is a statistic developed by Adolphe Quetelet in the 1900’s for evaluating body mass by dividing the bodyweight in kilograms by height in meters squared.

Statistical analysis

Statistical Package for Social Science (SPSS) version 13 computer software was used for data analysis. The means and standard deviations of variables were calculated and T-test was used for comparison (significant level was set at $p \leq 0.05$).

RESULTS

Table 1 shows the baseline characteristics of the test group and control group. There is no significant difference in age between the two groups (mean ± SD = 50.1 ± 14 and 50.2 ± 11.1 for the control group and the test group respectively ($p = 0.06$)). Weight, height and BMI show significant differences between the test and control groups. The mean weight was 74.5 ± 12.2 kg for the control group and 79.7 ± 22.8 kg for the test group ($p = 0.032$). The mean height was 171 ± 10 cm for the control group and 164 ± 10 cm for the test group ($p = 0.0006$). Mean BMI was 25.2 ± 3.2 for the control group and 29.5 ± 8.1 for the test group ($p = 0.0004$).

Table 1: Baseline characteristics of the respondents

<table>
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<th>Variables</th>
<th>Control groups (n = 100)</th>
<th>Test groups (n = 300)</th>
<th>p-value</th>
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<td>Age (years)</td>
<td>50.1 ± 14 (22 - 75)</td>
<td>50.2 ± 11.1 (23 - 75)</td>
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<tr>
<td>Weight (kg)</td>
<td>74.5 ± 12.2 (52 - 105)</td>
<td>79.7 ± 22.8 (50 - 180)</td>
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<tr>
<td>Height (m)</td>
<td>171 ± 10 (152 - 196)</td>
<td>164 ± 10 (135 - 190)</td>
<td>0.0006</td>
</tr>
<tr>
<td>BMI (w/h$^2$)</td>
<td>25.2 ± 3.2</td>
<td>29.5 ± 8.1</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Figure 1 shows a significant strong positive correlation between BMI and plasma MDA in the test group ($r = 0.69, p = 0.001$). Figure 2 shows a significant moderate negative correlation between BMI and

Fig. 1: Scatter plot shows the relationship between BMI and MDA in the test group (n = 300) ($r = 0.69, p$-value $= 0.001$)
plasma zinc in the test group \((r = -0.59, p = 0.01)\). Figure 3 shows significant moderate negative correlation between BMI and plasma vitamin A in the test group \((r = -0.42, p = 0.002)\). Figure 4 shows significant moderate negative correlation between BMI and plasma vitamin E in the test group \((r = -0.30, p = 0.03)\). Figure 5 shows significant weak negative correlation between BMI and plasma vitamin C in the test group \((r = -0.20, p = 0.1)\).

**DISCUSSION**

Type 2 DM is a progressive condition in which the body becomes resistant to the normal effects of insulin or gradually loses the capacity to produce enough insulin in the pancreas. The prevalence of diabetes mellitus in Sudan, as in many other low-income countries, is increasing to epidemic proportions, leading to the emergence of a public health problem of major socioeconomic impact\(^{[16]}\). Several studies on diabetes have been conducted in Sudan and concluded that diabetes is a common disease in Sudan and it is a major cause of mortality, but several studies indicate that diabetes is likely underreported as cause of death\(^{[16-18]}\). In the present study, we recorded a significant and strong positive correlation between BMI and plasma MDA among patients with type 2 diabetes. Our observation of increased MDA levels among obese diabetic people is in agreement with the literature support that obese subjects exhibit increased systemic oxidative stress and the concentration of serum MDA increases with increasing levels of BMI\(^{[19,20]}\). A study in Turkey has also reported significantly high MDA levels among a diabetic population\(^{[21]}\). Codoñer et al have also
observed similar results among a study population and concluded that MDA was the sole marker of oxidative damage that was positively correlated with BMI [22]. Another study by Edrees et al among Iraqi diabetic patient found that higher concentrations of MDA were recorded in diabetic obese group and a positive correlation was found between MDA and BMI [23].

Furthermore, we observed a decrease in total antioxidant vitamins (A, C and E) showing a moderate negative correlation with BMI. This finding is in agreement with many studies which suggested that oxidative stress is induced in obese subjects due to alterations in MDA and other oxidative stress markers such as vitamin E, C and A [24,25]. A study in north India conducted among the Punjabi population to analyze oxidative status in obese subjects with respect to normal healthy subjects suggested that oxidative stress is induced in obese subjects even in the absence of chronic disease such as DM, hypertension, hyperlipidemia and renal or liver disease [26]. Another study conducted by Ugwuja et al reported a non-significant relationship between plasma antioxidant vitamins and BMI [27], while some studies reported oxidative stress was shown to be associated with low plasma concentrations of antioxidants in patients with severe obesity [28].

In addition, we extended our study to evaluate the relationship between BMI and plasma zinc in the test group and found moderate negative correlation with BMI. Our observations are in agreement with the literature reports that concentrations of zinc in the serum showed no statistically significant difference between the control and the obese groups [29]. Another study conducted by Dourado et al did not find any significant difference in plasma zinc concentration between the obese and the control groups [30]. In general, most studies on humans and animals show controversial results. Some studies have shown that antioxidant enzymes increase in obesity. Other studies have identified no significant difference in antioxidant enzymes concentrations in obesity and chronic.

CONCLUSION

Our study shows a positive correlation between MDA and BMI. Also, our results found a moderate negative correlation with vitamins A, E, and C and plasma zinc. These findings suggest that oxidative vitamins are induced in obese subjects with type 2 diabetes mellitus by altering the levels of MDA.

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Conflict of Interest: I declare that there is no conflict of interest.

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Original Article

Assessment of the success of drugs to reduce the emergence agitation in children following Adenotonsillectomy

Hatice Ates Gullu¹, Zeynep Nur Orhon² Gul Ozbilen Acar² Osman Ilkay Ozdamar², Melek Gura Celik¹
¹Department of Anesthesiology and Reanimation, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey
²Department of Otorhinolaryngology- Head and Neck Surgery, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objective: To investigate the effects of remifentanil infusion and single dose dexmedetomidine on postoperative agitation after sevoflurane induction in pediatric patients who underwent adenotonsillectomy

Design: A controlled, double blind study

Setting: Operating room and postoperative recovery area

Subjects: The study was controlled, double blind with 60 pediatric patients, aged 2 - 14 years who underwent the procedures of tonsillectomy/adenoidectomy and were randomized into remifentanil (group R, n = 20, 0.1 µg/kg/min infusion) or dexmedetomidine (group D, n = 20, 0.3 µg/kg single dose) or control (n = 20, 50% ⁰₂, 50% N₂, 1-2% sevoflurane) groups.

Interventions: All of the patients underwent adenotonsillectomy and were randomized into remifentanil (n = 20), dexmedetomidine (n = 20) or control (n = 20) groups.

Main outcome measures: Postoperative emerging agitation was evaluated by Modified Aldrete Scoring (MAS) System, Riker sedation-agitation score (RS) and Aono’s four-point scale. Data were analyzed by descriptive statistics, paired one-way variance analysis, Newman Keuls and Tukey multiple comparison and Chi square tests.

Results: Mean extubation time, the time of MAS reaching 9-10, mean heart rate, and mean arterial blood pressure were higher in group R (p >0.05). Mean RS score of group D was statistically significantly lower than the other groups (p = 0.041). There were no statistically significant differences in mean values of ETCO₂ and SpO₂ between the groups.

Conclusions: We conclude that a dose of dexmedetomidine 0.3 µg/kg administered after induction of anesthesia reduces the post sevoflurane agitation in children with no adverse effects.

INTRODUCTION

A child who emerges from anesthesia may experience a variety of behavioral disturbances that are interchangeably described in the literature as postanesthetic excitement, delirium, and agitation[1]. The term “delirium” is often replaced with the descriptive terms “agitation” or “excitation” because it is not feasible to fully evaluate the psychological state of young children during the emergence[2]. Emergence agitation (EA) is a common side effect of sevoflurane anaesthesia in children. It generally manifests itself with a state of mild restlessness and mental distress that does not always suggest a significant change in behaviour[3]. Agitation can indicate any number of sources, including pain, physiological compromise, or anxiety[4].

The incidence of EA and emergence delirium (ED) largely depends on definition, age, anesthetic technique, surgical procedure, and application of adjunct medication. Generally, it ranges from 10 - 50%, but may be as high as 80%. Agitation incidence is at peak level in the first 30 minutes, and then it recovers spontaneously. However, episodes lasting up to two days have also been reported in some studies[5].

Despite much scientific work that deals with pediatric EA/ED, its underlying cause remains
obscure. Many factors related to anesthesia, surgery, patient, and adjunct medication have been suggested to play a potential role in its initiation.

In our study, it was aimed to investigate the effects of remifentanil, a potent ultrashort-acting synthetic opioid analgesic infusion and single dose dexmedetomidine (a more selective α-2 adrenoceptor agonist than clonidine) on postoperative agitation after sevoflurane induction in pediatric patients who underwent tonsillectomy and/or adenoidectomy.

SUBJECTS AND METHODS

The study was performed in the Department of Anesthesiology and Reanimation at Goztepe Training and Research Hospital of Istanbul Medeniyet University between August 2011 and September 2011. After obtaining approval from the Institutional Review Board and informed consent from parents, 60 pediatric patients, aged 2 - 14 years (American Society of Anesthesiologists class I, II) who underwent elective tonsillectomy/adenoidectomy were enrolled in this controlled, randomized, double blind study. Patients were excluded from the study if they refused to participate in the study (15 patients’ parents refused to participate in the study), if they had fever over 38°C, any other systemic disorders (i.e. hepatic, renal, cardiovascular, psychiatric, allergic, or metabolic), and also if they were suspected for malignancy, receiving chronic steroid treatment and chronic analgesics.

Patients were randomized into three groups with 20 patients each using a computer-generated sequence of numbers and a sealed envelope assignment which were prepared and kept by a research coordinator. All patients received pre-oxygenation for 3 minutes before the induction; anesthesia was performed with 50% oxygen, 50% nitrous oxide and 8% sevoflurane. The patients were not pre-medicated. The same anesthetist (H.A.G) gave the anesthesia to all patients. After anesthetic induction and placement of the IV line, isotonic sodium chloride infusion (6 mg/kg/h) was started. All patients received 1 µg/kg dose of fentanyl intravenously and endotracheal intubation was performed after the administration of rocuronium 0.5 mg/kg. Anesthesia was maintained by 50% O₂, 50% N₂O, 1 - 2% sevoflurane in control group (group C); by 50% O₂, 50% N₂O, 1 - 2% sevoflurane and remifentanil infusion (0.1 µg/kg/min) in the remifentanil group (group R); and dexmedetomidine 0.3 µg/kg was administered 10 minutes after induction (group D) with sevoflurane.

Baseline, perioperative and postoperative measurements of mean arterial blood pressure (MAP), heart rate (HR) and SpO₂ were recorded. Perioperative hypotension, hypertension, bradycardia, arrhythmia episodes and atropine amounts, planned to be administered at 0.01 - 0.02 mg/kg IV if bradycardia (<45 beats/min) was encountered, were also recorded.

More than 30% decrease in systolic arterial blood pressure (SAP) values was accepted as hypotension. In such conditions, primarily volatile anesthetic agent was decreased, and in terms of progression, remifentanil infusion dose was planned to be decreased by 50%, and if there was still no response, isotonic sodium chloride of 20 ml/kg was planned to be given in 5 to 20 minutes. In conditions of hypertension (more than 30% increase in SAP when compared to the basal values), volatile anesthetic agent was increased by up to 50% concentration. If no response was obtained, then fentanyl 1 µg/kg was planned to be given intravenously.

Intravenous paracetamol was administered at 20 mg/kg dose 10 minutes before the operation ended to all cases to provide postoperative analgesia. Modified Aldrete Scoring (MAS) System was used to transfer the patient from the operation-room to the postoperative care unit, and during the postoperative follow-up. Patients with MAS score of 9 and above were discharged to the postoperative care unit. During the emergence, agitation was scored and recorded by using Riker sedation-agitation score (RS) and Aono’s four-point scale.

Statistical analysis of the study was performed by using the NCSS 2007 package program. During data analysis, along with descriptive statistical methods (mean, standard deviation), paired one-way variance analysis for repetitive measurements of multiple groups, Newman Keuls multiple comparison test for subgroup comparisons, one-way variance analysis for comparisons between the groups, Tukey multiple comparison test for subgroup comparisons, and Chi square for qualitative data comparisons were employed. The level of significance was accepted as p <0.05.

RESULTS

There were no statistically significant differences in mean age and gender distribution between the groups (mean ages for R = 6.9 ± 3.29 years, D = 6.4 ± 2.93 years, C = 6.5 ± 2.86 years) (p >0.05). Mean extubation time in group R (4.15 ± 1.95 min) was significantly longer than those in group D (2.95 ± 1.4 min) and group C (2.65 ± 1.14 min) (p = 0.007). There were statistically significant differences in MAS reaching the score of 9 - 10 (MAS 9 - 10 Time) between the groups, and it was longer in group R than groups D and C (both p = 0.003) (Table 1).

MAP changes in all 3 groups were significant within the groups in pre-, intra-, and postoperative evaluation parameters (p = 0.0001), whereas statistically significant differences were observed at minutes 15 and 30 in the emergence room after extubation between the groups.
MAP in group R was statistically significantly higher than that of group D at minute 15 and at minute 30 (p = 0.005 and p = 0.017, respectively) (Tukey multiple comparison test).

For mean HR, there was a statistically significant difference between the groups only at post-induction time (p = 0.008). Mean HR of group R was statistically higher than that of group C (p = 0.006).

Postoperative agitation evaluation results are shown in figures 1 and 2 by using RS and Aono’s four-point scale. Statistically significant difference

Fig. 1: Comparison of cases for agitation by Riker sedation agitation score

Fig. 2: Comparison of cases for agitation by Aono’s four point scale
TABLE 2: Mean arterial blood pressure (MAP) values of cases measured at different time points

<table>
<thead>
<tr>
<th>Time points</th>
<th>Remifentanil Group (95% CI) †</th>
<th>Dexmedetomidine Group (95% CI) †</th>
<th>Control Group (95% CI) †</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>92.1 ± 15.7 (84.75 – 99.45)</td>
<td>91.2 ± 9.6 (86.71 – 95.69)</td>
<td>84.6 ± 14.1 (78 – 91.2)</td>
<td>1.9</td>
<td>0.158</td>
</tr>
<tr>
<td>Post-induction</td>
<td>70.1 ± 12.5 (64.25 – 75.95)</td>
<td>71.6 ± 13.4 (65.33 – 77.87)</td>
<td>65.8 ± 9.2 (61.49 – 70.11)</td>
<td>1.3</td>
<td>0.283</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>87.9 ± 24.8 (76.29 – 99.51)</td>
<td>78.8 ± 14.9 (71.83 – 85.77)</td>
<td>79.3 ± 14.4 (72.56 – 86.04)</td>
<td>1.5</td>
<td>0.228</td>
</tr>
<tr>
<td>Post-incision</td>
<td>96.6 ± 12.9 (90.36 – 102.64)</td>
<td>91.9 ± 11.3 (86.61 – 97.19)</td>
<td>93.6 ± 14.6 (86.97 – 100.63)</td>
<td>0.7</td>
<td>0.511</td>
</tr>
<tr>
<td>Min 5</td>
<td>92.1 ± 11 (86.95 – 97.25)</td>
<td>87.7 ± 13.2 (81.52 – 93.88)</td>
<td>88.2 ± 12.2 (84.29 – 93.91)</td>
<td>0.8</td>
<td>0.468</td>
</tr>
<tr>
<td>Min 10</td>
<td>86.3 ± 10.7 (81.29 – 91.31)</td>
<td>84.2 ± 7.1 (80.88 – 87.52)</td>
<td>87.0 ± 14.7 (80.12 – 93.88)</td>
<td>0.3</td>
<td>0.725</td>
</tr>
<tr>
<td>Min 15</td>
<td>88.7 ± 10.3 (83.88 – 93.52)</td>
<td>83.3 ± 12.4 (77.5 – 89.1)</td>
<td>83.7 ± 12.7 (77.76 – 89.64)</td>
<td>1.1</td>
<td>0.359</td>
</tr>
<tr>
<td>Min 20</td>
<td>85.6 ± 8.7 (81.53 – 89.67)</td>
<td>78.5 ± 9.3 (74.15 – 82.85)</td>
<td>84.0 ± 12.5 (78.15 – 89.85)</td>
<td>1.9</td>
<td>0.166</td>
</tr>
<tr>
<td>Min 25</td>
<td>86.6 ± 9.1 (82.34 – 90.86)</td>
<td>78 ± 8.8 (73.88 – 82.12)</td>
<td>77.6 ± 12.1 (71.94 – 83.26)</td>
<td>2.8</td>
<td>0.078</td>
</tr>
<tr>
<td>Post-extubation</td>
<td>99 ± 13.6 (92.63 – 105.37)</td>
<td>95.3 ± 8.7 (91.23 – 99.37)</td>
<td>91.8 ± 11.7 (86.32 – 97.28)</td>
<td>2</td>
<td>0.151</td>
</tr>
<tr>
<td>Min 1</td>
<td>91.8 ± 13.1 (85.67 – 97.93)</td>
<td>89.4 ± 11.2 (84.16 – 94.64)</td>
<td>89.5 ± 10.4 (84.63 – 94.37)</td>
<td>0.3</td>
<td>0.766</td>
</tr>
<tr>
<td>Min 15</td>
<td>92.9 ± 11 (87.75 – 98.05)</td>
<td>82.6 ± 10.4 (77.73 – 87.47)</td>
<td>89.5 ± 8.6 (85.47 – 93.53)</td>
<td>5.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Min 30</td>
<td>92.1 ± 10.8 (87.05 – 97.15)</td>
<td>82.9 ± 11.2 (77.66 – 88.14)</td>
<td>87 ± 8.7 (82.93 – 91.07)</td>
<td>4.0</td>
<td>0.023</td>
</tr>
<tr>
<td>F</td>
<td>4.6</td>
<td>7.7</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In the emergence room
† 95% Confidence Intervals (indicated in parenthesis on table)

In mean RS score was detected only at minute 15 (p = 0.021). Mean RS score of group D was statistically significantly lower than those in groups R and C (p = 0.041) (Tukey multiple comparison test).

According to Aono’s four point scale, there were statistically significant changes within groups R and C (p = 0.009 and p = 0.020, respectively). In comparisons within group R, mean score at minute 1 was statistically significantly higher than the values at minute 15 and minute 30 (p = 0.042 and p = 0.017, respectively). In comparisons within group C, mean of Aono’s four point scale at minute 30 was statistically significantly lower than the values at minute 1 and minute 15 (p = 0.024 and p = 0.042, respectively) (Newman Klaus multiple comparison test).

For mean MAS scores, statistically significant changes were defined in comparison within the three groups (p <0.05), and mean MAS values at minute 1 were significantly lower within all groups when compared with their counterparts at minute 15 and minute 30 (Table 3).

For nausea-vomiting scores of the groups, there were borderline significance in changes within groups D and C (p = 0.048 and p = 0.043, respectively). The means of nausea-vomiting score at minute 1 were significantly higher than the values at minute 30 in both groups D and C (p = 0.028 and p = 0.042, respectively).

There were no statistically significant differences in mean values of ETCO2 and SpO2 between the groups during the study.

DISCUSSION

The results of this study revealed that single dose dexmedetomidine 0.3 µg/kg administration reduces EA after sevoflurane anesthesia in children undergoing tonsillectomy and/or adenoidectomy.

Ibacache et al[6] reported in their study that agitation rates among patients who received 0.1 µg/kg and 0.3 µg/kg dexmedetomidine administrations after 10 minutes of the induction were 17% and 10% respectively, whereas it was 37% in the control group. In our study, we defined similar results to those of Ibacache et al that agitation rate at 15th minute in group D was significantly lower than the values in groups R and C (p = 0.041). However, there was no statistically significant difference between groups R and C (p = 0.999).

Guler et al[7] performed a study on 60 pediatric patients aged between 3 and 7 years of age, and they administered a single dose of dexmedetomidine 0.5 µg/kg 5 minutes before the surgery. They reported that postoperative agitation rate was lower than the control group, but emergence and extubation times were longer. In this present study, duration of extubation and emergence were no longer in the dexmedetomidine group than those in the control group.

In the study of Erdil et al[8], which was about the effects of dexmedetomidine and fentanyl on emergence

**Table 3: Comparison of cases within the groups for MAS**

<table>
<thead>
<tr>
<th>MAS</th>
<th>Remifentanil group</th>
<th>Dexmedetomidine group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min 1 vs. Min 15</td>
<td>0.042</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Min 1 vs. Min 30</td>
<td>0.021</td>
<td>0.005</td>
<td>0.01</td>
</tr>
<tr>
<td>Min 15 vs. Min 30</td>
<td>0.330</td>
<td>0.330</td>
<td></td>
</tr>
</tbody>
</table>

*Newman Keuls multiple comparison test
Mean MAS values at minute 1 were significantly lower within all groups when compared with their counterparts at minute 15, and Minute 30
in children who underwent adenotonsillectomy operation, it was reported that extubation time was shorter in the dexmedetomidine group; eye-opening time was longer in the fentanyl group; agitation score was lower in the dexmedetomidine and fentanyl groups when compared with the control; and hemodynamic parameters were similar in all three groups. In this study, fentanyl was used to suppress the autonomic response during laryngoscopy and endotracheal intubation at the induction phase. We defined RS at a significantly lower level in the dexmedetomidine group at the 15th minute (p = 0.041), but no difference was defined according to Aono’s four point scale within the three groups.

Isik et al[8] reported that dexmedetomidine 1 µg/kg administration decreased post-procedure agitation in children who had magnetic resonance imaging without any changes in the hemodynamic parameters. In our study, we also observed that hemodynamic parameters of subjects were stable during anesthesia in both remifentanil and dexmedetomidine groups, and no episodes of severe hypotension and bradycardia was recorded.

Dong et al[10] reported that addition of remifentanil 1 µg/kg/min to sevoflurane anesthesia of preschool children who underwent adenotonsillectomy decreased the agitation rate. Ozturk et al[11] performed their study on preschool children who underwent fiberoptic bronchoscopy under sevoflurane anesthesia, and they reported that administration of remifentanil infusion 0.15 µg/kg/min following 1 µg/kg bolus caused decreased emergence time, whereas increased agitation after bronchoscopy. They suggested that the increase in agitation might be due to hypoxemia secondary to toxic rigidity in the remifentanil group. Choi et al[12] administered sevoflurane and N2O to one group of pediatric patients who had adenotonsillectomy, and sevoflurane and remifentanil to the other group. They reported that postoperative pain rate was decreased, but agitation rate was not affected in the patients. In the study performed on children who had adenotonsillectomy operation by Kim et al[13], alfentanil 10 µg/kg administered after the induction caused decreased agitation rate without any effect on durations of extubation and emergence. In this study, the agitation rate in the remifentanil group was not decreased, as mentioned in the study of Choi et al[12], which was contrary to the study conducted by Ozturk et al[11]. We defined extubation time (p = 0.043, p = 0.008) and emergence time (p = 0.007) longer in the remifentanil group compared to the values in the dexmedetomidine and control groups. During the study, dexmedetomidine was given as a single dose after the induction, remifentanil was infused until the bleeding control was performed and inhalation agent was stopped at the end of the operation. We believe that longer extubation and emergence durations in remifentanil group may result from quite short durations of operations.

Various agents have been used to prevent EA. Davis et al[14] reported that agitation rate was 14% in patients who received ketorolac and 38% among the non-receivers. Cohen et al[15] reported that fentanyl 2.5 µg/kg given during the induction decreased the agitation rate; Finkel et al[16] reported that 2 µg/kg fentanyl decreased the rate by 50%. However, there are also contradictory results in the literature. Demirbilek et al[17] reported that fentanyl 2.5 µg/kg did not decrease the agitation rate in children with adenoidectomy and/or tonsillectomy. We administered fentanyl 1 µg/kg to suppress the autonomic response during laryngoscopy and endotracheal intubation in all of the patients. Moreover, we administered 20 mg/kg dose of paracetamol 10 minutes before the surgery was completed in all of our cases so that impact of postoperative pain on EA could be eliminated.

Severe nausea and retching were included in vomiting in many studies like in the study by Splinter et al[18]. We believe that this approach has caused high rates of vomiting in many studies. Aspiration of gastric content method was not performed to decrease nausea and vomiting. Also, we did not rely on the patient’s report about nausea and vomiting, because it was hard to take a reliable history from children aged between 2 and 6 years. Therefore, to perform objective evaluation for vomiting, observation of vomitus was required.

CONCLUSION
In conclusion, our study demonstrates that dexmedetomidine 0.3 µg/kg after anesthetic induction significantly decreases the occurrence of emergence agitation in children undergoing sevoflurane anaesthesia. The bolus administration of dexmedetomidine in this dose was safe, and it did not lead to an increased incidence of adverse effects. However, more studies are needed to determine both the efficacy and safety of dexmedetomidine either in different types of surgery or at larger doses.

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Conflict of interest: None

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Correlation of bronchoalveolar lavage and brushings with bronchial biopsy in the diagnosis of lung malignancies – Mubarak Al-Kabeer hospital experience

Kusum Kapila¹, Sara Shirly George², Smiley Annie George³, Bashayer Adnan Alramadhan⁴, Prem Nath Sharma², ⁴, Issam M Francis¹
¹Department of Pathology, Faculty of Medicine, Kuwait University, Kuwait
²Health Science Centre, Faculty of Medicine, Kuwait University, Kuwait
³Histopathology Laboratory, Mubarak Al-Kabeer Hospital, Kuwait
⁴Cytopathology Laboratory, Mubarak Al-Kabeer Hospital, Kuwait

ABSTRACT

Objectives: To determine the role and diagnostic utility of bronchoalveolar lavage (BAL), bronchial brushings (BB) and bronchial biopsy in the diagnosis of bronchogenic carcinoma

Design: Retrospective study

Setting: Cytopathology and histopathology laboratories, Mubarak Al-Kabeer hospital, Kuwait

Subjects: Total of 225 cases with BB and/or BAL and bronchial biopsy reviewed from January 2010 to December 2015

Intervention: Demographical data, cytological diagnosis, histological diagnosis and tumor type were reviewed

Main outcome measure: To document the efficacy of BAL and BB in the diagnosis of bronchogenic carcinoma. To the best of our knowledge, this data is not available from Kuwait.

Results: Of the 225 cases, 81 (36%) were females and 144 (64%) were males, ages ranging from 12 – 83 years. In 73 bronchial biopsies with malignancy, there were 9 small cell carcinoma, 17 adenocarcinoma, 9 non-small cell carcinoma, 24 squamous cell carcinoma, 3 adenosquamous carcinoma, 5 lymphoreticular malignancy and 6 miscellaneous tumors. The cytology in these 73 cases was positive for malignancy in 8, 4 and 24 cases of BAL alone, BB alone and both BAL and BB respectively. The sensitivity, specificity, negative predictive value and positive predictive value of BAL and BB were 32.3%, 100%, 73.8%, 100% and 59.1%, 95.5%, 53.8%, 96.3% respectively. A significant association between the bronchial biopsy and BB and BAL was observed (p < 0.001).

Conclusion: Combination of BB and BAL complement each other and enhance the diagnostic efficacy of lung tumors in conjunction with bronchial biopsy. Thus, all these techniques should be used concurrently to diagnose lung carcinomas.

KEYWORDS: bronchial biopsy, bronchial brushing, bronchoalveolar lavage, lung carcinoma

INTRODUCTION

Lung cancer is the leading cause of worldwide cancer mortality with a gradual increase in its incidence worldwide[1]. In Kuwait, lung cancer constitutes 13 percent of all cancer cases and is the fourth most common form of cancer. Kuwait has an incidence rate of 17 for males and 8.4 for females per 100,000 individuals[2].

The flexible bronchoscope has revolutionised the detection of bronchogenic carcinoma as bronchial brushings (BB) and/or bronchoalveolar lavage (BAL) or a combination of the two can be performed at the same time as the bronchoscopic biopsy[3-8]. Both BB and BAL have been shown to be very effective in the diagnosis of bronchogenic carcinoma[3,8]. However, bronchial biopsy has been used as the gold standard diagnostic test to assess the efficacy of other cytological techniques[9]. In general, the concordance between cytology and histopathology ranges from 70 - 90%[9].

In view of the importance of cytological methods
in the diagnosis of lung carcinoma and the paucity of studies from Kuwait to document this expertise, the current study was planned. The aim of our study was to correlate the cytology of BB and/or BAL with bronchial biopsy in the diagnosis of lung carcinomas. To the best of our knowledge, this type of study has not been reported from Kuwait.

**SUBJECTS AND METHODS**

This 6-year retrospective study was conducted in the cytology laboratory of Mubarak Al-Kabeer hospital from January 2010 to December 2015. The study was performed according to the guidelines of the local ethics committee which conforms to the Helsinki Declaration. A total of 225 cases with available BAL and/or BB and a concurrent bronchial biopsy were included in the study. The samples were obtained by a flexible optic bronchoscope performed by different endoscopists. BB material was smeared directly onto clean glass slides, fixed in 95% ethyl alcohol and stained with Papanicolaou stain. BAL specimens were sent immediately to the laboratory in normal saline, then centrifuged, the supernatant fluid was discarded and the sediment material resuspended in Thin prep fluid and processed in ThinPrep 2000 (Cytyc)\(^{[10]}\). The ThinPrep preparation was stained by Papanicolaou technique. The smears were categorised by different cytopathologists using standard diagnostic criteria as malignant, suspicious/atypical, negative for malignant cells with or without inflammation and unsatisfactory. Only unequivocal malignant features were considered to be positive. The malignant cells were further typed as small cell carcinoma, squamous cell carcinoma, non small cell carcinoma (NSCLC), NSCLC favor adenocarcinoma, adenocarcinoma, adenosquamous carcinoma and malignant tumor not otherwise specified (NOS).

Bronchial biopsy taken simultaneously as the cytological specimens were examined, and the size and number of pieces were documented. The tissues were processed as per standard procedures, 4-5 µ thick sections were cut on microtome and stained by hematoxylin and eosin stain. The stained slides were examined. The diagnosis and typing of tumor was done according to the World Health Organisations classification\(^{[11,12]}\).

**Statistical analysis**

Comparing the results of cytologic and histopathologic examinations, the sensitivity, specificity, positive predictive value, and negative predictive value were calculated. For preparing two way table for statistical analysis, benign, inflammation, atypical cytology and suspicious for carcinoma were grouped together as negative category. Carcinoma cases were classified in the malignant group. Patients with non-diagnostic cytology were excluded from the calculations. The following definitions were used in this analysis:

- **Sensitivity:** True positive / (True positive + False negative)
- **Specificity:** True negative / (True negative + False positive)
- **Positive predictive value:** True positive / (True positive + False positive)
- **Negative predictive value:** True negative / (True negative + False negative)

All statistical calculations were performed using IBM SPSS Statistics 19 for Windows program.

**RESULTS**

Of the 225 bronchial biopsies with BB (76 cases) and/or BAL (215 cases) received in the 6 years of our study, the age ranged from 12 – 83 years with 81 (36%) females and 144 (64%) males and a male to female ratio of 1.8:1. There were 149 cases of BAL only, 10 cases of BB only and 66 cases of both BAL and BB (Table 1). Of these, the biopsy was reported as benign or inflammatory in 123 cases and was unsatisfactory for rendering a diagnosis in 29 cases. These were excluded from the study. Thus, 73 cases reported as malignant (Table 1) formed the focus of our study. The histological diagnosis rendered (Table 2) was bronchogenic carcinoma; namely 9 small cell carcinoma, 17 adenocarcinoma, 9 NSCLC, 24 squamous cell carcinoma, 3 adenosquamous carcinoma, 5 lymphoreticular malignancy and 6

<table>
<thead>
<tr>
<th>Cytological Diagnosis</th>
<th>BAL only (n = 149)</th>
<th>BB only (n = 10)</th>
<th>BAL &amp; BB (n = 66)</th>
<th>Bronchial Biopsy (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Benign/Inflammation</td>
<td>76</td>
<td>57</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Atypical Cytology</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Suspicious Cytology</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malignant</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>60</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

| BAL: bronchoalveolar lavage; BB: bronchial brushings |

Table 1: Distribution of diagnoses in various bronchial preparations
miscellaneous tumors comprising of malignant mesothelioma (two cases), metastatic carcinoma (one case) and undifferentiated tumor (three cases).

The cytohistological correlation of the 73 cases is shown in Table 3. Of the 73 cases, the cytological diagnosis was benign/inflammation in 25 (34.2%) and unsatisfactory in 2 (2.7%). In 6 of the 9 (66.7%) small cell carcinomas diagnosed on biopsy, the BAL/BB was reported as atypical/suspicious in 3 and small cell carcinoma in 3. In 19 of the 24 (79.2%) squamous cell carcinoma reported on bronchial biopsy, 8 were diagnosed as squamous cell carcinoma, 5 as NSCLC, 5 as atypical/suspicious cytology and 1 as malignant tumor NOS. In 12 of the 17 (70.6%) cases of adenocarcinoma, the cytology reported 5 as adenocarcinoma, 4 as NSCLC favor adenocarcinoma and 1 each as atypical/suspicious cytology, NSCLC and malignant tumor NOS. In 2 of the 3 adenosquamous carcinoma, 1 was reported on cytology as adenosquamous carcinoma and 1 as NSCLC. In 4 of the 9 cases of NSCLC, the cytology report was 2 cases each of NSCLC and malignant tumor NOS. Only 1 of the 5 cases of lymphoreticular malignancy was reported as atypical cytology and 2 of 6 miscellaneous tumors were reported as NSCLC favor adenocarcinoma and malignant tumors NOS respectively. Thus, cytology was useful in identifying 6 of the 9 (66.9%) small cell carcinomas, 19 of the 24 (79.2%) squamous cell carcinoma, 19 of the 24 (79.2%) squamous cell carcinoma, 12 of the 17 (70.6%) adenocarcinoma, 2 of the 3 (66.7%) adenosquamous carcinoma, and 4 of the 9 (44.4%) NSCLC.

In our study, satisfactory cytological material was available in 46 cases, and of these, 10 were reported

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Male</th>
<th>Female</th>
<th>Total n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma</td>
<td>9</td>
<td>0</td>
<td>9 (12.3)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>20</td>
<td>4</td>
<td>24 (32.9)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>13</td>
<td>4</td>
<td>17 (23.3)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>2</td>
<td>1</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>7</td>
<td>2</td>
<td>9 (12.3)</td>
</tr>
<tr>
<td>LRM</td>
<td>4</td>
<td>1</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Miscellaneous tumors</td>
<td>4</td>
<td>2</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>14</td>
<td>73</td>
</tr>
</tbody>
</table>

NSCLC: non small cell lung carcinoma; LRM: lymphoreticular malignancy

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Male</th>
<th>Female</th>
<th>BAL</th>
<th>BB</th>
<th>BAL &amp; BB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NSCLC</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>NSCLC favor adenocarcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Malignant NOS</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

BAL: bronchoalveolar lavage; BB: bronchial brushings; NSCLC: non small cell lung carcinoma; NOS: not otherwise specified.
as atypical/suspicious cytology. Thus, in 36 (49.3%) cases, a cytological diagnosis of tumor was rendered in which BAL alone, BB alone and both BAL and BB were contributory in 8, 4 and 24 cases respectively (Table 4). We tried to analyse these 24 cases to see the accuracy of diagnosis of these two techniques in the same sitting (Table 5). BB and BAL identified the tumor concordantly in 4 of 6 squamous cell carcinoma, 2 of 2 adenocarcinoma and 3 of 7 cases of NSCLC, respectively.

In this study, cytohistological correlation of total BAL (215 cases) was found to have a sensitivity of 32.3% and a specificity of 100% with a positive predictive value and negative predictive value of 100% and 73.8% respectively. Similarly, total BB (76 cases) had a sensitivity of 59.1% and a specificity of 95.5% with a positive predictive value and negative predictive value of 96.3% and 53.8% respectively. There was one false positive case diagnosed as NSCLC on BB which the corresponding biopsy reported as benign. A significant association was seen between BAL and bronchial biopsy (p <0.001); BB and bronchial biopsy (p <0.001) and also between BAL and BB (p <0.01).

**DISCUSSION**

Lung carcinoma is the leading cause of cancer–related death world wide. The incidence rates and mortalities are still low in the Arab world as compared to Europe or USA; however, they are increasing in the region[13]. In the Gulf Cooperation Council, the highest age-standardized rate for lung carcinoma was in Bahrain (34.3 for males, 12.1 for females), followed by Qatar (18.5 for males, 5.5 for females) and Kuwait (13.8 for males, 4 for females); and the lowest rate was in Saudi Arabia (4.8 for males, 1.3 for females)[14]. It is the sixth cancer site in Kuwait[15]. The discovery of genetic abnormalities especially related to epidermal growth factor receptor and anaplastic lymphoma kinase have revolutionised the treatment of lung carcinomas. Small biopsies or cytological specimens are the source of tissue diagnosis in nearly 70% of lung carcinomas[16]. Discrepancies between cytology and biopsy are important to recognise and review, because they can lead to confusion in the decision–making process for patient management. The present study was conducted to evaluate the efficacy of BB and/or BAL in the diagnosis of lung tumors in our hospital and the results were correlated with the bronchial biopsy. To the best of our knowledge, this type of study has not been reported from Kuwait.

In this study on bronchial biopsy, we found squamous cell carcinoma (32.9%) to be the most common subtype, followed by adenocarcinoma (23.3%) with small cell and non-small cell carcinoma (each 12.3%). Other studies have reported varying frequencies. One study from a University hospital in Saudi Arabia also found squamous cell carcinoma to be the most common cell type in their study[16]. In the United States of America and many other countries, adenocarcinoma has become the most commonly diagnosed type of lung cancer, while in Europe, despite squamous cell carcinoma remaining the most predominant cell type, the rates of adenocarcinoma have steadily increased[17]. In Asian countries, squamous cell carcinoma has been reported as the most common cell type, followed by small cell carcinoma and adenocarcinoma[18]. Very scarce data is available from the GCC countries, where squamous cell carcinoma has been reported to be the most frequently diagnosed histological type[14], except from Qatar, where adenocarcinoma was the most frequent histological type[17].

In this study, the cytological specimens were positive in 36 (49.3%) of the 73 carcinoma cases in biopsy. BAL alone was positive in 8 (22.2%); BB in 4 (11.1%) and a combination of the two in 24 (66.7%) cases (Table 4). In the 24 cases of lung carcinoma where both BAL and BB were available, the carcinoma was

### Table 5: Correlation of BAL and BB findings in 24 cases where both were available

<table>
<thead>
<tr>
<th>Cytological Diagnosis on BAL</th>
<th>Total cases</th>
<th>Small cell carcinoma</th>
<th>Squamous cell carcinoma</th>
<th>Adeno carcinoma</th>
<th>NSCLC</th>
<th>NSCLC favor Ad Ca</th>
<th>Malignant NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign / Inflammation</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Atypical cytology</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suspicious cytology</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Note:** BAL: bronchoalveolar lavage; BB: bronchial brushings; NSCLC: non small cell lung carcinoma; NSCLC favor Ad Ca: Non small cell lung carcinoma favor adeno carcinoma; NOS: not otherwise specified.
diagnosed in all the 24 cases on BB, but was identified in only 13 of 24 BAL specimens (3 cases reported as benign or inflammatory, one as unsatisfactory, 5 as atypical cytology and 2 as suspicious cytology) (Table 5). Marked variance has been reported in the diagnostic yield of bronchial washings. No significant difference was found between sensitivity of pre-biopsy washing and post biopsy washing\[3,7,8\]. Many studies have reported that the diagnostic yield did not increase when bronchial washings were added to studies have reported that the diagnostic yield did not increase when bronchial washings were added to bronchial biopsy\[6\]. However, others have suggested that bronchial biopsy, brushing and washing should be performed to obtain optimal diagnostic yield\[18\]. In our study, the sensitivity and specificity for BAL specimens was 32.3% and 100%, while it was 59.1% and 95.5% for BB. Hence, our study also supports the view that all the three specimens augment the chances of diagnosing bronchogenic carcinoma. We had only one false positive case on cytology which was reported as NSCLC and the bronchial biopsy in this case revealed necrotic material, but a repeat biopsy confirmed the tumor. Studies have shown that increasing the number of attempts at obtaining BAL sampling can improve its sensitivity, specificity and accuracy\[19\]. The statistical values in our study were obtained with a single sample, which may be the reason why our values are less than the previous studies.

The limitations of our study is that we have resorted only to morphology for characterisation of the tumor. As is well known, there is a dire need to separate adenocarcinoma from squamous cell carcinoma for management purposes\[18\]. All NSCLC should be further categorised. For this, molecular studies are incorporated and cytology samples are a good specimen source for these studies\[15,18\]. However, we felt it was important to document the morphological diagnosis on cytology in the characterization of lung tumors due to the paucity of literature from the Middle East.

CONCLUSION

This retrospective study demonstrates that a judicious combination of BAL, BB or both along with bronchial biopsy are highly valuable in the diagnosis of bronchogenic carcinoma. In Kuwait, squamous cell carcinoma was the most common tumor type, followed by adenocarcinoma and small cell carcinoma. Subtyping of NSCLC needs to be done by immunohistochemistry and molecular studies.

ACKNOWLEDGMENTS

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REFERENCES


Cystectomy and urinary diversion improves health-related quality of life in female patients with non-malignant urologic diseases

Senol Tonyali, Sertac Yazici, Batuhan Aydogan, Ali Ergen
Department of Urology, Hacettepe University School of Medicine, Ankara, Turkey

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ABSTRACT

Objective: To evaluate the health related quality of life (QoL) in female patients with non-malignant diseases after cystectomy and ileal conduit and to assess postoperative complications

Design: Retrospective cohort study

Setting: Department of Urology, Hacettepe University School of Medicine

Subjects: All patients that underwent simple cystectomy and an ileal conduit for the treatment of refractory non-malignant diseases between 1 January 2005 and 1 January 2015

Intervention: None

Main outcome measure: Post-operative complication, health-related QoL

Results: The study included 13 female patients. The underlying urological diseases included were interstitial cystitis (7/13), neurogenic bladder (5/13) and hemorrhagic cystitis (1/13). Mean duration of surgery was 231.9 ± 20.97 minutes and mean estimated blood loss was 1219 ± 873.5 mL. The mean preoperative serum creatinine level was 1.25 ± 0.73 mg dL⁻¹ (range: 0.49 - 2.8 mg dL⁻¹), versus 1.55 ± 1.21 mg dL⁻¹ (range: 0.48 - 4.65 mg dL⁻¹) a median 56.9 months post surgery. In all, nine patients (69.2%) had grade I-III complications within 30 days of surgery, according to Clavien-Dindo classification. Three patients died a mean 34.4 months post surgery. The remaining 10 patients reported significant improvements in all domains of SF-36 after cystectomy and ileal conduit.

Conclusion: Cystectomy plus ileal conduit can be performed earlier in highly selected, treatment-refractory, and well-informed patients with non-malignant diseases, and can be an effective method for improving QoL, despite the associated high morbidity rate.

INTRODUCTION

Cystectomy plus urinary diversion is the standard treatment for muscle-invasive, non-metastatic urothelial tumors. Nonetheless, cystectomy is associated with many minor and major postoperative complications, and the reported morbidity and mortality rates are 20 - 64% and 0.3 - 9.5%, respectively[1]. In addition to oncologic treatment, cystectomy could be considered an alternative for the treatment of complex treatment-refractory non-malignant diseases, such as bladder pain syndrome/interstitial cystitis (BPS/IC), neurogenic bladder, hemorrhagic cystitis, radiation-induced cystitis, and urinary fistula. According to American Urology Association and European Urology Association guidelines, surgery is recommended as a last resort for treating refractory BPS/IC[2,3]. Precise preoperative evaluation is mandatory in all patients scheduled to undergo cystectomy. Additionally, patients must be well informed about the procedure and its irreversibility; as such, patients must play a central role in the decision to perform cystectomy.

The literature includes only a few studies and inconsistent findings on cystectomy in patients with non-malignant diseases and its effect on quality of life (QoL)[4,5]. To the best of our knowledge, no study

KEYWORDS: female, ileal loop, interstitial cystitis, neurogenic bladder, pelvic surgery

Address correspondence to:
Senol Tonyali, MD, FEBU, Hacettepe University School of Medicine, Department of Urology 06100 Sihhiye, Ankara, Turkey. Tel: +90 312 305 1885; E-mail: senoltonyali@hotmail.com
has examined the effect of cystectomy and an ileal conduit on QoL in female patients with non-malignant diseases. The present study aimed to measure QoL in female patients with non-malignant diseases following cystectomy and an ileal conduit, and to assess postoperative complications. It was hypothesized that cystectomy and an ileal conduit would improve QoL in female patients with non-malignant disease (with an acceptable complication rate), and could prove to be the preferred early treatment option.

SUBJECTS AND METHODS
Following the approval of the study protocol by the local Ethics Committee, the medical records of all patients that underwent simple cystectomy and an ileal conduit for the treatment of refractory non-malignant diseases, including BPS/IC, intractable urinary incontinence, neurogenic bladder, and hemorrhagic cystitis, between 1 January 2005 and 1 January 2015 were retrospectively analyzed. The parameters that were analyzed included patient demographics, primary diagnosis, history of medical and/or surgical treatment, duration of surgery, intraoperative bleeding and complications, surgical procedure, the preoperative and postoperative creatinine (Cr) level, final pathology findings, and early (within postoperative 30 days) and late (within postoperative 90 days) complications. Complications were defined according to Clavien-Dindo classification.

The Medical Outcomes Study-Short Form 36 (SF-36®), a widely used scale, was administered twice currently to assess pre- and post- operative health-related QoL. The SF-36 questionnaire includes 36 questions in the following 8 domains: general heath (GH); physical functioning (PF); social functioning (SF); physical role limitations (RP); emotional role limitations (RE); bodily pain (BP); vitality (VT); and mental health (MH). Each domain has a scoring scale of 0 - 100, with higher scores indicative of better domain-specific QoL[6,7]. SF-36 was used in the present study because it is a self-administered questionnaire that can be completed in 5 - 10 minutes; it is not disease, age, or cohort-specific; and it has a validated Turkish version[7]. Interpretation of the SF-36 scores was made on norm-base scores with a mean of 50 ± 10, rather than 0 = 100 scores to avoid erroneous conclusions, to make interpretation simply. In addition to SF-36, the patients were also asked 2 questions post surgery: “Do you have any regrets about having undergone cystectomy?” and “Would you have undergone cystectomy sooner knowing what you know now?”

RESULTS
The study included 13 female patients, of which 10 (76.9%) completed the SF-36 a mean 63.7 ± 38.7 months (range: 17 - 140 months) post surgery. Patient demographics and characteristics are shown in Table 1. Mean age of the patients was 58.6 years (range: 39 - 72 years).

Among the patients, one had hemorrhagic cystitis due to cyclophosphamide treatment for Behcet’s disease; she received intravesical alum instillation, which provided transient symptom relief.

In total, seven patients were diagnosed as BPS/IC, and all underwent cystoscopy with hydrodistention. Hydrodistention provided transient symptom relief in 57.1% of these seven patients. In addition, cystoscopy showed that three of these seven patients had Hunner’s lesions. All seven BPS/IC patients were using various oral medications, including antidepressants, antihistamines, gabapentin, H1 receptor blockers, and antibiotics, and underwent intravesical installation of hyaluronic acid or a cocktail consisting of heparin, corticosteroids, and prilocaine. Of the seven BPS/IC patients, one received an intradetrusor onabotulinumtoxinA injection and one had sacral neuromodulation failure.

The remaining five BPS/IC patients had an intractable neurogenic bladder. Neurogenic bladder was caused by acquired disease, trauma, and congenital abnormalities. In one patient, neurogenic bladder was due to falling from a height. Two patients had undergone several procedures for urinary incontinence, including cystocele repair, bladder neck injection, and trans-vaginal taping. Two patients had a small fibrotic bladder due to prolonged urinary catheterization; as such these patients had an indwelling urinary catheter for three and fifteen years, respectively. All five patients with a neurogenic bladder were suffering from severe urinary incontinence, and cystectomy was the treatment of choice not only to alleviate functional and social difficulty, but also for preservation of the upper urinary tract and perineum. Augmentation cystoplasty and intermittent catheterization was offered to one patient, but she chose to undergo cystectomy due to physical impairment and lack of ancillary support. Preoperatively, medical history was positive for chronic kidney disease in four patients, coronary artery disease in four, and cerebrovascular disease in two.

All 13 patients underwent open total cystectomy and an ileal conduit, and four also underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy. Mean duration of surgery was 231.9 ± 20.97 minutes and mean estimated blood loss was 1219 ± 873.5 mL. The mean preoperative serum Cr
level was 1.25 ± 0.73 mg dL⁻¹ (range: 0.49 - 2.8 mg dL⁻¹), versus 1.55 ± 1.21 mg dL⁻¹ (range: 0.48 - 4.65 mg dL⁻¹) a median 56.9 months post surgery. Definitive pathologic evaluation showed inflammation in all patients, with additional squamous metaplasia in five patients.

In all, nine patients (69.2%) had grade I-III complications within 30 days of surgery, according to Clavien-Dindo classification. Among those patients, two (14.2%) had grade I complications, three (21.4%) had grade II complications, and four (30.7%) had grade IIIa-IIIb complications. In total, three patients required blood transfusion during surgery and one other underwent explorative laparotomy due to a prolonged ileus. Parastomal hernia developed in three patients (23%), and three other patients (23%) developed incisinal hernia within 90 days of surgery. None of the hernia cases were serious enough to require surgery. In all, two patients with BPS/IC and one patient with a neurogenic bladder died a mean 34.4 months post surgery due to chronic kidney disease and sepsis.

### Health-related QoL outcomes

The pre-operative and post-operative SF-36 scores by domain are given in Table 2. All 10 patients that completed the SF-36 reported significant improvement in all 8 domains (PF, RP, BP, GH, VT, SF, RE, and MH) following cystectomy and ileal conduit. The greatest improvement was in MH and

<table>
<thead>
<tr>
<th>Pts. No</th>
<th>Age</th>
<th>Primary disease</th>
<th>Prior surgery – intervention</th>
<th>Initial diagnosis to cystectomy time</th>
<th>Operation procedure</th>
<th>Pre-op Cr</th>
<th>Post-op Cr</th>
<th>Postop early complications (within 30 days)</th>
<th>Postop late complications (within 90 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>48</td>
<td>IC/BPS</td>
<td>C&amp;HD; II</td>
<td>3 years</td>
<td>SC + ileal conduit</td>
<td>2.8</td>
<td>3.2</td>
<td>Vagen cuff dehissance</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>IC/BPS</td>
<td>C&amp;HD; TAH; II</td>
<td>20 years</td>
<td>SC + ileal conduit</td>
<td>0.51</td>
<td>0.57</td>
<td>None</td>
<td>Parastomal hernia</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>IC/BPS</td>
<td>C&amp;HD; TAH+USO; internal uretrotomy x3; II</td>
<td>4 years</td>
<td>SC + ileal conduit + USO</td>
<td>1.08</td>
<td>0.74</td>
<td>None</td>
<td>Parastomal hernia</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>Neurogenic bladder</td>
<td>TAH; BNI x3 unknown op related to incontinence</td>
<td>30 years</td>
<td>SC + ileal conduit</td>
<td>0.78</td>
<td>0.92</td>
<td>Hemoglobin decrease</td>
<td>Incisinal hernia</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Hemorrhagic cystitis</td>
<td>Intravesical alum</td>
<td>10 years</td>
<td>SC + ileal conduit + bilateral iliac artery ligation</td>
<td>1.41</td>
<td>2.36</td>
<td>Ileus</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>Neurogenic bladder</td>
<td>Oophorectomy, cystocele repair, BNI</td>
<td>4 years</td>
<td>SC + ileal conduit + USO</td>
<td>1</td>
<td>1.34</td>
<td>Postop fever</td>
<td>Parastomal hernia</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>Neurogenic bladder</td>
<td>Indwelling urethral catheter during 15 years</td>
<td>15 years</td>
<td>SC + ileal conduit</td>
<td>0.49</td>
<td>0.48</td>
<td>Hemoglobin decrease</td>
<td>None</td>
</tr>
<tr>
<td>8*</td>
<td>60</td>
<td>IC/BPS</td>
<td>C&amp;HD; II</td>
<td>5 years</td>
<td>SC + ileal conduit + TAH + BSO</td>
<td>2.55</td>
<td>4.65</td>
<td>Wound infection</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>Neurogenic bladder</td>
<td>None</td>
<td>10 years</td>
<td>SC + ileal conduit + TAH + BSO</td>
<td>0.77</td>
<td>0.81</td>
<td>Fascia dehissance</td>
<td>Incisinal hernia</td>
</tr>
<tr>
<td>10*</td>
<td>53</td>
<td>Neurogenic bladder</td>
<td>Pyelolithotomy, Tur, indwelling urethral catheter during 3 years</td>
<td>10 years</td>
<td>SC + ileal conduit</td>
<td>1.6</td>
<td>1.82</td>
<td>Wound infection</td>
<td>Incisinal hernia</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>IC/BPS</td>
<td>C&amp;HD; II</td>
<td>3 years</td>
<td>SC + ileal conduit + TAH + BSO</td>
<td>0.75</td>
<td>0.8</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>66</td>
<td>IC/BPS</td>
<td>C&amp;HD; II</td>
<td>4 years</td>
<td>SC + ileal conduit + TAH + BSO</td>
<td>1.69</td>
<td>0.86</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>72</td>
<td>IC/BPS</td>
<td>Partial nephrectomy, TAH; C&amp;HD; II</td>
<td>7 years</td>
<td>SC + ileal conduit</td>
<td>0.83</td>
<td>0.86</td>
<td>Hemoglobin decrease</td>
<td>None</td>
</tr>
</tbody>
</table>

TAH: total abdominal hysterectomy; IC: interstitial cystitis; BPS: bladder pain syndrome; USO: unilateral salpingooophorectomy; BSO: bilateral salpingooophorectomy; BNI: bladder neck injection; SC: simple cystectomy; C&HD: cystoscopy and hydrodistention; II: intravesical instillation; * Exitus
the least improvement was in PF. The reported level of improvement in BP in the patients with interstitial cystitis was significantly higher than in those with a neurogenic bladder. None of the 10 patients reported regretting undergoing cystectomy, all indicating that they would have undergone cystectomy sooner than they did, based on what they knew post surgery.

**DISCUSSION**

BPS/IC is a debilitating condition of unknown etiology. It is described as an unpleasant sensation (pain, pressure and discomfort) associated with the urinary bladder that is accompanied by lower urinary tract symptoms of >6 weeks in duration in the absence of any identifiable cause. Multimodal treatment approaches, including behavioral modification, physical therapy, pharmacology, intravesical instillation and injection, and neuromodulation have the potential to be successful. In carefully selected patients, major surgery such as substitution cystoplasty and urinary diversion with or without cystectomy can be a last resort[2]. In contrast, some researchers suggest urinary diversion without cystectomy in BPS patients because of the severe surgical trauma associated with cystectomy and inconclusive results data[8].

Pain is a primary characteristic of BPS/IC. Some patients even consider suicide due to the unbearable pain, but they must be clearly informed that cystectomy for BPS/IC might not lead to pain relief and that they may continue to experience intractable pain after cystectomy[9]. All seven BPS/IC patients in the present study were suffering from pain prior to cystectomy and all 7 reported pain alleviation after cystectomy and ileal conduit. In addition, other treatment-refractory benign conditions, such as neurogenic bladder, bleeding, infection, incontinence, and fistulas can be clinically challenging and require aggressive surgery.

In patients with neurologic bladder dysfunction, the primary aim of urologic treatment is preservation of renal function, as well as prevention of general complications such as ulcer and fistulas[20], but of course, patient QoL must also be considered. Although self-intermittent catheterization is the first line of treatment, lack of ancillary support, cognitive impairment, and neurologic deficit such as paralysis and limited dexterity can lead to treatment failure[10].

It was reported that complete cystectomy for severe treatment-refractory benign disease was an effective and morbid procedure, with a symptom resolution rate of 73% at 90 days post surgery and a grade ≥III complication rate of 47% within 30 days of surgery[4]. Guillotreau et al.'s[11] prospective study examined the effect of cystectomy and ileal conduit urinary diversion on QoL in patients with neurogenic bladder dysfunction. They reported that cystectomy reduced the limitations and constraints, improving urinary QoL; however, they did not observe any effect of the procedure on general QoL.

Surgical procedure and type of urinary diversion can affect surgical outcome and QoL. Kim et al.[1] compared the early and late complications of two types of urinary diversion (neobladder and ileal conduit) combined with radical cystectomy. The early complication rate in the neobladder group was 54.8% versus 45.2% in the ileal conduit group; the difference was not significant. They also reported that QoL and prognosis—in terms of duration of hospitalization, late complications, and major morbidity—might not be worse in neobladder patients than ileal conduit patients, in contrast to what many clinicians think.

In the present study, major complications occurred in 30.7% of the patients, a rate similar to that in earlier studies[12]. Ileal conduit was used in the present study instead of neobladder because of the higher complication and morbidity rates associated with neobladder. In addition, neobladder candidates must have sufficient renal function; as such, neobladder might have negatively affected renal function in the present study’s patients. Moreover, four patients in the present study had chronic kidney disease preoperatively. Lastly, the need for self-intermittent catheterization associated with neobladder was a consideration for not using it.
In the present study, total abdominal hysterectomy was performed in addition to cystectomy in postmenopausal patients and patients with gynecological problems in consultation with gynecologist; however, internal genital organs should be spared while performing cystectomy, so as to preserve sexual function and fertility potential. Laparoscopic or robot-assisted cystectomy could be an appropriate alternative to open surgery. The advantages of these procedures—even in oncologic cases—have been reported and include decreases in intraoperative and postoperative morbidity, mortality, and duration of hospitalization. In addition, laparoscopic or robot-assisted intracorporeal ileal conduit or neobladder can be performed safely by experienced surgeons, and contribute to improved body image.

A recent study on QoL and functional outcome in patients that underwent cystectomy and urinary diversion for treatment-refractory disease secondary to radiation therapy included 12 patients with refractory fistulas, 12 with radiation cystitis, four with pelvic pain, and one with incontinence. Improvement was reported in all eight SF-36 domains in all patients; the greatest improvement was in the RE domain. In the present study, cystectomy plus ileal conduit resulted in significant improvement in health-related QoL, especially in psychological domains.

In the present study, major complications occurred in 30.7% of the patients, which is comparable to previous reports. In all, one patient with chronic kidney disease, one with hypertension, and one with cerebrovascular disease (mean age: 53.6 years) died 26, 27, and 50 months after cystectomy respectively, which clearly shows that comorbidity is associated with increased mortality. These findings indicate that cystectomy could be considered a treatment option before renal function and/or other organ systems are affected.

The present study has some limitations. The study included patients with various non-malignant urologic diseases (BPS/IC, neurogenic bladder, and hemorrhagic cystitis) and some measurements were performed retrospectively. Due to the paucity of suitable patients (13 in 10 years), we concluded that it was not possible to perform the study prospectively. Moreover, due to the study’s retrospective design, it was not possible to collect QoL data before cystectomy. To avoid recall bias, we performed two surveys, first regarding preoperative and the second regarding postoperative (actual) QoL, one month apart.

CONCLUSION

Patients with treatment-refractory diseases, such as neurogenic bladder, interstitial cystitis, and hemorrhagic cystitis, can experience significant decreases in QoL and physical functioning. Cystectomy plus ileal conduit can be performed earlier in highly selected, treatment-refractory, and well-informed patients with non-malignant diseases, and can be an effective method for improving QoL, despite the associated high morbidity rate.

REFERENCES


ABSTRACT

Objective: In this study, we evaluated the pathological results and clinical presentation of patients with retroperitoneal tumors
Design: Retrospective study
Setting: Department of Urology at Hitit University, Çorum Erol Olçok Training and Research Hospital, and Department of Urology at Haydarpasa Numune Training and Research Hospital
Subjects: Fourteen patients with retroperitoneal tumors
Intervention: Retroperitoneal mass and clinical suspicion of tumor
Main outcome measures: The symptoms at presentation and pathologic reports of the tumors were recorded in these patients.
Results: Of the patients evaluated for retroperitoneal tumor, eight patients were male. The mean age of the study group was 55.7 ± 11.4 years with a range of 41 to 75 years. Liposarcoma was the most common pathological diagnosis of the retroperitoneal tumors in these patients (35.7%). Schwannoma and gastrointestinal stromal tumor were reported in two patients. The other retroperitoneal masses were diagnosed as atypical lipomatous tumor, paraganglioma, myelolipoma, lipomatous hemangiopericytoma and Castleman disease.

Conclusion: Retroperitoneal tumors are rare neoplasms in daily urological practice. With the development of radiological imaging techniques in recent years, most of the patients have been diagnosed incidentally at abdominal imagings for other purposes. The management of these patients is important because of the aggressive behavior of sarcomas.

INTRODUCTION

The retroperitoneum is a complex potential area bounded anteriorly by the peritoneum, ipsilateral colon and mesocolon, liver, pancreas and stomach, and the posterior side is composed of the psoas, quadratus lumborum, transverse abdominal and iliacus muscles, diaphragm, ipsilateral kidney, ureter and gonadal vessels[1,2]. The retroperitoneum offers an environment for a wide spectrum of pathologies, including a variety of rare benign lesions and malignant neoplasms that can be either primary or metastatic. The malignant neoplasms occur four times more frequently than benign lesions[3]. Soft tissue sarcomas, 1% of all newly diagnosed malignancies, are mesenchymal tumors[4]. The retroperitoneum is the second most common site of origin of malignant mesenchymal tumors, after the lower extremities[5]. Sarcomas were reported to account for one-third of all retroperitoneal tumors. Other retroperitoneal tumors include primary lymphoproliferative tumors (Hodgkin’s and non-Hodgkin’s), epithelial tumors and metastatic disease from known or unknown primary sites[6]. Benign tumors of the retroperitoneum are schwannomas, neurofibromas, paragangliomas, fibromatosis, renal angiomyolipomas and lipomas[7]. We evaluated the patients who underwent retroperitoneal exploration secondary to the retroperitoneal tumor retrospectively.

SUBJECTS AND METHODS

A total of twenty-two patients managed with retroperitoneal surgery between January 2011 and March 2015 were evaluated retrospectively. The patients were diagnosed by ultrasonography; computerized tomography (CT) and magnetic resonance imaging (MRI) were used for differential diagnosis. Figures 1 and 2 show the retroperitoneal tumor mass preoperatively. The patients whose pathologic report of the surgical excision showed a...
non-tumoral mass were excluded from the study. The clinical symptoms, the age and gender of the patients, radiological and pathological findings of the 14 patients with retroperitoneal tumor were recorded. All surgical procedures were performed with open surgical techniques using subcostal Chevron incision. Total tumor excision was performed in all patients.

Fig 1: Computerized tomography image of the retroperitoneal mass (liposarcoma)

Fig 2: Magnetic resonance imaging showing the lesion (Schwannoma)

Of the study group, liposarcoma was reported in five patients with four well differentiated and one undifferentiated histology. Lipomatous hemangiopericytoma, atypical lipomatous tumor, paraganglioma, myelolipoma and Castleman diseases (CD) were detected in one patient histologically. Schwannoma and gastrointestinal stromal tumor were diagnosed in two patients. Pathological results and clinical presentations are shown in Table 1. Immunohistochemical study was performed in seven patients. Smooth muscle actin (SMA), CD34,99,117, desmin, S-100, Ki67, Bcl-2, melanoma-specific melanoma marker (MART), inhibin, synaptophysin and chromogranin were used for immunohistochemical examination.

Table 1: Presentations and pathological results of the patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Symptom</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>75</td>
<td>Flank pain</td>
<td>Lipoma</td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>Nonspecific</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>Abdominal swelling</td>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td>Female</td>
<td>65</td>
<td>Hot flushes</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>Abdominal pain</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>Flank pain</td>
<td>GIST</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>Abdominal swelling</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Female</td>
<td>65</td>
<td>Nonspecific</td>
<td>Myelolipoma</td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>Flank pain</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>Abdominal pain</td>
<td>Schwannoma</td>
</tr>
<tr>
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<td>48</td>
<td>Flank pain</td>
<td>GIST</td>
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<tr>
<td>Female</td>
<td>55</td>
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<td>Liposarcoma</td>
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<td>Female</td>
<td>44</td>
<td>Hematuria</td>
<td>Castleman</td>
</tr>
<tr>
<td>Male</td>
<td>75</td>
<td>Flank pain</td>
<td>Liposarcoma</td>
</tr>
</tbody>
</table>

GIST: gastrointestinal stromal tumor

The mean follow up was 61.14 ± 6.93 months. During the follow up period, there was only one recurrence in a patient who was diagnosed as liposarcoma. A second surgical operation was done. One patient died three years after the operation because of myocardial infarction.

DISCUSSION

The retroperitoneum offers an environment to the tumors to originate and grow to a large size before the patients become symptomatic. Retroperitoneal tumors are usually diagnosed or identified with cross sectional imaging for other problems. Most of the patients present with abdominal mass, increase in girth, palpable mass, early satiety and abdominal discomfort. Patients may present with signs of bowel and/or ureteral obstruction, because of either compression or invasion of nearby structures. Although the most common complaint is abdominal or back pain, weight loss and anemia are the other symptoms. Flank pain and abdominal complaints (71.42%) are the main symptoms of the patients in this study.
Sarcomas account for 33% of all retroperitoneal tumors, with two histological subtypes predominating, namely liposarcoma (70%) and leiomyosarcoma (15%)\(^6\). There is no predominance in terms of gender and race. The patients are usually diagnosed between 54 and 65 years of age\(^8\). These tumors can be found anywhere in the body, with 50% in the extremities, 10-15% in the trunk, less than 10% in the head and 15% in the neck retroperitoneum. Sarcoma was diagnosed in five patients, comprising 35.71% of the patients in the present study. Most of the patients were male (80%) and the mean age was 56.4 years. All patients had liposarcoma and the ratio of well differentiated to poorly differentiated was 4:1. Nephrectomy was performed in two patients because of local invasion of the sarcoma, the other patients were treated with tumor removal without nephrectomy (Fig 3).

Schwannoma is usually a benign tumor that originates from Schwann cells of the peripheral nerve sheath\(^9\). These tumors can occur in any neural tissue where Schwann cells are present\(^10\). Schwannomas are commonly found in cranial and peripheral nerves; the retroperitoneal schwannomas comprise 3% of all schwannomas\(^11\). Retroperitoneal schwannomas are approximately 1 - 5% of all retroperitoneal masses (Fig 2). The patients are usually asymptomatic. Although retroperitoneal schwannomas are almost benign, they may very rarely undergo malign transformation\(^12\). Schwannomas are composed of Schwann cells with regions of high and low cellularity termed Antoni A and Antoni B areas, with positive staining of S-100 microscopically\(^11\). Two patients had schwannoma in this study, with an incidence of 1.4%. The patients presented with flank pain and abdominal pain.

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract and represents less than 1% of all malignancies\(^13\). GIST arises from the wall of gastrointestinal tract and is thought to originate from the cells called Interstitial Cells of Cajal and regulate the motility of the gastrointestinal tract. These tumors originate from the stomach, small intestine, colon and esophagus with a ratio of 40 - 70%, 20 - 40%, 5 - 15% and 5% respectively. These tumors may rarely occur outside the gastrointestinal tract and are called extra gastrointestinal stromal tumor\(^14\). CD 117 protein is the most specific and important marker, expressed in more than 95% of cases. GIST were reported in two patients in pathological evaluation. CD 117, Ki-67, S 100, CD 34, SMA and desmin were performed in these patients. CD 117 was positive (Fig 4a), S-100 and desmin were negative in two patients. CD 34 (Fig 4b) and SMA were positive in one patient. Ki-67 was less than 10% in the patients. Using the Fletcher classification scheme\(^15\), one patient’s tumor had high risk, and the other had intermediate risk for aggressive behaviour.

Myelolipoma is an uncommon benign tumor of the adrenal gland which consists of mature fat and mixed myeloid and erythroid cells\(^16\). Proportion of fat and myeloid tissue is the key factor for preoperative diagnosis by CT or MRI. Presence of calcifications, necrosis and intratumoral hemorrhage may confuse the diagnosis. Differential diagnosis include adrenal adenomas, retroperitoneal lipomatous masses such as liposarcoma, lipoma and angiomylipoma. One patient was diagnosed with adrenal myelolipoma in the present study.

CD is an unusual benign lymphoid tumor\(^17\). It is classified into two groups with localized and multicentric subtypes. Three histological variants
(hyaline-vascular, plasma cell and mixed types) have been described. Multicentric type of CD has a worse prognosis than localized type. CD may arise wherever lymphoid tissue is found. The most common site of origin is mediastinum; and the retroperitoneum is an uncommon localization which accounts for 7% of cases\(^\text{18}\). Complete surgical resection is an effective treatment and suggested for localized disease\(^\text{17}\).

Chemotherapy and immunotherapy are effective for multicentric types of CD, if the diagnosis is confirmed histologically by lymphnode biopsy\(^\text{19}\).

Paragangliomas are rare tumors which arise from the neural crest tissue that develops into sympathetic and parasympathetic paraganglia throughout the body\(^\text{20}\). Paraganglioma of adrenal medulla is known as pheochromocytoma, while paragangliomas located outside of the adrenal gland are called as extra adrenal paragangliomas. These tumors can be divided into functioning and non-functioning based on their ability to secrete hormones. Extra adrenal paragangliomas account for 10 - 15% of all paragangliomas and the age of the diagnosed is between 30 and 45 years\(^\text{21}\). The most common site for retroperitoneal paragangliomas is between the origin of inferior mesenteric artery and the aortic bifurcation that is known as organ of Zuckerkandl\(^\text{23}\). Clinical presentations of retroperitoneal paragangliomas are based on location and ability to secrete hormones such as fluctuating or episodic hypertension, headache, and sweating. Nonfunctioning paragangliomas are usually asymptomatic and diagnosed incidentally as a mass. While CT scan also has a sensitivity of around 90% for identifying extra adrenal paragangliomas, MRI sensitivity for extra adrenal paragangliomas. PET scan has more sensitivity when compared to MIBG scintigraphy\(^\text{22}\). Our patient presented with sweating and hot flushes for three months. MIBG scintigraphy was used for diagnosis and detected positive findings for paraganglioma. Immunohistochemical study was performed with MART, inhibin, synaptophysin, chromogranin and Ki-67. Synaptophysin and chromogranin were positive (Fig 5); MART and inhibin were negative; and Ki-67 was less than 1%.

Hemangiopericytoma is a rare benign tumor derived from a type of smooth muscle cell attached to pericytoma, capillaries also known as Zimmerman pericytes and initially described by Stout and Murray in 1942\(^\text{23}\). The new edition of the World Health Organization Classification classified hemangiopericytoma into three groups; solitary fibrous tumor, incluing giant cell angiofibroma and lipomatous hemangiopericytoma\(^\text{24}\). Lipomatous hemangiopericytoma is a rare benign mesenchymal neoplasm that grows slowly and consists of mature adipocytes and hemangiopericytoma like areas\(^\text{25}\). The common sites of this tumor are the deep soft tissues of the lower extremity and the retroperitoneum. Nielsen described this unique variant of hemangiopericytoma in 1995\(^\text{26}\). Positive staining of CD 34 and 99 can be helpful in immunohistochemical study for the diagnosis\(^\text{25}\). The tumor size of the patients was 16 cm and immunohistochemical study revealed positive staining for CD 31, 34, 99, Bcl-2, SMA, desmin, S100 and negative staining for CD 117 in pathological evaluation.

The retrospective design of the study and small number of patients are the main limitations of this study. The patients were treated and diagnosed by different pathologists and surgeons respectively.
CONCLUSION

The retroperitoneal tumor is a rare condition in urology practice. With widespread use of ultrasonography and other imaging techniques, retroperitoneal tumor incidence is increasing in urology practice. Preoperative evaluation is very important because of limited diagnostic accuracy.

REFERENCES

Original Article

Alternate approaches for effective reduction in incidence of cervical anastomotic leakage after esophageal cancer resection: a prospective cohort study

Baoping Lang¹, Xiao Zhang¹, Song Zhao²
¹Department of Thoracic Surgery, Luoyang Central Hospital Affiliated To Zhengzhou University, Luoyang 471000, Henan Province, China
²Department of Thoracic Surgery, the First Affiliated Hospital Of Zhengzhou University, Zhengzhou 450052, Henan Province, China

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ABSTRACT

Objective: To investigate the method of operation for esophageal cancer to reduce incidence of cervical anastomotic leakage after resection
Design: Prospective study
Setting: Department of Thoracic Surgery, Luoyang Central Hospital Affiliated to Zhengzhou University
Subjects: All esophageal cancer resection patients from August 2009 to August 2014 were included and grouped according to the admission time.
Intervention: Mechanical cervical esophagogastric anastomosis through the highest point of the tubular stomach in addition to embedment and suspension of the anastomosis (group A, from August 2009 to November 2011, n = 37), mechanical cervical esophagus-tubular stomach anastomosis at the plane of the terminal branches of the right gastroepiploic vessels plus embedment and suspension of the anastomosis with redundant tubular stomach removed (group B, from December 2011 to August 2012, n = 39) and without (group C, from September 2012 to August 2014, n = 62).
Main outcome measures: The incidence of cervical anastomotic leakage
Results: All approaches were performed successfully and the anastomoses were tension-free. The incidence of cervical anastomotic leakage was 24.3% (9/32) in group A, 25.6% (10/37) in group B, and 1.6% (1/62) in group C, respectively. There was no statistical difference between groups A and B, while the anastomotic leakage incidence was much lower in group C than the other two groups (P <0.05).
Conclusions: The mechanical cervical esophagus-tubular stomach anastomosis approach without embedment and suspension of the anastomosis may lead to lower cervical anastomotic leakage after esophageal cancer resection.

INTRODUCTION

Esophageal carcinoma is the eighth most common cause of cancer worldwide⁴, with surgical resection still considered the gold standard treatment⁵. For middle and upper esophageal carcinoma, surgical approaches include subtotal esophagectomy, cervical esophagogastric anastomosis, and thoracolaparoscopic esophagectomy with two-field lymph node dissection. These approaches can effectively reduce the incidence of postoperative recurrence and metastasis. However, a surgical approach involving three incisions of the right thoracic and abdominal portions as well as the cervical anastomosis has a number of disadvantages, including significant surgical trauma, more complications, and lengthy operating times, which are not ideal for either patient or surgeon. Recent studies have shown minimally invasive esophagectomy (MIE) to be safe and effective⁵. Continued improvements in endoscopic techniques have resulted in the development of a combined thoracoscopic and laparoscopic esophagectomy approach. However, anastomotic leakage remains a common complication, with an incidence ranging from 3 – 23.5%⁵. Compared with intrathoracic anastomotic leakage, cervical anastomotic leakage is associated with lower mortality rates⁶, and healing times can be shortened by opening

Address correspondence to:
Song Zhao, Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, 1 liansedong Road, Zhengzhou 450052, Henan Province, China. Tel: +86-0371-67967151; E-mail: songzhaode@126.com
the cervical incision, together with adequate drainage. Nevertheless, this complication still has some adverse effects on patients, such as increased clinical burden and prolonged hospitalization that may lead to anastomotic stenosis, which adversely influences quality of life.

A number of studies have been conducted with the aim of reducing the incidence of cervical anastomotic leakage after surgical resection. Some approaches have included the modification of anastomotic methods, the development of new methods for esophagus reconstruction, and delays in the reintroduction of oral food intake after surgery. However, further improvements to these approaches are required to enhance their efficacy. It is clear, therefore, that further research is required to effectively reduce the incidence of postoperative cervical anastomotic leakage in patients suffering from esophageal carcinoma, which is the rationale of the present research.

Thus, the aim of this study was to investigate approaches to effectively reduce cervical anastomotic leakage after esophageal cancer resection. To meet this goal, we investigated three methods of anastomosis and compared the incidence of anastomotic leakage in a patient population divided into three treatment groups. The most effective method for decreasing the incidence of cervical anastomotic leakage was identified.

**SUBJECTS AND METHODS**

**Patient information**

A total of 138 patients were recruited for this study from August 2009 to August 2014 and combined thoracoscopic and laparoscopic esophagectomy was performed. An endoscopic examination and biopsy was performed on each patient and a diagnosis of esophageal cancer was confirmed by pathology prior to the assigned surgical procedure. Besides regular examinations, all patients underwent chest CT and an upper gastrointestinal radiography test to assess the extent of the lesion and its relationship with the surrounding tissues. Furthermore, the possibilities of surgical resection were evaluated.

**Surgical procedures**

A combined intravenous-inhalational anesthesia was performed on each patient and an artificial pneumothorax was used during surgery. The operational procedures involved positioning the patient in the left lateral decubitus position with the subaxillary lifted by a cushion. The esophagus was isolated under a thoracoscope. The lymph nodes along the esophagus, together with the left and right recurrent laryngeal nerves and the subcarinal nodes, were dissected. An intrathoracic drain was placed.

Phlegm was removed under suction before the lungs were inflated. The surgical openings were sewn closed and dressed.

The patient was then placed in a supine position with the head positioned higher than the feet. The patient’s head was turned to the right. Through an incision along the anterior border of the left sternocleidomastoid muscle, the cervical segment of the esophagus was isolated and divided. Then the stomach was isolated using a laparoscope. The incision under the cartilago ensiformis was extended by about 4 cm. The esophagus was amputated and fixed on a traction suture. The stomach and esophagus were pulled out by the traction suture through the abdominal incision. Fragments of the esophagus and lesser curvature were removed using a 75 mm disposable linear stapler (Johnson & Johnson product). The remnant stomach was processed into a tubal form. Suturing was performed at the highest point of the tubular stomach. Once it was confirmed that the stomach was not twisted, it was pulled out from the left cervical incision by the traction suture through the esophageal hiatus and right chest.

Three anastomosis approaches were used based on the order that the patients were admitted to the hospital. Group A included the first 37 patients admitted. The anastomosis approach in this group involved performing a mechanical cervical esophagogastric anastomosis through the highest point of the tubular stomach using a 25 mm disposable circular stapler (Johnson & Johnson product). The anastomosis was embedded and suspended using four silk sutures (Johnson & Johnson product). Group B included the next 39 hospital admissions. The anastomosis approach performed in this group was a mechanical cervical esophagus-tubular stomach anastomosis at the plane of the terminal branches of the right gastroepiploic vessels using a 25 mm disposable circular stapler (Johnson & Johnson product). Then the redundant tubular stomach was resected. The anastomosis was embedded and suspended using four silk sutures (Johnson & Johnson product). Group C included the last 62 patients admitted to hospital during the recruitment period. The anastomosis approach in this group was the same as group B, except that the embedding and suspension process for anastomosis was not carried out. None of the patients received neoadjuvant chemotherapy. The three surgical techniques are shown in Figure 1. All anastomoses were performed successfully and were tension-free. Gastrointestinal decompression and duodenal nutrition tubes were also placed during surgery. A drainage strip was placed in the cervical incision. Cervical and abdominal incisions were then closed using sutures. There were no significant differences.
Fig 1: Operation schematic diagram of the three techniques

**Operation schematic diagram of group A**

- Performing anastomosis at the highest point of the tubular stomach
- Embedding and suspension after the anastomosis
- The first branch of the right gastroepiploic artery
- The right gastroepiploic artery arch
- Tubular stomach

**Operation schematic diagram of group B**

- The cervical segment of the esophagus
- Embedding and suspension after the anastomosis
- The first branch of the right gastroepiploic artery
- The right gastroepiploic artery arch
- Tubular stomach
- Resection of redundant tubular stomach

**Operation schematic diagram of group C**

- The cervical segment of the esophagus
- Without embedding and suspension after the anastomosis
- The first branch of the right gastroepiploic artery
- The right gastroepiploic artery arch
- Tubular stomach
- Resection of redundant tubular stomach

Alternate approaches for effective reduction in incidence of cervical anastomotic leakage...
in gender, age, disease region, nutritional condition, preoperative complications, or the preparation of the tubular stomach among these three groups. The incidence of anastomotic leakage was recorded and analyzed. All operations were performed by the same cohort surgeons.

**Diagnosis of postoperative anastomotic leakage**

Clinical manifestations of postoperative anastomotic leaks included swelling, heat, pain in cervical incisions, fever, subcutaneous effusion, pneumatosis, and fluctuation of symptoms. Purulent or malodorous secretions, which probably contained gastric juice and food residue, are also seen when the incisions are braced. The complete blood count (CBC) test results may be abnormally high. The esophagogram will show an abnormal flow direction of the contrast agent. When methylene blue is administered orally, the blue liquid flows out from cervical incisions.

**Statistical analysis**

Statistical analysis was performed using SPSS version 17.0 software. The comparison of the incidence of anastomotic leakage among the three groups was performed using the χ² test. Results were considered statistically significant when p ≤ 0.05. The STROBE checklist was consulted and followed[7].

**RESULTS**

Patient characteristics for the three groups are shown in Table 1. The sample patient population consisted of 75 males and 63 females aged from 45 - 78 years (mean age: 64.1 years). Squamous cell carcinoma accounted for 136 cases and two cases were due to adenocarcinoma. From the total 138 patients, the tumors of 40 cases were located in the upper esophagus, 72 were in the middle esophagus, and 26 were in the lower esophagus. In group A, nine patients were diagnosed with anastomotic leakage. In groups B and C, the numbers were ten and one patients, respectively. Thus, the incidence in groups A, B, and C were 24.3%, 25.6%, and 1.6%, respectively. Through opening cervical incisions and adequate drainage, the anastomotic leakages healed after about two weeks for all patients except one, where a small sinus that had not healed developed. During this study, no patients died as a result of surgery. The incidence of anastomotic leakage for the three groups is shown in Table 2. There were no significant differences in incidence of anastomotic leakage between groups A and B (p > 0.05). In contrast, the incidence in group C was significantly lower than that in the other two groups (p < 0.05). There was one patient with postoperative anastomotic stenosis in group B. We treated him with further surgery.

**DISCUSSION**

The traditional surgical approaches to the treatment of esophageal carcinoma include cervico-right thoracic-abdominal triple incision, right thoracic-abdominal double incision, and left thoracic single incision[9]. For the middle and upper esophageal carcinoma, subtotal esophagectomy plus cervical esophagus-gastric anastomosis combined with thoracolaparoscopic esophagectomy with two-field lymph node dissection can effectively reduce the incidence of postoperative recurrence and metastasis. This technique is regarded as the ideal surgical method for the treatment of middle and upper esophageal carcinoma. However, the right thoracic approach requires three incisions plus cervical anastomosis and has several disadvantages. These include major surgical trauma, more complications, longer operating times, and higher mortality rates, all of which limit its application in clinical practice. The objective is to develop new surgical methods that can not only remove tumors effectively and dissect associated lymph nodes, but can also reduce surgical trauma and lower the incidence of postoperative complications and mortality.
Recent studies have shown that MIE is both safe and effective\(^{[3,4]}\). Compared to traditional open surgical procedures, MIE poses some significant advantages. These include reduced intraoperative hemorrhage\(^{[8,9]}\), decreased ICU and hospitalization time\(^{[8,10]}\), fewer perioperative and pulmonary complications, and lower incidences of arrhythmia\(^{[15]}\) and incision infection rate\(^{[12]}\) together with decreased postoperative incision pain. Additionally, in terms of postoperative quality of life and functional recovery, MIE is significantly superior to open procedures\(^{[13]}\). Minimally invasive esophagectomy can reduce the risk of mortality during surgery\(^{[14]}\), but is not significantly different from traditional open surgical procedures in terms of total cost of hospitalization and postoperative survival rates\(^{[10]}\).

There are two types of MIE approaches for the treatment of esophageal carcinoma. A previous study\(^{[15]}\) suggested that MIE plus mechanical intra-thoracic esophagogastric anastomosis can reduce the possibility of anastomotic leakage and injury of recurrent laryngeal nerves. Unfortunately, the procedures involved in this approach are complicated, costly, and require lengthy operating times. More importantly, however, once the anastomotic leakage develops, mortality is significantly higher than it is for cervical anastomosis. For this reason, this surgical procedure is not typically used in clinical practice. Combined thoracoscopic and laparoscopic esophagectomy plus cervical esophagogastric anastomosis is a more widely adopted approach. Nevertheless, anastomotic leakage remains a common postoperative complication with an incidence of 3 – 23.5\(^{[9]}\), which is not significantly different to the incidence for traditional three-incision open chest surgery. The mortality rates as a result of cervical anastomotic leakage is significantly lower than that of intrathoracic anastomotic leakage\(^{[8]}\), and type I-II carries a relatively high possibility of death\(^{[16]}\). The leakage can heal in a short time through opening the cervical incision and adequate drainage. Nonetheless, complications prolong the length of time patients are required to stay in hospital, together with the associated economic burden. Moreover, it can cause postoperative anastomotic stenosis, which can adversely influence the quality of life of patients.

A number of studies have been conducted to investigate methods that can prevent postoperative cervical anastomotic leakage. Kondra et al\(^{[17]}\) found that a partially stapled cervical esophagogastric anastomosis (stapled posterior wall and hand-sewn anterior wall) could effectively reduce the leakages. Despite this, 12.7% of patients who underwent this approach developed an anastomotic leakage. Fang and colleagues\(^{[18]}\) showed in their study that for patients with a systemic lymph node dissection, a prolonged nasal-gastric drainage of more than seven days could significantly decrease the incidence of leakage to 9.1%. In another study\(^{[19]}\), the authors suggested an esophageal-tubular stomach hand-sewn two-layer anastomosis method. This method had a lower incidence of anastomotic leakage than esophageal-whole stomach hand-sewn two-layer anastomosis. However, an incidence of 5.5% persisted. Further research\(^{[20]}\) reported end-to-side anastomosis using a circular stapler. The anastomosis and remaining esophagus were embedded into the stomach. This approach reduced the incidence of anastomotic leakage to 3.3%. However, the incidence of strictures was 11.4%. Zheng et al suggested that omentoplasty could significantly reduce the incidence of cervical anastomotic leakage down to 3.3% following esophageal carcinoma surgery\(^{[21]}\). Other researchers\(^{[3]}\) have found that delaying oral consumption of food after esophagectomy (up to 12 days) could reduce the incidence of cervical anastomotic leakage from 14% to 3%.

A study conducted by Behzadi and colleagues suggested that for both cervical and intrathoracic anastomosis, the stapled approach was superior to the hand-sewn technique in preventing leakage\(^{[22]}\). In our study, we adopted the mechanic anastomotic approach for all patients. The patients in groups A and B underwent mechanical cervical esophagus-tubular stomach end-to-side anastomosis plus embedding and suspension of the anastomosis. The postoperative leakage rates were 24.3% and 25.6% respectively, which are consistent with previously published data. The patients in group C underwent mechanical cervical esophagus-tubular stomach end-to-side anastomosis without any treatment of the anastomosis. The leakage rate was reduced to 1.6%, which was significantly lower than the rates in groups A and B, as well as the rates reported by other studies.

The incidence of anastomotic leakage in groups A and B did not achieve statistical significance. Moreover, embedding of anastomosis can reduce the anastomotic tension. Compared to groups A and B, the incidence of anastomotic leakage in group C was significantly less. The tubular stomach is long enough for three type of anastomosis without tension. There were differences in anastomosis site in terms of anastomotic blood flow for group A compared to groups B and C. In terms of postoperative anastomotic fistula, there was no statistical difference between groups A and B; but there was significant difference for group C compared to groups A and B. These results suggest that there is no significant association between anastomotic leakage and anastomotic tension or local blood supply. The result of upper gastro-enterography for all three groups also showed no significant inter-
group differences in the passage of contrast agent and the shape of the reconstructed esophagus. This finding suggests that there is no significant association between local tension and anastomotic leakage. In addition, there were no significant differences between these three groups in other factors including gender, age, diseased region, nutritional state, preoperative complications, and preparation of the tubular stomach, which excluded the effects of factors such as nutrition and complications. We considered that because the anastomotic leakage was not embedded and suspended, this enhanced the anastomotic patency and reduced the pressure in the upper esophagus. It caused hypertrophy of the anastomotic surrounding tissue and formed a high-pressure area. When patients coughed and swallowed, the esophageal pressure through anastomotic conduction was blocked. This increased the incidence of anastomotic fistula. The mechanism of the approach in group C in reducing the incidence of anastomotic leakage was not embedded and suspension of the anastomosis. This enhanced the anastomotic patency and decreased the pressure in the upper esophagus. It caused hypertrophy of the anastomotic surrounding tissue and formed a high-pressure area. When patients coughed and swallowed, the esophageal pressure through anastomotic conduction was blocked. This increased the incidence of anastomotic fistula. The mechanism of the approach in group C in reducing the incidence of anastomotic leakage remains unclear at present and is suggested as a topic for future research.

CONCLUSION

Compared with mechanical cervical esophagogastric anastomosis through the highest point of the tubular stomach in addition to embedment and suspension of the anastomosis, there was no improvement on anastomotic leakage occurrence by taking mechanical cervical esophagus-tubular stomach anastomosis at the plane of the terminal branches of the right gastroepiploic vessels plus embedment and suspension of the anastomosis with redundant tubular stomach removed, but has gained a major change with no embedment and suspension of the anastomosis.

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REFERENCES


Original Article

Bone mineral changes after renal transplantation

Paulin A Gandhi1, Aruna V Vanikar1,2, Himanshu V Patel3, Rashmi D Patel1, Kamal V Kanodia1, Umang G Thakkar2
1Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Gujarat, India
2Department of Regenerative Medicine and Stem Cell Therapy, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Gujarat, India
3Department of Nephrology and Transplantation Medicine, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Gujarat, India

ABSTRACT

Objectives: Bone mineral abnormalities in post-renal transplant (RT) period can lead to mineral bone disease (MBD). We planned to analyze biochemical parameters reflecting bone mineral changes in a set of post-RT patients.

Design: This was a prospective single center study.

Setting: Institute of Kidney Disease and Research Center, Institute of Transplantation sciences, Ahmedabad.

Subjects: Sixty RT patients with mean age of 36.7 ± 9.4 years were included.

Intervention: Venous blood samples

Main outcome measure(s): Serum total calcium (S.Ca), phosphorus (S.PO4), alkaline phosphatase (S.ALP) and intact parathyroid hormone (S.iPTH) levels pre-RT and post-RT at 1 and 7 months respectively and correlated with serum creatinine (SCr) and calculated creatinine clearance.

Results: Mean pre-RT levels of estimated glomerular filtration rate (ml/min), SCr (mg/dL), S.Ca level (mg/dL), S.PO4 (mg/dL), S.iPTH (pg/mL) and S.ALP (IU/L) were 8.2 ± 2.1, 10.3 ± 3.2, 8 ± 1.1, 6 ± 2, 352 ± 315.2 and 147.2 ± 120 respectively. At mean follow-up of 1.08 ± 0.2 months post-RT, mean values changed to 57.3 ± 20.1, 1.6 ± 0.7, 8.9 ± 0.8, 2.8 ± 1, 135.8 ± 131.5, 123.3 ± 68; and at 7.3 ± 1.1 months, values changed to 65.3 ± 22.1, 1.3 ± 0.5, 8.9 ± 1.4, 3.5 ± 0.9, 100.5 ± 65.9 and 172.5 ± 93.4 respectively. At 1 month post-RT, all patients achieved stable graft function with hypocalcemia in 20%, hypophosphatemia in 61.7%, and high S.ALP level in 46.7%. In spite of significantly improved S.iPTH level, hyperparathyroidism was observed in 66.7% of the patients. At 7 months post-RT, hypercalcemia was found in 10.9%, hypophosphatemia in 26.1% and hyperparathyroidism in 47.8% of the patients.

Conclusion: Regular stringent monitoring of bone mineral markers like i-PTH, PO4, total Ca and ALP in serum can prevent progression of MBD in RT recipients with medical management.

INTRODUCTION

Renal transplantation (RT) largely restores defective exocrine and endocrine renal functions in patients with chronic kidney disease (CKD). With increasing life expectancy after RT, the prevention of long term complications has become an essential part of post-RT care. Mineral bone disease (MBD) is one of the most common complications that significantly influence the quality of life. This is possibly due to pre-existing bone damage acquired during dialysis therapy, renal insufficiency, deleterious effects of different immunosuppressive agents and post-RT mineral metabolic changes such as persistent post-RT secondary hyperparathyroidism (SHP) and post-RT hypophosphatemia (hypo-Pi)[1]. Among all these causes, the major obstacle to investigating MBD in RT recipients has been its unpredictable evolution under multiple biochemical and hormonal influences that regulate mineral metabolism and bone turnover independently.

Address correspondence to:
Aruna V. Vanikar, MD, FICP, PhD; D.Litt; Professor and Head, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology and Professor, Department of Regenerative Medicine and Stem Cell Therapy, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad- 380016, Gujarat, India. Tel: +91 79 22687387, Telefax: +91 79 2268 5454, E. mail: vanikararuna@yahoo.com
Persistent SHP found regularly for ≥2 years post-RT is a known factor for increased bone turnover and decreased bone density[2]. Moreover, hypo-Pi observed most frequently in early post-RT period is believed to be associated with severe alterations in bone turnover that include decrease in osteoblast activity, leading to osteomalacia[3]. We carried out a study to evaluate changes in bone mineral metabolism markers which included serum (S.) intact parathyroid hormone (S.iPTH), S. phosphorus (S.PO), S. calcium (S.Ca) and S. alkaline phosphatase (S.ALP) at 1 and 7 months post-RT period. Serum creatinine (SCr) was considered for evaluation of graft function status.

SUBJECTS AND METHODS

This was a prospective single center clinical study to observe bone mineral changes at 1 month and 7 months post-transplant in 60 post-RT patients with a mean age of 36.7 ± 9.4 years. Patients above 18 years were included in the study. We excluded patients with a history of bone disease due to causes other than CKD or any metabolic disorders affecting bone minerals. All the patients were on the same immunosuppression regimen. The calculated creatinine clearance was measured by using Cockcroft and Gault formula[4]. Cut-off values considered to define hypercalcemia, hypophosphatemia and hyperparathyroidism were >10.5 mg/dL, <3 mg/dL and >75 pg/mL, respectively.

Ethical approval and consent to participate

The study was approved by our institutional review board and study number was IKDCR CITS- LAB-03-01-2016. Consent for publication was obtained from all the patients.

Statistical analysis

Statistical analysis was performed using SPSS version 20. All values are expressed as mean ± SD. Comparison of pre-RT and post-RT results were made with student’s paired-t test, Wilcoxon Signed Rank test and correlations were calculated with Pearson correlation coefficient. A p-value <0.05 was considered as statistically significant. Inter-patient coefficient of variance (CV%) for each analyte of interest was calculated by the formula “CV% = (SD*100) / Mean”.

RESULTS

Out of 60 patients, 48 (80%) were males and 12 (20%) were females. Mean SCr was 1.6 ± 0.7 mg/dL with calculated creatinine clearance of 57.3 ± 20.1 ml/min at 1 month post-RT, and 1.3 ± 0.5 mg/dL with calculated creatinine clearance of 65.3 ± 22.1 ml/min at 7 months post-RT. S. iPTH, S.Ca, S.PO and S.ALP at mean 1.08 ± 0.2 and 7.3 ± 1.1 months post-RT respectively is shown in Table 1. Inter-patient CV% for SCr at pre-RT, 1 month and 6 months post-RT was 26.2%, 35.1% and 33.8% respectively.

There was a significant decrease in mean level of S.iPTH (in pg/mL) from 352 ± 315.2 to 135.8 ± 131.5 (p <0.001) and 100.5 ± 65.9 (p <0.01) at mean 1 and 7 months post-RT respectively. However, 66.7% (n = 40) and 47.8% (n = 24) of the patients had persistent SHP at 1 and 7 months post-RT respectively (Figure 1).

### Table 1: Comparison of bone mineral markers in renal transplant patients at Pre and Post transplant 1 month and 7 months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biological Reference Range</th>
<th>Pre-RT (Mean ± SD) (n=60)</th>
<th>Post-RT 1.08 ± 0.2 months (Mean ± SD) (n=60)</th>
<th>Post-RT 7.3 ± 1.1 months (Mean ± SD) (n=46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated creatinine clearance (ml/min)</td>
<td>&gt; 90</td>
<td>8.2 ± 2.4</td>
<td>57.3 ± 25.5</td>
<td>65.3 ± 21.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>S. Creatinine (mg/dL)</td>
<td>0.8 - 1.4</td>
<td>10.3 ± 3.0</td>
<td>1.6 ± 0.7</td>
<td>1.3 ± 0.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>S. intact parathyroid hormone (pg/mL)</td>
<td>13 - 75</td>
<td>352.2 ± 304.6</td>
<td>135.8 ± 116.1</td>
<td>100.5 ± 56.1</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>S. Calcium (mg/dL)</td>
<td>8.5 -10.5</td>
<td>8.0 ± 1.1</td>
<td>8.9 ± 0.8</td>
<td>8.9 ± 1.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>S. Phosphorus (mg/dL)</td>
<td>3.5 - 5</td>
<td>6.0 ± 2.1</td>
<td>2.8 ± 0.9</td>
<td>3.5 ± 0.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>S. Alkaline phosphatase (IU/L)</td>
<td>34-108</td>
<td>147.2 ± 134.1</td>
<td>123.3 ± 67.3</td>
<td>172.5 ± 100.0</td>
<td>0.43 (NS)</td>
</tr>
</tbody>
</table>

March 2019

Bone mineral changes after renal transplantation
Fig 1: Comparison of serum iPTH level at pre-renal transplant and at 1 and 7 months post renal transplant

Fig 2: Comparison of serum phosphorus level at pre-renal transplant and at 1 and 7 months post renal transplant
No significant changes were found between values of S.iPTH levels at 1 and 7 months (p = 0.486). Inter-patient CV% for S.iPTH at pre-RT, 1 month and 6 months post-RT was 89.5%, 96.9% and 65.1% respectively.

S.Po level (in mg/dL) was decreased significantly from 6.0 ± 2.0 to 2.8 ± 1.0 (p <0.001) and 3.5 ± 0.9 (p <0.001) at 1 and 7 months post-RT respectively. Overall, 61.7% (n = 37) of patients had hyp Pi at 1 month, and 26.1% of patients (n = 12) had hyp Pi at 7 months post-RT (Figure 2). There was also a significant change between level of S.Po at 1 and 7 months post-transplant (p <0.001). Inter-patient CV% for S.Po at pre-RT, 1 month and 6 months post-RT was 33.5%, 37.1% and 25.9% respectively. Total S.Ca level (in mg/dL) increased from 8.0 ± 1.1 to 8.9 ± 0.8 (p <0.001) at 1 month and thereafter remained steady at 8.9 ± 1.4 (p <0.05) at 7 months post-RT. Inter-patient CV% for S.Ca at pre-RT, 1 month and 6 months post-RT was 13.8%, 9.4% and 15.6% respectively. Moreover, we noticed that out of 68% pre-RT hypocalcemic patients (n = 41), 23.3% (n = 14) and 32.6% (n = 15) had persistent hypocalcemia at 1 and 7 months post-RT respectively (Figure 3). In addition, 10.9% (n = 5) of the patients developed hypercalcemia at 7 months. We observed that there was no significant alteration in S.ALP level at 1 month post-RT. However, a significant rise in mean S.ALP level at 7 months post-RT compared to pre-RT level (p <0.001) and 1 month post-RT level (p <0.001) was observed. Mean levels of S.ALP (IU/L) were 147.2 ± 120.7, 123.3 ± 68, 172.5 ± 93.4 at pre-RT, at 1 month and 7 months post-RT respectively. Inter-patient CV% for S.ALP at pre-RT, 1 month and 6 months post-RT was 82%, 55.1% and 54.2% respectively.

DISCUSSION

Successful RT restores the main abnormalities responsible for SHP. In this study, we prospectively evaluated data of 60 post-RT patients with stable renal function as reflected by calculated creatinine clearance and SCr level.

Changes in S.iPTH level

Though we observed significant decrease in mean S.iPTH level after RT, it persisted to higher than acceptable reference ranges at 1 and 7 months post-RT in spite of stable graft function. Overall, 66.7% and 47.8% of our patients had elevated S.iPTH levels at 1 month and 7 months post-RT respectively. The prevalence of SHP in our study is quite high compared with the study in European children by Marjolein et al., who showed persistent hyperparathyroidism in 41% of patients at 9 - 12 months post-transplant. Our
findings fairly correlate with the findings of Heide et al who showed 50% of patients having higher value of S. iPTH at 1 year and 27% of patients after 2 years post RT[2], although our follow-up period is less compared to those of Heide et al.

In CKD, there is a decrease in Vitamin-D and S.Ca level whereas increase in fibroblast growth factor-23 (FGF-23) and S.PO₄ level. All these abnormalities ultimately act on the parathyroid gland through their respective receptors and lead to parathyroid cell proliferation, thereby increasing S. iPTH synthesis and its secretion[6-8]. In addition to very high S. iPTH level before transplant, longer duration of dialysis and older age, and development of tertiary hyperparathyroidism due to nodular transformation from a polyclonal hyperplasia into a monoclonal adenoma post-transplant may contribute to persistently high S. iPTH level[8,9].

Persistent SHP stimulates bone resorption by indirect effect on osteoclast. It binds with the receptor present on osteoblast, up-regulates the expression of receptor activator of nuclear factor kappa-B ligand which bind with the receptor activator of nuclear factor kappa-B present on osteoclast, and thereby gives signal to bone marrow derived osteoclast precursor. Ultimately this stimulates fusion, differentiation and activation of osteoclast, eventually leading to bone resorption[3,7,10].

**Changes in S.PO₄**

Hypo-Pi is a frequent problem found after RT. In our study, we found 61.7% of the patients with hypo-Pi at 1 month post-transplant and 26.1% of patients with hypo-Pi at 7 months post-RT, which fairly correlated with the study of Ulrich Kunzendorf et al. They found hypo-Pi in 90% of RT recipients for the first 4 months and in 20 – 40% of patients at 1 year post-transplant[1].

Inappropriately high S.iPTH with recovered tubular function is considered to be the most relevant hypophosphatemic factor in RT patients[11,12]. Apart from that, elevated level of one of the more recently defined phosphaturic factor FGF-23, also known as “Phosphatonin”, continues to be elevated in early post-RT period even with normal serum iPTH level[13-16]. Another factor contributing to post-RT hypo-Pi is steroid therapy, which increases PO₄ excretion by

![Fig 4: Comparison of serum alkaline phosphatase at pre-renal transplant and at 1 and 7 months post renal transplant](image)
inhibiting Na/Pi co-transporter\textsuperscript{[16,11]}, Bellorin-Font \textit{et al} showed S.Po\textsubscript{4} level correlated negatively with the number of apoptotic osteoblasts and positively with the numbers of active osteoblasts, suggesting a role of hypo-Pi in the mechanism that leads to post-RT MBD\textsuperscript{[17]}.

Changes in S.Ca

In this study, we observed that 68\% (n = 41) of the patients had pre-RT hypocalcemia, and subsequently 36.5\% (n = 15) of the patients had persistent hypocalcemia at 7 months post-RT. This indicates that about 63.5\% of patients recovered from hypocalcemia at 7 months after transplantation (Figure 3). Moreover, 10.9\% (n = 5) of patients had developed hypercalcemia at 7 months post-RT. This suggests gradual increase in S.Ca level during 7 months follow-up after transplantation, which may progress to hypercalcemia over a longer duration of follow-up. This finding supports the studies of Messa \textit{et al}, who observed hypercalcemia in 23\% of patients at 6 months and in 27\% of patients at 12 months post-RT follow-up\textsuperscript{[6,11]}. The possible mechanisms for increasing S.Ca level after transplantation are persistent SHP, recovery of response of iPTH-receptor to iPTH, increased calcitriol availability and hypo-Pi\textsuperscript{[6,18-20]}.

Limitations of the present study

We could not perform serum levels of vitamin-D and FGF-23 which might have thrown light on potential etiological mechanisms of post-RT MBD.

CONCLUSION

Regular stringent monitoring of bone mineral markers like iPTH, PO\textsubscript{4}, total Ca and ALP in serum can prevent progression of MBD in RT recipients with medical management.

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Authors’ Contribution: PA Gandhi designed the study, carried out all the lab work and wrote the manuscript. AV Vanikar, RD Patel, KV Kanodia, KS Suthar and LA Nigam supervised all the lab work and approved the manuscript. HV Patel was the treating physician for all patients and approved the manuscript. AV Vanikar and UG Thakkar participated in study design and finalized the manuscript.

REFERENCES


Original Article

Comparison of intrathecal low-dose levobupivacaine with levobupivacaine-fentanyl and levobupivacaine-sufentanil combinations for cesarean section

Mehmet Cakirca¹, Saziye Sahin², Muge Cakirca¹, Alpaslan Apan⁴
¹Ankara Training and Research Hospital, Anesthesiology and Reanimation Clinic, Ankara, Turkey
²Gazi University, Faculty of Dentistry, Anesthesiology and Reanimation Clinic, Ankara, Turkey
³Ankara Numune Training and Research Hospital, Anesthesiology and Reanimation Clinic, Ankara, Turkey
⁴Giresun University, Anesthesiology and Reanimation Clinic, Giresun, Turkey

ABSTRACT

Objectives: To compare the effectiveness and side effects of intrathecal low-dose levobupivacaine with levobupivacaine plus fentanyl or sufentanil in cesarean section
Design: Prospective study
Setting: Training and Research Hospital, Ankara, Turkey
Subjects: A total of 45 pregnant women were enrolled to study.
Interventions: Using combined spinal epidural technique, 2 ml of 0.5% levobupivacaine was added to 1 ml of saline in group I, 1 ml of 15 µcg of fentanyl in group II and 1 ml of 1.5 µcg sufentanil in group III by intrathecal administration.
Main outcome measures: Hemodynamic parameters, sensory and motor blockade levels, intraoperative and postoperative visual analogue scale (VAS) pain scores, the time to the first analgesic requirement and adverse effects were recorded.

Results: The sensory block levels were lower in group I when compared to groups II and III (p <0.05). Intraoperative and postoperative VAS scores were higher in group I than groups II and III (p <0.05). The time to first analgesic requirement in the postoperative period (VAS ≥3) and the time to the application of first analgesic dose by epidural catheter was significantly shorter in group I than in groups II and III (p <0.05). Nausea (n: 0, 9, 8), vomiting (n: 0, 2, 0), bradycardia (n: 0, 1, 2), and hypotension (n: 5, 10, 9) were the adverse effects found in groups I, II and III respectively.

Conclusion: Intrathecal levobupivacaine 10 mg in 3 ml solution does not provide adequate anesthesia during elective cesarean section. We found that the major adverse effect of adding fentanyl or sufentanil to levobupivacaine is the increase in nausea.

INTRODUCTION

Spinal anaesthesia is the preferred anaesthetic technique for elective Cesarean deliveries. The primary objective of the spinal technique is to produce effective surgical anaesthesia which is accomplished with minimal adverse effects on the mother and their unborn child.

The local anaesthetic dose is appropriate for sensory nerve block to achieve success in surgical anaesthesia¹. Levobupivacaine is the S-enantiomer of bupivacaine and it seems to be a suitable alternative to racemic bupivacaine for spinal anaesthesia because it has a lower risk of cardiovascular and central nervous system toxicity than bupivacaine in both animal and human studies. However, these advantages do not appear to be clinically significant when lower levobupivacaine doses used in cesarean spinal anaesthesia is considered²-⁴.

Adding an opioid may offer a low local anesthetic-sparing effect on levobupivacaine and reduce the frequency of intra-operative pain⁵. Fentanyl, which is the ideal opioid in obstetrics, is much more lipid soluble than morphine and hence does not tend to spread intrathecally to the fourth ventricle in sufficient concentrations to cause respiratory depression. Sufentanil, the most lipophilic, clinically available

Address correspondence to:
Muge Cakirca, Beypazarı cad. 29-5 Varlık mih, Ankara, Turkey. Tel: 905054433177; E-mail address: mugeturkoglu81@gmail.com
opioid, is a common adjunct to local anaesthetics. Its quality can be improved by intrathecal addition of opioids to local anaesthetics[6-9]. There are few studies in which the use of levobupivacaine with fentanyl or sufentanil is compared to its use without these opioids in spinal anesthesia for cesarean section.

In this study, we aimed to compare the spinal block characteristics and adverse effects of intrathecal levobupivacaine alone, levobupivacaine with fentanyl, and levobupivacaine with sufentanil when used in cesarean section anesthesia[10-12].

SUBJECTS AND METHODS

Approval for the study (decision no 099) was granted by the Ethics Committee of Kırıkkale University Medical Faculty, Kırıkkale, Turkey. The study involved 45 pregnant women, aged 18 - 45 years, and the inclusion criteria were those classified by American Society of Anesthesiologists score I and were to undergo elective cesarean section for a single live term fetus. Written informed consent was obtained from all the patients. The exclusion criteria were multiple pregnancies, preterm labor, eclampsia, preeclampsia, concomitant diabetes mellitus, asthmatic patients, allergy to local anesthetics, those on monoamine oxidase inhibitors, fentanyl or sufentanil contraindications for regional anesthesia.

The study was designed as a double blind, prospective study involving patients being assigned to one of three study groups (groups I-III), using a computer-generated random number table. One anesthesiologist prepared the drugs and the sealed envelopes while another chose an envelope containing one of the drugs at random for administration to the patient.

The vital signs of the patients including heart rate (using an electrocardiogram), the blood pressure, respiratory rate, and oxygen saturation (using pulse oxymetry) were monitored every 15 minutes. Written informed consent was obtained from all the patients. The exclusion criteria were multiple pregnancies, preterm labor, eclampsia, preeclampsia, concomitant diabetes mellitus, asthmatic patients, allergy to local anesthetics, those on monoamine oxidase inhibitors, fentanyl or sufentanil contraindications for regional anesthesia.

The study was designed as a double blind, prospective study involving patients being assigned to one of three study groups (groups I-III), using a computer-generated random number table. One anesthesiologist prepared the drugs and the sealed envelopes while another chose an envelope containing one of the drugs at random for administration to the patient.

The spinal needle was removed and the epidural catheter was inserted 2 - 3 cm into the epidural space and aspirated; no test dose was given. Patients were immediately positioned supine with a 15º – 20º left lateral tilt along surgery so as to control for hypotension to prevent aorto-caval compression.

Surgery was commenced after achieving spinal blockade at T6 at most 20 minutes after the patient received the spinal anaesthetic medications. Heart rate (HR), mean systolic and diastolic arterial pressures (MAP, SAP and DAP) and peripheral oxygen saturation (SpO₂) values were measured at one-minute intervals in the first five minutes and every five minutes until the end of the surgery. After the intrathecal injection, the motor blockade was assessed using the Bromage scale[13] (I: Free movement of legs and feet, II: Just able to flex knees with free movement of feet, III: Unable to flex knees, but with free movement of feet, IV: Unable to move legs or feet) at five minute intervals for the first 20 minutes and then at 15 minute intervals until the end of the surgery. Adding opioids to levobupivacaine was to enhance the duration of action of motor blockade and efficacy of the spinal anaesthesia. After the surgery, the patient was monitored at 30 minute intervals until the Bromage score was back to I. The time of onset, degree, and duration of motor blockade, the maximum Bromage score and the time to achieve the maximum Bromage score were all recorded.

Sensory block level was assessed using the pinprick test at two minute intervals for the first 20 minutes and at 15 minute intervals thereafter until the end of the surgery. The onset time of sensory block, the maximum sensory block level and the time to reach the maximum sensory block level were noted. After the operation, the sensory block level was monitored at 30 minute intervals until T12 level was achieved and that time was recorded.

For intraoperative and postoperative pain, a 100 mm visual analog scale (VAS, 0 mm: no pain, 100 mm: worst imaginable pain) was used. VAS scores were recorded until the first application of epidural analgesia (VAS ≥3) in postoperative period and that time was recorded.

The adverse effects of the medications used for anaesthesia such as nausea and vomiting, hypotension, pruritus, bradycardia and others were recorded.

SPSS 18.0 software was used for statistical evaluation. The parametric data were evaluated using analysis of variance (ANOVA) and post-hoc Bonferroni tests corrections. Non-parametric variables were assessed using ANOVA and the Kruskal-Wallis test. A value of p <0.05 was accepted as statistically significant.
RESULTS
The mean age, weight, height and the surgery time for the patients in the three groups are presented in Table 1. SAP, DAP, MAP, spO₂, and HR were similar in all groups. SAP, DAP and MAP values throughout the first 20 minutes were significantly lower compared with the baseline values in all groups \( (p < 0.05) \), (Figure 1).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 15)</th>
<th>Mean ± SD</th>
<th>Group II (n = 15)</th>
<th>Mean ± SD</th>
<th>Group III (n = 15)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.8 ± 7.4</td>
<td></td>
<td>25.5 ± 5.2</td>
<td></td>
<td>27.4 ± 7.1</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.7 ± 5.1</td>
<td></td>
<td>162.1 ± 5.1</td>
<td></td>
<td>160.7 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 12.4</td>
<td></td>
<td>82.6 ± 11.5</td>
<td></td>
<td>77.9 ± 11.2</td>
<td></td>
</tr>
<tr>
<td>Operation time (m)</td>
<td>64.0 ± 14.8</td>
<td></td>
<td>64.3 ± 11.2</td>
<td></td>
<td>58.0 ± 8.4</td>
<td></td>
</tr>
</tbody>
</table>

The three groups compared using ANOVA and when no significant difference was obtained, a post hoc test using the Bonferroni test. \( p > 0.05 \), data were similar between all groups.

The sensory block levels were significantly lower in group I when compared to group II \( (p < 0.05) \). The time to reach the maximum level of sensory block was similar between the groups. The regression time of the sensory block level to T12 dermatome was significantly shorter in group I than others \( (p < 0.05) \), (Figure 2).

<table>
<thead>
<tr>
<th>Findings</th>
<th>Group I (M±SD)</th>
<th>Group II (M±SD)</th>
<th>Group III (M±SD)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (min)</td>
<td>15 ± 5</td>
<td>15 ± 4</td>
<td>14 ± 4</td>
<td>0.795</td>
</tr>
<tr>
<td>Desc(min)</td>
<td>42 ± 15</td>
<td>56 ± 18</td>
<td>46 ± 19</td>
<td>0.106</td>
</tr>
<tr>
<td>LT12(min)</td>
<td>123 ± 41*†</td>
<td>168 ± 41*</td>
<td>184 ± 45†</td>
<td>0.001</td>
</tr>
<tr>
<td>VAS3(min)</td>
<td>131 ± 41‡§</td>
<td>203 ± 38‡</td>
<td>209 ± 46§</td>
<td>0.001</td>
</tr>
<tr>
<td>Analg(min)</td>
<td>145 ± 381¶</td>
<td>223 ± 381§</td>
<td>226 ± 41¶</td>
<td>0.001</td>
</tr>
</tbody>
</table>

High: time to reach the highest level of the block; Desc: time to start to descend the highest level of the block; LT12: landing time T12 dermatome level of block level; VAS 3: reaching time in the postoperative period (first suffer pain); Analg: the first analgesic requirement time through epidurally in the postoperative period. \( P < 0.05 \) significant difference

\*: 0.017, †: 0.001, ‡: 0.001, §: 0.001, ¶: 0.001, 11: 0.001, ¶: 0.001

in group III. Hypotension was observed in five, ten and nine patients in groups I, II and III, respectively, (treated by ephedrine) and there was no significant difference between the groups. Pruritis were not found in any patients.

The application of first analgesic dose by the epidural catheter were significantly shorter in group I than in groups II and III (Table 3).

None of the patients in group I had nausea, but nine patients in group II and eight patients in group III experienced nausea. Vomiting was assessed in two patients in group II, and none of the patients in the other two groups experienced vomiting. Bradycardia was not observed in any patients in group I, but was seen in one patient in group II, and in two patients

Table 1: The mean age, weight, height and the operation time of the groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 15)</th>
<th>Mean ± SD</th>
<th>Group II (n = 15)</th>
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<td>Operation time (m)</td>
<td>64.0 ± 14.8</td>
<td></td>
<td>64.3 ± 11.2</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Visual analogue scale scores in three groups

<table>
<thead>
<tr>
<th>VAS values</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASincision 0/1/2/3/4 (n)</td>
<td>14/0/1/0/0</td>
<td>14/0/0/1/0</td>
<td>14/0/1/0/0</td>
<td>0.943</td>
</tr>
<tr>
<td>VASbirth 0/1/2/3/4 (n)</td>
<td>9/1/2/1/2</td>
<td>14/0/0/1/0</td>
<td>13/0/0/2/0</td>
<td>0.115</td>
</tr>
<tr>
<td>VASintraoperative 0/1/2/3/4(n)</td>
<td>6/1/5/3/10*†</td>
<td>14/0/1/0/0*</td>
<td>12/1/2/0/0*</td>
<td>0.001</td>
</tr>
<tr>
<td>VASpostoperative 0/1/2/3/4 (n)</td>
<td>3/3/7/2/0‡§</td>
<td>14/0/1/0/0‡</td>
<td>12/1/2/0/0‡§</td>
<td>0.001</td>
</tr>
</tbody>
</table>

\( p < 0.05 \) significant difference; *: 0.002, †: 0.010, ‡: 0.001, §: 0.001
DISCUSSION

This study shows that intrathecal 10 mg levobupivacaine is not adequate to provide anesthesia and analgesia for cesarean section anesthesia, but adding low-dose sufentanil or fentanyl does. Studies have shown that the addition of intrathecal fentanyl or sufentanil to local anesthetics reduced the need for local anesthetics and improved the quality of anesthesia and analgesia[9,14-17]. However, the most effective dose and combination of less toxic racemic bupivacaine to be used in spinal anesthesia has not yet been fully clarified[4,18]. The use of low doses of local anesthetics provides advantages including faster recovery of bladder function, and early ambulation. The lowest clinically effective dose of levobupivacaine for spinal anesthesia has been reported to be 10.58 mg for cesarean section[19]. In another study, the ED50 and ED95 of levobupivacaine plus intrathecal 2.5 mg sufentanil or 100 µg morphine for cesarean section were 6.2 and 12.9 mg, respectively. Nausea, vomiting and hemodynamic adverse effects were reported to be similar. The authors recommended a combined spinal epidural technique if lower doses of levobupivacaine were to be used[20]. Therefore, in the current study, the lowest possible dose of 2 ml 0.5% 10 mg levobupivacaine and combined spinal epidural anesthesia was preferred for use.

In the fentanyl administration with levobupivacaine study, targeting the T10 dermatome level in urological surgery, the use of 2.6 ml of 0.5% levobupivacine, and 2.3 ml 0.5% levobupivacine plus 0.3 ml 15 µg fentanyl were compared. The block onset time, sensory block level, the degree of motor block and hemodynamic findings were reported to be similar in both groups[20]. In our study, we found increased sensorial block levels in the opioid groups. However, the authors stated that the use of low dose local anesthetics would cause a lower degree of sympathetic blockade and consequently less hypotension[20]. We have to keep in mind that in our study, patients were parturients with increased intraabdominal pressure which explains our high sensitive blockade levels with opioids. However, 2 ml 0.5% levobupivacine was found to give inadequate levels of sensory blockade in cesarean section when used alone.

In another study, 7.5 mg of levobupivacaine with 15 µg fentanyl was recommended for elective cesarean sections[8]. When 10 mg levobupivacaine with 0.1 mg morphine was compared with 10 mg levobupivacaine with 20 µg of fentanyl for cesarean section, Glaser et al observed that the fentanyl group experienced more adverse effects[18]. This study showed adding much smaller doses of opioids in 10 mg levobupivacaine increased the sensorial block levels, but still found more adverse effects than the group that was given levobupivacaine alone (nausea (0,9,8), vomiting (0,2,0), bradycardia (0,1,2), and hypotension (5,10,9) respectively). Pruritus has been reported to be the most important complication seen in 30% of patients with the addition of intrathecal fentanyl[21]. However, we did not experience any case of pruritis in any of our groups.

Van De Velde et al reported that an intrathecal sufentanil-bupivacaine combination provides the most effective anesthesia and analgesia for labor analgesia[22]. Buyse et al reported a 4-fold decrease in the requirement of local anesthetics using epidural sufentanil[23]. However, intrathecal 2.5 µg sufentanil added to 8 mg levobupivacaine did not provide adequate anesthesia and analgesia in cesarean section[24]. Adding 1.5 µg sufentanil to 10 mg intrathecal levobupivacaine provided adequate anesthetic and analgesic effects, but the frequency of nausea also increased.

Levobupivacaine is hypobaric at 37 °C, and this causes changes in the level of sensory and sympathetic blockade, making the spread of the drug unpredictable[6]. Preparation of hyperbaric levobupivacaine may be troublesome for the clinician as its density can be variable[25]. When hyperbaric bupivacaine has been used with or without fentanyl, no changes have been determined in the incidence and severity of hypotension[14]. There is currently no licensed form of hyperbaric levobupivacaine. Therefore, differences in the level of sensory and sympathetic blockade should be an expected result. In addition, levobupivacaine provides a longer duration of anesthesia and a higher level of sensory and sympathetic blockade than bupivacaine[6,13].

Intrathecal opioids have been shown to increase the level of sensory block, although they do not cause sympathetic blockade[26,27]. Local anesthetic requirements are reduced by the addition of opioids, and low sympathetic blockade and high sensory blockade levels can be achieved with the use of low-dose local anesthetics. Consequently, the frequency of hypotension would be reduced[20]. The sufentanil-levobupivacaine combination has been reported to cause less severe hypotension than bupivacaine during caesarean delivery[28]. In our study, opioid groups had high sensorial blockade levels and peri-intraoperative low VAS scores. Thus, anesthesia quality were increased in these groups.

CONCLUSION

The results of this study showed that spinal anesthesia with 10 mg of levobupivacaine in a total of 3 ml volume did not provide efficient and adequate analgesia for cesarean section. The addition of fentanyl and sufentanil to levobupivacaine increased the quality of anesthesia and analgesia.
REFERENCES


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Is there any relationship between urinary pH and any cystometric parameter?

Mehmet Zeynel Keskin, Yusuf Ozlem Ilbey, Cem Yucel, Taha Cetin
Tepecik Training and Research Hospital, Urology Clinic, Izmir, Turkey

ABSTRACT

Objective: To explore a possible relationship between urinary pH and various cystometric parameters

Design: A retrospective study

Setting: Department of Urology, Tepecik Training and Research Hospital, Izmir, Turkey

Subjects: One hundred and eight patients

Intervention: The urinary pH and cystometric parameters of 108 patients were subjected to statistical analyses.

Main outcome measures: Patients were divided into three groups in terms of urinary pH: acidic (group 1), normal (group 2), and alkaline (group 3). We sought to define significant differences in cystometric parameters among the three groups. A p-value <0.05 was considered to reflect statistical significance.

Results: The urine volume at the time of first-morning desire to void was significantly higher in the acidic than the alkaline group (p = 0.027), and both this volume and that at the time of first-morning urinary urgency were higher in the normal than the alkaline group (p = 0.033, p = 0.026, respectively). No significant difference in any cystometric parameter was evident between the acidic and normal groups.

Conclusion: Although significant relationships were evident between pH and cystometric parameters, including the bladder volume at the times of first desire to void and first urinary urgency, more prospective questionnaire studies are required; the literature is essentially silent on the topic.

INTRODUCTION

Urinary pH ranges from 4.6 to 8, and is normally about pH 6. Urinary tract infections render the pH alkaline; the pH becomes acidic in patients with uncontrolled diabetes mellitus or gout, or those on acidic drugs[1-4]. Lower urinary tract symptoms (LUTS) are present in a considerable proportion of patients presenting to urology outpatient clinics. LUTS is caused by many factors including urethral pathologies, benign prostatic hyperplasia, an overactive bladder, and urinary tract infections. A complete urinalysis (CUA) (a basic diagnostic test used to evaluate LUTS complaints) is a very useful way to detect (especially) cystitis, an important cause of LUTS. Advanced, urodynamic diagnostic tests include techniques such as cystometry. Few studies have investigated the relationship between urinary pH and LUTS[5-6]. Herein, we explored whether any relationship was evident between the urinary pH and cystometric parameters.

MATERIALS AND METHODS

We retrospectively reviewed the files of all LUTS patients who presented to our urology outpatient clinic in 2015 - 2016. We evaluated data on 140 patients who underwent both CUA and cystometry. Patients under the age of 18 years; those with enlarged prostates or nodules evident on digital rectal examination; urethral strictures; bladder calculi; any significant neurological problem; a history of previous prostate surgery; a bladder tumor; a prostate tumor; a urinary tract infection; and those who were pregnant were excluded. We finally enrolled 108 patients who were divided into three groups based on urinary pH: Group 1 (pH <6, acidic pH), Group 2 (6 ≥ pH < 7, normal pH), and Group 3 (7 ≥ pH ≤ 8, alkaline pH).

During the filling cystometric phase, we measured the bladder volume at the time of first-morning desire to void, that at the first-morning time of urinary urgency, and that at the time of first urinary

Address correspondence to:
Mehmet Zeynel Keskin, Department of Urology, Tepecik Training and Research Hospital, Izmir, Turkey. Tel: +905301184583; E-mail: zeynel_aka@hotmail.com
incontinence (if any). These volumes were included in the evaluation.

IBM SPSS software ver. 22 was used for all statistical analyses and a p-value <0.05 was considered to reflect statistical significance.

**RESULTS**

Of the 108 patients, 33 were in group 1 (acidic urine), 45 in group 2 (normal), and 30 in group 3 (alkaline). Their demographic and cystometric data, by urine pH, are listed in Table 1. No cystometric parameter differed significantly among the three groups (Kruskal-Wallis test, p >0.05). Pairwise comparisons (using the Mann-Whitney U-test) revealed that the volumes at the times of first desire to void and first urinary urgency were higher in group 2 than group 3 patients (p = 0.033, p = 0.026, respectively); and the volume at first desire to void was significantly higher in group 1 than group 3 patients (p = 0.027). No significant difference was apparent between group 1 and group 2 patients (p >0.05).

**DISCUSSION**

The C-fibers of the bladder urothelium are normally inactive, but cooling or chemical irritation may trigger LUTS development. Acid receptors such as TRPV1 and ASIC, expressed on the ends of C-fibers, are stimulated by hydrogen ions, triggering symptoms as TRPV1 and ASIC, expressed on the ends of C-fibers, may trigger LUTS development. Acid receptors such as TRPV1 and ASIC, expressed on the ends of C-fibers, may trigger LUTS development.

**Table 1: Patient demographic and cystometric data by urinary pH**

<table>
<thead>
<tr>
<th>Group (PH)</th>
<th>Age (years)</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Urinary pH</th>
<th>Volume at the time of first desire to void (mL)</th>
<th>Volume at the time of first urinary urgency (mL)</th>
<th>Volume at the time of first increased urinary urgency (mL)</th>
<th>Maximum capacity (mL)</th>
<th>Volume at the time of first urinary incontinence (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (acidic PH)</td>
<td>62.60 ± 13.17</td>
<td>10 (30.3)</td>
<td>23 (69.7)</td>
<td>5.31 ± .24</td>
<td>146.92 ± 89.74</td>
<td>181.50 ± 83.78</td>
<td>253.36 ± 80.25</td>
<td>304.72 ± 121.44</td>
<td>136.33 ± 63.57</td>
</tr>
<tr>
<td>Group 2 (normal PH)</td>
<td>53.82 ± 18.27</td>
<td>16 (35.5)</td>
<td>29 (64.5)</td>
<td>6.15 ± .023</td>
<td>143.54 ± 91.27</td>
<td>207.72 ± 92.03</td>
<td>325.60 ± 153.34</td>
<td>347.28 ± 199.42</td>
<td>199.42 ± 148.29</td>
</tr>
<tr>
<td>Group 3 (alkaline PH)</td>
<td>57.09 ± 18.79</td>
<td>11 (27.2)</td>
<td>19 (72.8)</td>
<td>7.55 ± .023</td>
<td>82.22 ± 47.62</td>
<td>132.50 ± 79.14</td>
<td>317.00 ± 89.22</td>
<td>264.45 ± 92.14</td>
<td>92.14 ± 38.55</td>
</tr>
<tr>
<td>Total (n = 108)</td>
<td>57.48 ± 16.93</td>
<td>37 (32.5)</td>
<td>71 (67.5)</td>
<td>6.01 ± .74</td>
<td>137.23 ± 88.09</td>
<td>189.64 ± 79.14</td>
<td>299.46 ± 132.99</td>
<td>321.26 ± 153.72</td>
<td>153.72 ± 115.59</td>
</tr>
</tbody>
</table>

In patients with urinary tract infections, the bacteria decompose urea, rendering the urine alkaline and damaging the urothelium[1]. Also, the urine becomes alkaline when foods such as oranges and lemons are consumed[13]. Such citrus fruits are rich in vitamin C; ingestion of high doses of vitamin C (especially as supplements) increase the incidence with gout, hyperuricemia, diabetes mellitus, and metabolic syndrome; the latter condition has been reported to aggravate LUTS[2-4]. Ueda et al found that urinary alkalinization via citrate treatment of patients with hypersensitive bladder syndrome significantly reduced pain symptoms and sleep problems[10]. Christopher et al explored the relationship between pain and urinary pH; urine alkalinization did not significantly reduce pain[11]. Demirbas et al compared urine pH values between 329 patients diagnosed with overactive bladders and 201 controls; the urinary pH value was significantly more acidic in the former group and alkalinization significantly reduced symptoms[6].

Given the limited number of relevant studies, the general view is that LUTS symptoms are exacerbated in those with acidic urine and that urine alkalinization aids in symptom control. However, our study differs from others; we are the first to examine the relationship between urinary pH and cystometric parameters. We found that the bladder volumes of the acidic and normal pH groups were higher at the time of first desire to void than in the alkaline group, and the volume at the time of first urinary urgency was higher in the normal than the alkaline group.

Ions dissolved in urine can sometimes condense into microscopic crystals, the type of which varies by urine pH. Calcium carbonate, calcium phosphate, triple phosphate (magnesium ammonium phosphate), amorphous phosphate, and calcium carbonate crystals are often seen in alkaline urine[12]. It is possible that the lower urine volume in patients with alkaline urine at the times of the first desire to void and first urinary urgency were attributable to irritation of bladder urothelial C-fibers by such crystals.

In patients with urinary tract infections, the bacteria decompose urea, rendering the urine alkaline and damaging the urothelium[1].
of LUTS\(^{14}\); the final breakdown product of vitamin C is oxalate (an alkaline substance), which enhances stone formation\(^{15}\). A need to urinate more quickly and more frequently triggered by a urinary tract infection or consumption of such foods may be attributable to irritation of bladder C-fibers by alkaline urine.

A limitation of our study was that no questionnaire was used to evaluate the relationship between urinary pH values and LUTS; the work was retrospective in nature.

CONCLUSION

In conclusion, we found no significant inter-group difference between urinary pH and any cystometric parameter, but pairwise comparisons (acidic-normal, normal-alkaline, acidic-alkaline) revealed significant relationships between urinary pH and the cystometric parameters of the times of first desire to void and first urinary urgency. However, prospective studies with higher patient numbers are required, as is data collection via questionnaire. Urine pH values are susceptible to diet-mediated changes and can also be altered with the aid of certain medications, partially preventing LUTS.

CONFLICT OF INTEREST

The authors have no conflict of interest.

REFERENCES

Original Article

Clinico-microbiological study on 100 HIV seropositive patients from Bangladesh

Sharmin Rozhana¹, Muhammad Nazmul Baqui²
¹Unit of Microbiology, Faculty of Medicine, AIMST University, Kedah, Malaysia
²Unit of Pathology, Faculty of Medicine, AIMST University, Kedah, Malaysia

Kuwait Medical Journal 2019; 51 (1): 66 - 71

ABSTRACT

Objective: This study was carried out to find the pattern of opportunistic pathogens among HIV sero-positive patients from Bangladesh.

Design: Cross sectional study

Setting: Department of virology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Ashar Alo Society (an NGO working with HIV infected patients), Dhaka, Bangladesh

Subjects: Randomly selected 100 HIV sero-positive patients

Interventions: None

Main outcome measure: CD4 cell count was done during the enrollment of HIV seropositive patients. Blood, sputum, throat swab, stool and urine samples were collected and tested for presence of opportunistic pathogens according to standard microbiological procedure. Data were analyzed using SPSS 17 and association between the opportunistic pathogen and CD4 cell count were calculated.

Results: Out of 100 cases, opportunistic pathogens were detected in 50 patients. Mycobacterium tuberculosis was found to be the most common (26%) opportunistic pathogen followed by Candida species (22%). Cryptosporidium parvum (12%) was found to be the most common opportunistic parasite causing diarrhoea. Enterobacter species was important opportunistic pathogen causing urinary tract infections. Significant association was found between these opportunistic pathogens and low CD4 cell count of the patients.

Conclusion: The pattern of HIV-associated opportunistic pathogens from Bangladesh is different from neighbouring countries and showed significant association with low CD4 count of blood. This knowledge may be useful to take prompt therapeutic measures by early detection of these opportunistic pathogens, and thereby help to reduce morbidity and mortality of HIV infected patients from Bangladesh.

KEYWORDS: CD4, HIV, HIV seropositive, opportunistic infections, opportunistic pathogens

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) due to human immunodeficiency virus (HIV) is now regarded as one of the major public health problems in the world[3]. Presently, Bangladesh is considered as a low-prevalence, high-risk country for HIV infections and the numbers of HIV infected patients are progressively increasing[2]. The morbidity and mortality of the HIV infected patients depends on opportunistic infections by opportunistic pathogens rather than HIV itself[3]. The CD4 cell count is considered as the most authenticated predictor of developing opportunistic infections by opportunistic pathogens in HIV infected patients, and therefore play an important role in planning appropriate treatment. The spectrum of opportunistic pathogens in HIV infected patients also have regional variations[4]. At present, there is no such data on the opportunistic infections by opportunistic pathogens among HIV infected patients from Bangladesh and their association with CD4 cell count. This study was designed to find out the spectrum of opportunistic pathogens among Bangladeshi HIV infected patients along with their association with CD4 cell count. We believe that this observation can be a model for a resource limited country like Bangladesh in taking decisions on initiation of prophylaxis and treatment, especially in remote areas where sophisticated diagnostic tools are not available.

Address correspondence to:
Sharmin Rozhana, MBBS, MPhil, Lecturer, Unit of Microbiology, AIMST University, Jalan Semeling Bedong, 08100, Kedah, Malaysia. Tel: +60143155644; Email: srozhana@gmail.com
SUBJECTS AND METHODS

This cross-sectional study was carried out over a period of one year from January 2012 to December 2012. Data were collected from randomly selected 100 seropositive HIV patients who are registered at the department of virology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Asbar Alo Society (an NGO working with HIV infected patients). Only patients who have CD4 cell count measured at the day of enrollment and have given informed written consent were included in the study. From each patient, blood, sputum, throat swab, stool and urine samples were collected taking all aseptic precautions.

Blood samples were processed for detection of hepatitis B surface antigen (HBsAg) and Anti hepatitis C virus (HCV) by enzyme linked immunosorbant assay method.

Three specimens of early morning sputum were collected from each patient over a period of two days. Wet film examination was done for pus cells followed by Gram staining and Ziehl-Neelsen (Z-N) staining for identification of pus cells and bacteria. Microscopy of sputum was recorded according to WHO 2001 guideline on standard operating procedures for laboratory diagnosis of HIV opportunistic infections. Each sample was inoculated on blood agar, chocolate agar and MacConkey agar media, incubated at 37 °C for 24 - 48 hours and examined for growth after overnight incubation. Isolates were identified by appropriate biochemical tests. The identified organism was considered pathogenic only when it was associated with considerable number of pus cells and clinical symptoms.

Throat swab was collected and wet film was prepared and examined for presence of pus cells and yeasts. Gram stain was done to detect Candida yeast. Culture was done in Sabouraud’s dextrose agar and incubated at 37 °C for 24 - 48 hours for isolation of Candida species. Germ tube test was performed for identification of Candida. The identified Candida was considered pathogenic only when it was associated with considerable number of pus cells and clinical symptoms.

A saline wet mount was used for the initial microscopic examination of stools, primarily to demonstrate worm eggs, larvae, protozoan trophozoites, presence of red blood cells and white blood cells. Iodine wet mount was used mainly to stain glycogen and the nuclei of the cyst, if present. Modified Z-N stain was done after concentration procedure by formalin-ether method to identify oocysts of cryptosporidium, isospora, cyclospora and microsporidia. Culture of the stool specimens was done on MacConkey agar for isolation of Salmonella and Shigella. Appropriate biochemical tests were done for identification of specific organisms. After centrifugation of urine, the supernatant was discarded and a drop or two of the sediment placed on the grease free slide, cover slip was applied and examined under the microscope using the high power field. Urine was then inoculated onto MacConkey agar plates. The inoculated plates were then incubated at 37 °C for 24 hours. Blood agar plates were also inoculated and incubated at 37 °C for 24 hours. A urine culture was considered positive when more than 10⁵ bacterial counts per millilitre of urine. Appropriate biochemical tests such as catalase, coagulase, motility, urease, sugar fermentation, and indole tests were also performed for confirmation of species.

This study was approved by the Institutional Review Board, BSMMU and the obtained data were statistically analyzed by using SPSS software version 17. Association of isolated pathogens with CD4 cell count was done by chi square test with Fisher’s exact correction. P-value <0.05 was considered statistically significant for all tests.

RESULTS

This study was carried out among 100 HIV infected seropositive patients. The mean age of the patients was 33.46 ± 8.54 years with age range of 18 to 60 years. Among them, 51 patients were male, 47 patients were female and 2 patients were transgender. Eighty-eight were married and ten were unmarried. Among 100 patients, 27 patients had CD4 count <200 cells /µl and 73 had CD4 count >200 cells /µl.

Out of 100 cases, opportunistic pathogens were detected from 50 cases. The distributions of opportunistic pathogens are shown in Table 1.

Table 1: Distribution of opportunistic pathogens among study patients (n = 50)

<table>
<thead>
<tr>
<th>Opportunistic pathogens</th>
<th>Number of case</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory bacterial pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB smear positive cases</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal bacterial pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella species</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Urinary bacterial pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Oral fungal pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Gastrointestinal parasite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidium parvum</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Cyclospora</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

AFB : Acid-Fast Bacilli
Table 2: Association of pathogens isolated from different samples with CD4 cell count (X² with Fisher’s exact test).

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Findings</th>
<th>Total</th>
<th>CD4 &lt;200 cells/µl (%)</th>
<th>CD4 &gt;200 cells/µl (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Present</td>
<td>3</td>
<td>2 (66.67)</td>
<td>1 (33.33)</td>
<td>0.1765</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>97</td>
<td>25 (25.77)</td>
<td>72 (74.23)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Present</td>
<td>1</td>
<td>1 (100.00)</td>
<td>0</td>
<td>0.2700</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>99</td>
<td>26 (25.26)</td>
<td>73 (73.74)</td>
<td></td>
</tr>
<tr>
<td>Throat swab sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td>Present</td>
<td>11</td>
<td>9 (81.81)</td>
<td>2 (18.19)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>89</td>
<td>18 (20.23)</td>
<td>71 (79.77)</td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Present</td>
<td>13</td>
<td>12 (92.31)</td>
<td>1 (7.69)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>87</td>
<td>15 (17.24)</td>
<td>72 (82.76)</td>
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</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Present</td>
<td>8</td>
<td>2 (25.00)</td>
<td>6 (75.00)</td>
<td>1.0000</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>92</td>
<td>25 (27.17)</td>
<td>67 (72.83)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
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<td>1 (100.00)</td>
<td>0</td>
<td>0.2700</td>
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<tr>
<td></td>
<td>Absent</td>
<td>99</td>
<td>26 (25.26)</td>
<td>73 (73.74)</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter species</em></td>
<td>Present</td>
<td>6</td>
<td>3 (50.00)</td>
<td>3 (50.00)</td>
<td>0.3393</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>94</td>
<td>24 (25.53)</td>
<td>70 (74.47)</td>
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<tr>
<td><em>Pseudomonas</em> species</td>
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<td>2 (50.00)</td>
<td>2 (50.00)</td>
<td>0.2942</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>96</td>
<td>25 (26.04)</td>
<td>71 (73.96)</td>
<td></td>
</tr>
<tr>
<td>Stool</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>Oocysts of Cryptosporidium</em></td>
<td>Present</td>
<td>6</td>
<td>4 (66.67)</td>
<td>2 (33.33)</td>
<td>&lt;0.0439*</td>
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<tr>
<td></td>
<td>Absent</td>
<td>94</td>
<td>23 (24.47)</td>
<td>71 (75.53)</td>
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<tr>
<td><em>Oocysts of Cyclopsora</em></td>
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<td>1 (50.00)</td>
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<td>26 (26.53)</td>
<td>72 (73.47)</td>
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<tr>
<td><em>Cysts of Giardia lamblia</em></td>
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<td>5</td>
<td>3 (60.00)</td>
<td>2 (40.00)</td>
<td>0.1202</td>
</tr>
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<td>95</td>
<td>24 (25.26)</td>
<td>71 (74.74)</td>
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<tr>
<td><em>Larvae of S. Stercoralis</em></td>
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<td>4</td>
<td>1 (25.00)</td>
<td>3 (75.00)</td>
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</tr>
<tr>
<td></td>
<td>Absent</td>
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<td>26 (27.08)</td>
<td>70 (72.92)</td>
<td></td>
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<tr>
<td><em>Eggs of T. trichiura</em></td>
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<td>2 (100.00)</td>
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<td>73 (74.49)</td>
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<tr>
<td><em>Eggs of A. lumbricoides</em></td>
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<td>2 (66.67)</td>
<td>1.0000</td>
</tr>
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<td>26 (26.80)</td>
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<tr>
<td><em>Cysts of E. histolytica</em></td>
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<td>7 (100.00)</td>
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<tr>
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<td>Absent</td>
<td>93</td>
<td>27 (29.03)</td>
<td>66 (70.97)</td>
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<tr>
<td><em>Salmonellae</em> species</td>
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<td>1 (20.00)</td>
<td>4 (80.00)</td>
<td>1.0000</td>
</tr>
<tr>
<td></td>
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<td>95</td>
<td>26 (27.37)</td>
<td>69 (72.63)</td>
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<tr>
<td>Urine</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
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<td>2 (33.33)</td>
<td>4 (66.66)</td>
<td>0.6598</td>
</tr>
<tr>
<td></td>
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<td>69 (73.40)</td>
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<tr>
<td><em>Pseudomonas</em> species</td>
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<td>4</td>
<td>2 (50.00)</td>
<td>2 (50.00)</td>
<td>0.2942</td>
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<tr>
<td></td>
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<td>96</td>
<td>25 (26.04)</td>
<td>71 (73.96)</td>
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</tr>
<tr>
<td><em>Enterococcus</em> species</td>
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<td>3</td>
<td>2 (66.66)</td>
<td>1 (33.33)</td>
<td>0.1765</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>97</td>
<td>25 (25.77)</td>
<td>72 (74.23)</td>
<td></td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
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<td>1 (50.00)</td>
<td>0.3840</td>
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<td>Absent</td>
<td>98</td>
<td>26 (26.53)</td>
<td>72 (73.47)</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
<td>Present</td>
<td>5</td>
<td>4 (80.00)</td>
<td>1 (20.00)</td>
<td>0.0181*</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>95</td>
<td>23 (24.21)</td>
<td>72 (75.79)</td>
<td></td>
</tr>
</tbody>
</table>

*: statistically significant

Among organisms detected from blood, throat swab, sputum, stool and urine, only *Candida* species (p <0.0001), *Mycobacterium tuberculosis* (p <0.0001), *Cryptosporidium* (p <0.0439) and *Enterobacter* (p = 0.0181) showed significant association with CD4 cell count. (Table 2)

**DISCUSSION**

In the present study, 51% of patients were male, 47% of patients were female and two patients were transgender. The male: female ratio was 1.08:1. Similar studies carried out in Nepal studied 150 HIV patients, and showed that 66.7% were male and 33.3% were female[6,7]. Male dominance was also reported in similar studies, with male: female ratio of 3.3:1, 2:1 and 2.42:1 respectively[8,9]. However, none of the above studies included any transgender patients.

Hepatitis B (HBV) and HCV viruses did not show any significant association with CD4 cell count in the present study. Available literatures suggest a very variable rate for co-infections of HCV and HBV among HIV infected patients[8-10]. All three viruses HIV, HBV

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and HCV share a common mode of transmission and common risk groups\textsuperscript{11}. In a study among Nepalese blood donors, HIV/HBsAg co-prevalence was recorded in 0.033% cases\textsuperscript{12}. Higher co-prevalence rate was reported in a study done in Delhi, India, where 28% of the HIV infected patients harbored HBV simultaneously in contrast to 2% among controls\textsuperscript{13}. But none of the above studies show any significant association of CD4 count with hepatitis B and C viral infections.

In the present study, \textit{Mycobacterium tuberculosis} (Acid-Fast Bacilli smear positive case) was the most common (50\%) among AIDS related opportunistic infections. There was significant association between \textit{Mycobacterium tuberculosis} and CD4 cell count of blood. \textit{Mycobacterium tuberculosis} is the leading cause of death in HIV infected persons globally\textsuperscript{14}. Various studies from Malaysia, Cambodia, Nepal and India also found tuberculosis to be the most common AIDS defining illness with prevalence of 48\%, 43\% and 15.4\% respectively\textsuperscript{14-16}. A study from central Nepal documented 23\% prevalence of tuberculosis in HIV infected patients\textsuperscript{17}. It has been found that bacterial pneumonia occurs at a rate many times higher in the HIV infected population than the general population\textsuperscript{11}. In the present study, respiratory bacterial pathogen were distributed as \textit{Staphylococcus aureus} 8(16\%), \textit{Acinetobacter} 6 (12\%), \textit{Pseudomonas} 4(8\%) and \textit{Streptococcus pneumoniae} 1(2\%). These pathogens did not show any significant association with CD4 cell count of blood. Studies from different regions of India reported \textit{Staphylococcus aureus} among 4\% to 12.69\% cases of HIV infected patients\textsuperscript{18-20}. \textit{Pseudomonas} was found in 10.5\% and 12.69\% of patients\textsuperscript{19,20}. A study from central Nepal reported \textit{Streptococcus pneumoniae} as the second common (28.7\%) opportunistic pathogen in HIV infected patients\textsuperscript{3}. In another study from Italy, \textit{Streptococcus pneumoniae} was identified as the most frequent (60\%) pathogen among HIV patients\textsuperscript{21}. These differences may be due to a different disease pattern in different geographical locations.

Oral candidiasis is considered to be the earliest manifestation of an HIV infected person\textsuperscript{22}. The rate of Candida infection is inversely proportional to the CD4 count of the patient\textsuperscript{23}. In the present study, Candida species was the second most common (22\%) opportunistic pathogen among HIV infected patients. Candida species were detected from throat swab of 11 patients and a significant association (p <0.0001) was obtained between low CD4 cell counts with pathogenic Candida species. Several studies have reported Candida species as the most common opportunistic pathogen\textsuperscript{23,24-26}. Candida was found to be the second most common pathogen in other studies\textsuperscript{6,27,28}. These studies also reported significant association of presence of pathogenic Candida species with low CD4 cell count. Oral candidiasis is one of the clinical markers of immunosuppression, and antiretroviral therapy should be initiated in patients with persistent oral candidiasis if facilities for performing CD4 cell count are not available. These findings may help clinicians to use oral candidiasis as a helpful tool for the diagnosis and detection of progression of HIV in resource poor countries like Bangladesh.

Parasitic infections of gastrointestinal tract are universally considered as a common problem among patients with HIV infection. Down regulation of immune system in HIV patients may lead to diarrhea due to these parasites and may cause life threatening complications\textsuperscript{29}. In the present study, enteric parasites were detected in stool samples of 29 patients, of which 15 patients reported persistent or intermittent diarrhea for more than one month. Diarrhea with parasitic infections was present in the patients infected with \textit{Entamoeba histolytica}, \textit{Cryptosporidium parvum}, \textit{Giardia lamblia} and \textit{Cyclospora}. In the present study, \textit{Cryptosporidium parvum} and \textit{Cyclospora} were detected from stool in 6\% and 2\% of patients. These two parasites are considered as opportunistic pathogens in HIV infected patients. \textit{Entamoeba histolytica}, \textit{Giardia lamblia}, \textit{Ascaris lumbricoides}, \textit{Trichuris trichiura} and \textit{Strongyloides stercoralis} were also frequently encountered but are not currently considered as opportunistic pathogens in HIV patients\textsuperscript{30}. In this study, the most frequent intestinal parasite detected from stool in this study was \textit{Entamoeba histolytica} (7\%). The observed frequency indicates that the parasite probably acted as a commensal, only becoming highly pathogenic following the suppression in immune function. \textit{Entamoeba histolytica} did not show any significant association with CD4 cell level in blood (p = 0.1846). In this study, \textit{Cryptosporidium parvum} (12\%) was an important opportunistic pathogen among HIV infected patients. In respect to CD4 cell count, it was found that \textit{Cryptosporidium parvum} infection occurs when CD4 cell count was below 200 cells/\mu l of blood, resulting in significant association (p <0.0439). The significance of this result is the involvement of this parasite in enhancing the progression of HIV to full blown AIDS by elaboration of chronic diarrhea, which results in drastic loss of water and electrolytes, and the subsequent dehydration and weight loss in HIV patients. Thus, the frequency of occurrence of \textit{Cryptosporidium parvum} serves as a good predictor of advanced HIV disease or full blown AIDS. Several studies have reported \textit{Cryptosporidium parvum} as one of the most common organisms causing diarrhea in 10.5\% and 20\% of patients\textsuperscript{30,31}. 

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A study of parasitic protozoal infections among HIV patients detected *Entamoeba histolytica* (62.8%), *Giardia lamblia* (61.6%) and *Cryptosporidium* species (24.1%)[32]. Studies from India reported *Cyclospora* in 0.7% to 1% of patients[32,33]. These findings are similar with the finding of the present study, where *Cyclospora* was detected in the stool of 2 (4%) patients. A study from Ethiopia found *Ascaris lumbricoides* in 2.5% of cases, and this finding is also similar with finding of present study where *Ascaris lumbricoides* was found in 3% of cases. Although the present study detected *Strongyloides stercoralis* in 4% of patients only, a study from Ethiopia has reported a higher incidence (11.5%) of *Strongyloides stercoralis*.[34]

In the present study, pathogens were detected from urine specimen in 20% of patients, with isolates occuring more in females (55%) than males (45%). This may be due to the anatomical structure of the female genital tract that makes women susceptible to urinary tract infections, compared to males. *Enterobacter* was isolated from 5 (10%) cases. When plotted against CD4 cell count in the blood, *Enterobacter* showed a significant association (p = 0.018). Other pathogens from urine samples revealed *E. coli*, *Pseudomonas*, *Enterococcus* and *Staphylococcus aureus* in 6 (12%), 4 (8%), 3 (6%) and 2 (4%) samples respectively. In a study from Nigeria, *E. coli*, *Staphylococcus aureus*, *Enterococcus* and *Pseudomonas* were reported in 64.8%, 41.3%, 36.4% and 30.5% cases respectively[35]. This difference in frequency of organism may be due to the fact that females were the predominant gender in that study. Association with CD4 cell count was also determined in a controlled longitudinal study with patients infected with HIV. The study concluded that persons infected with HIV who had CD4 cell count below 200 cells/µl were at an increased risk of bacteruria when compared with HIV infected patients with higher CD4 lymphocyte count[36].

**CONCLUSION**

In conclusion, it can be stated that *Mycobacterium tuberculosis* (26%) was found to be the most common opportunistic bacterial pathogen in our region, followed by *Candida* species (22%) isolated from oral patches. *Cryptosporidium parvum* (12%) was found to be the most common opportunistic parasite causing diarrhoea. *Enterobacter* species was another important opportunistic pathogen causing urinary tract infections. Significant association was found between low CD4 cell count and the presence of these pathogens, reflecting the immune suppression by HIV.

**REFERENCES**


Original Article

Hematologic profile in morbidly obese patients: A series of 282 patients

Tariq N Aladily, Leen Dabbas, Hanan Mansour
Department of Hematopathology, The University of Jordan, Amman, Jordan

Kuwait Medical Journal 2019; 51 (1): 72 - 77

ABSTRACT

Objective: Morbid obesity is a global disease that is associated with increased morbidity and mortality. Among the systemic complications is the disturbance in hematologic parameters. Anemia, polycythemia, iron deficiency and chronic inflammation are common findings. In this study, we evaluate the hematologic profile and gastric histopathologic study for a cohort of morbidly obese patients and compare the results with previous studies.

Design: Retrospective study
Setting: Department of Hematopathology, The University of Jordan, Amman, Jordan
Subjects: Two hundred and eighty-two morbidly obese patients were admitted to Jordan University Hospital between 2007 and 2015 for intervention.
Intervention: Sleeve gastrectomy operation
Main outcome measures: Hematologic profiles at the time of surgery and at 6-months follow up along with histopathologic evaluation of sleeve gastrectomy specimens

Results: Of the 282 patients, 43% had anemia at the time of surgery, predominantly normochromic normocytic. No polycythemia cases were encountered. 11% of patients had subclinical iron deficiency and 18% had subclinical vitamin B12 deficiency. Leukocytosis was present in 77% of patients. 92% had histologic evidence of chronic gastritis and 49% had Helicobacter Pylori. Upon follow up, the mean hemoglobin concentration increased by 1 g/dL, but serum ferritin dropped in 13% of patients

Conclusion: Anemia, nutritional deficiencies, chronic inflammation and Helicobacter pylori are common among morbidly obese patients. There is little correlation between hemoglobin level and the status of serum iron, ferritin and vitamin B12. We recommend performing a thorough hematologic assessment pre and post surgery and routine Helicobacter pylori examination.

KEY WORDS: anemia, chronic gastritis, helicobacter pylori, inflammation, subclinical iron deficiency

INTRODUCTION

Obesity is a global health problem with a significant socioeconomic impact. The World Health Organization defines obesity as a body mass index of 30 kg/m² or more. In 2014, there were over 600 million obese people worldwide, which have doubled since 1980[1]. Its prevalence in Arab countries has increased at an alarming rate during the last three decades. The modern lifestyle that accompanied urbanization of Arab countries resulted in this peak, which was apparent in the change in eating habits and the trend of sedentary life. It is estimated that 30% of men and 55% of women in Kuwait are obese, making it the highest prevalence of obesity in Arab-speaking states[2]. In Jordan, the prevalence is close, where 28% of men and 53% of women are obese, and the severity is more associated with older age, married status, low education and non-smokers[3].

Obesity is a risk factor for many chronic and metabolic diseases including type-2 diabetes, hyperlipidemia, coronary artery diseases, hypertension, obstructive sleep apnea and certain malignancies[4-6]. Other diseases that complicate obesity are vast, such as osteoarthritis, sexual dysfunction, gynecologic diseases, fatty liver, gall bladder diseases, depression and low self esteem[7-12]. Therefore, obesity is associated with inferior quality of life, lower life expectancy and expensive medical cost. Yet, it is preventable, as social and scientific measures are important in decreasing its effects.

Address correspondence to:
Tariq N Aladily, MD, P.O.Box 142725, Amman 11418, Jordan. Tel: +962798386036; Email: tnaladily@ju.edu.jo
The hematologic disturbances are among the complications that were investigated in obese people, and the focus was on abnormal iron metabolism. Obese patients tend to consume iron-poor food, show increased iron demand and develop dilutional hypoferremia. In addition, recent evidence points to persistent subclinical inflammation in obese people and higher level of hepcidin, which plays a key role in reducing iron absorption and increased sequestration\cite{13}, and anemia tends to persist after gastric bypass surgery\cite{14}. Thus, the classic two paradigms of iron deficiency anemia (IDA) and anemia of chronic disease (ACD) are common, and the distinction between them is less explained in previous studies\cite{13}. In this article, we aim at examining the hematologic profile of a cohort of morbidly obese patients at the time of surgery and post surgery, along with histopathologic assessment of gastric biopsy to identify major derangements from normal subjects.

SUBJECTS AND METHODS

We retrospectively identified morbidly obese patients who visited Jordan University Hospital between 2007 and 2015 and underwent sleeve gastrectomy operation. The study was approved by the Scientific Research Committee of the Faculty of Medicine and Institutional Review Board of Jordan University Hospital.

Clinical, hematologic and pathologic data were obtained from patients’ records in hematology and pathology laboratories. Values of hemogram tests were collected at the time of surgery and at six months after surgery, which included: hemoglobin (Hg) level, hematocrit (HCT) level, red blood cells (RBC) count, mean cell volume (MCV), mean cell hemoglobin (MCH), red cell distribution width (RDW), white blood cells (WBC) count, platelets (Plt) count, serum ferritin level, serum iron level, total iron binding capacity (TIBC), and serum vitamin B12 level. Additionally, all included cases had representative sleeve gastrectomy specimens which were morphologically evaluated for the presence of inflammation and *Helicobacter pylori* (*H. pylori*) by pathologists.

The normal references were as follows: Hg: 14 - 18 g/dl for men and 12 - 16 g/dl for women; HCT: 0.41 - 0.51 for men and 0.37 - 0.47 for women; RBC count: 4.5 - 6.5 x10^6 for men and 3.8 - 5.8 x10^6 for women; MCV: 80 - 100 fl; MCH: 26 - 34 pg/cell; RDW: 15.1 - 20.1; WBC: 4 - 10 x10^9/L; Plt: 140 - 440 x10^9/L. The hemogram test was performed using Cell Dyne (Abbott Diagnostic), normal references for Serum iron: 65 - 176 µg/dl for men and 50 - 170 µg/dl for women; TIBC: 250 - 370 µg/dl, using Cobas-C501 (Roche); Serum ferritin: 24 - 336 µg/dl for men and 11-307 µg/dl for women; serum vitamin B12 >200 pg/ml using Architect Plus-i2002 SR (Abbott). Normal reference ranges were provided by manufacturer. We used descriptive statistics including mean, standard deviation, median and interquartile range to analyze the data.

RESULTS

Clinical

A total of 282 patients were identified; 213 females and 69 males. The female: male ratio is 3:1. Their ages ranged from 13 to 64 years with a mean of 35 years. Hemoglobin test and histopathologic examination of the gastrectomy specimen were available for all patients.

Anemia

At the time of surgery, low Hg concentration/HCT level was present in 121/282 patients (43%), which was similar between women 90/213 (42%) and men 31/69 (45%). The mean level of hemoglobin was 12 g/dL (7.5 - 15.4) for women and 14 g/dL (8.9 - 17.6) for men. Most cases of anemia had normal MCV/MCH values: 72/115 (63%). The remaining cases were hypochromic microcytic: 43/115 patients (37%), which was more common in women (37/87, 43%) than in men (6/28, 21%). Macrocytic anemia was not encountered. Low MCH was in concordance with low MCV in all cases. The difference in denominators is due to non-availability of some results in patients’ charts.

Low RBC count was encountered in 20/116 (17%) of anemic patients; 11/86 (13%) women and 9/30 (30%) men. Erythrocytosis was present in two women; one had normal Hg level, while the second had hypochromic microcytic anemia (iron study was not available). RDW was increased in only 9 patients (8 women, 1 man), most of whom (8/9) had IDA.

Status of iron

Low serum level of iron was present in 39/118 (33%) of all patients, only 19 had low Hg (14 women and 5 men). Low ferritin level was detected in 24/180 (13%), (16 women and 8 men), only 4 patients had low Hg. High TIBC was present in 12/105 (11%, 9 women and 3 men), 7 of whom had low serum ferritin, while low TIBC was shown in 6/102 (6%, 2 men and 4 women) with normal serum ferritin.

Vitamin B12

Low serum vitamin B12 was detected in 35/157 (22%) patients; 22/121 (18%) women and 13/36 (36%) men. Only 7 of those patients had low Hg.
WBC and platelets

Leukocytosis was present in 211/275 (77%) of all patients with a similar frequency in both genders. Only 2/22 patients had mild thrombocytosis.

Gastric biopsy

Chronic inflammation was present in 260/282 (92%) of specimens (Fig 1). *H. Pylori* was present in 139/282 (49%) of patients (Fig 2). Both were in similar frequency between the two genders.

Follow up

One hundred and fourteen patients had a follow up hemogram test at 6 months post surgery. The anemia normalized in 19 women and 8 men (24%), while 1 woman and 1 man developed new anemia (1%). The remaining patients had a similar Hg level as pre-surgery. A follow up for serum ferritin level was available for 48 patients: in 12 patients (25%) the level dropped below normal, 3 patients (6%) normalized after being low, while the rest stayed the same.

DISCUSSION

Obesity is a global health problem that has received considerable attention as a major health hazard. The cause is a complex interaction between life style, genetic predisposition and environmental factors. It is associated with increased risk of chronic systemic disorders and death. Despite the excessive consumption of food, obese people, paradoxically, frequently have anemia[13]. Recent research demonstrated that association is complex and multi-factorial.

It is currently believed that obese people have a steady state of systemic inflammation. The current understanding of the adipose tissue as a major endocrine organ, with ability to secrete over 50 different molecules – collectively called “adipokines”- is the basis of this etiology. The increased adipose tissue mass and relative hypoxia in obese people promote excessive secretion of interleukin (IL)-1, IL-6, IL-8, IL-10 and monocyte chemoattractant protein-1[15-17]. It was found that obese people consistently have higher levels of serum C-reactive protein and IL-18, which fall down after losing weight[18-19]. The increased adipokines would suppress erythropoietin and activate synthesis of hepcidin, which in turn inhibits iron absorption from the gut and blocks iron transfer into RBCs, both culminating in emergence of ACD[20-23].

Most of the published research emphasizes the presence of abnormality in Hg and iron levels in morbidly obese patients, but there is little agreement on the findings and conclusions. The distinction between IDA and ACD is vague and the presence of anemia itself is sometimes discounted in favor of polycythemia. The abnormality is sometimes described simply as “iron deficiency” or “nutrient deficiency”[24]. For example, low serum ferritin and transferrin saturation, characteristic of iron deficiency anemia, is frequently found in obese adolescent patients in different studies[25-28]. On the other hand, a meta-analysis of 25 articles in the literature describes high serum ferritin concentration and low transferrin saturation in obesity, which is consistent with iron dysregulation related to inflammation model. Moreover, higher hemoglobin concentration –instead of anemia- was observed in other studies[29]. A possible explanation of this difference would be related to increased iron demand among growing adolescents compared to adults, while increased hemoglobin concentration is secondary to hypoxia in some patients.
Our study shows a high frequency of anemia and vitamin B12 deficiency among morbidly obese patients, which is consistent with previous reports. Although most of our cases are best categorized as ACD due to normal MCV, serum ferritin and TIBC levels, true iron deficiency -reflected by low serum ferritin level- is still common (13%) and is not restricted to adolescent groups. The chance of having concomitant IDA and ACD is still considered, and the definite distinction between the two diseases by examining iron stores in bone marrow is not routinely performed in clinical practice. Although no polycythemia cases are encountered, the effect of hypoxia can be predicted by the frequent presence of subclinical iron and vitamin B12 deficiencies, and occasional erythrocytosis. The low serum iron level provides little significance in distinguishing IDA from ACD, and is also known to have methodological and biological variations during the day, making it less accurate and stable than hemoglobin and ferritin tests.

The histopathologic changes of the stomach were studied in previous reports (Table 1). The most common pathologic finding was chronic gastritis, while others included active inflammation, follicular lymphoid hyperplasia and in rare cases, intestinal metaplasia and gastrointestinal stromal tumors. The frequency of H. pylori was variable. Our study documents the highest frequency of both H. Pylori and non-H. pylori inflammation, which is close to other Arabic populations. The type of diet, smoking and medications are confounding factors that may explain the higher rate of inflammation in our population.

Following bariatric surgery, most patients show an improvement in diabetes, hypertension and apnea. However, postoperative complications are frequent, among which is an alteration in nutritional status and worsening of anemia and iron deficiency. Blood loss and inflammation secondary to surgery, along with gut manipulation that alters natural absorption of nutrients play a major role in these changes. Patients also limit the intake of red meat and have diminished gastric acid secretion. The absorption of both heme, and to a lesser extent, non-heme iron supplements is reduced after surgery. Serum ferritin and total body iron also drop. The decrement was less with sleeve gastrectomy than in Roux en Y bypass. Thus, iron supplements must be taken and monitoring for iron and anemia should continue for a long time post surgery. Although there was mild improvement in Hg level in our patients after surgery, 21% of patients who had follow up developed new iron deficiency.

CONCLUSION
In short, our study provides statistical and morphologic evidence for multiple types of anemia, vitamin B12 deficiency and chronic inflammation model in morbid obesity in both genders. Compared to previous reports, it combines the hematologic and histopathologic features in the same cohort of patients. It also shows a poor correlation between hemoglobin concentration and the status of serum iron, ferritin and vitamin B12. Thus, we recommend screening all morbidly obese patients for these variables even if hemogram test was normal. Screening should continue after surgical intervention even with providing supplements.

ACKNOWLEDGMENT
Conflict of interest: none
Financial disclosure: none

REFERENCES

Table 1: The prevalence of chronic inflammation and H. Pylori in gastric biopsies of morbidly obese patients in different studies. The prevalence tends to be higher in Arabic populations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Chronic inflammation</th>
<th>H. Pylori</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>Kuwait</td>
<td>74%</td>
<td>7.3%</td>
</tr>
<tr>
<td>34</td>
<td>Saudi Arabia</td>
<td>33%</td>
<td>8.5%</td>
</tr>
<tr>
<td>35</td>
<td>Qatar</td>
<td>33%</td>
<td>40.9%</td>
</tr>
<tr>
<td>36</td>
<td>Israeli Jews</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td>37</td>
<td>Arabs</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>38</td>
<td>Brazil</td>
<td>47%</td>
<td>Not documented</td>
</tr>
<tr>
<td>39</td>
<td>New Zealand</td>
<td>38.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>40</td>
<td>Australia</td>
<td>7.2%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Our study</td>
<td>Jordan</td>
<td>92%</td>
<td>49%</td>
</tr>
</tbody>
</table>

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Search of house mite’s fauna and investigation of relationship between house dust mite and allergy in the province of Hatay, Turkey

Burcu Gulkan1, Serpil Degerli2, Gulnaz Culha1, Nazan Savas3, Semra Ozcelik2

1Department of Parasitology, Mustafa Kemal University Medical Faculty, Hatay, Turkey
2Department of Parasitology, Cumhuriyet University Medical Faculty, Sivas, Turkey
3Department of Public Health, Mustafa Kemal University Medical Faculty, Hatay, Turkey

ABSTRACT

Objective: This study aims to search house mite’s fauna and to investigate the relationship between house dust mite prevalence and house-related risk factors and allergic diseases.

Design: Cross sectional study

Setting: Two hundred houses in 25 different neighborhoods in Hatay province of Turkey. Hatay province is located in East Mediterranean Region with a population of 1,519,836. It has the border with Syria. The sample was selected by clustered sociodemographic region systematic random sampling method.

Subjects: Two hundred samples of house dust

Intervention: A survey was used. Pearson Chi-Square test was used.

Main outcome measure(s): Samples of house dust in total were analyzed according to Spieksma-Boezman method of lactic acid precipitation; and the identification of the samples in which mites were detected was made according to the Coloff’s type identification key.

Results: Out of 200 samples of house dust, mite was detected in 57.5% of them. The most frequently found type of mite was determined as D. pteronyssinus (72.2%). There was no significant relationship found between the mite prevalence and other criteria, except the number of rooms when the ground clearance of houses, the case of garden, carpet type, washing temperature and duration of duvets, times of the insolation of pillows and quilts, heating devices, cleaning times, insolation conditions, presence of a pet and the economic situation of the family were analyzed (p >0.05).

Conclusion: It is determined that mite prevalence in the province of Hatay, Turkey is higher than many regions.

INTRODUCTION

Asthma and other allergic diseases are important public health problems since they lead to physical troubles for millions of people in the world, especially children, causing lower quality of life and economic burden. House dust mites are considered to be the most significant source of indoor allergens that are related to allergic diseases. House dust mites are commonly found in people’s natural life environment, work environment and all other suitable environments produce strong allergens[1-3].

These allergens are found in mite’s body fragments, secretions and especially in their stools[3]. The allergens in mites’ stools are caused by the digestion of nutrients, and it is known that they are capable of producing stools 20 times a day[2,4].

The most widespread types of dust mites and allergens in the world are D. pteronyssinus (Der p), D. farinae (Der f), E. maynei and B. Tropicalis. Group 1 (Der p 1 and Der f 1) allergens found in D. pteronyssinus and D. farinae constitute the major threat for human beings’ health[4-6].

Address correspondence to:
Prof. Dr. Nazan Savas, Department of Public Health, Mustafa Kemal University Medical Faculty, Hatay, Turkey. Tel: +90 505 9386417; E-mail: drnazansavas@hotmail.com
Asthma, atopic dermatitis, allergic rhinitis, urticaria and anaphylactic shock can be seen when hypersensitive individuals get in contact with these allergens or receive them through inhalation\[^{3,4,7}\]. Although symptoms are generally seen in respiratory system (such as sneezing, itchy eyes, wheezing), they could cause death in the case of hypersensitive individuals due to wheezing, shortness of breath and even acute attacks of bronchial asthma\[^{4}\].

While allergic sensitivity to house dust is observed in 10% of the general population, the rate increases up to 45% among asthmatic patients\[^{8}\]. Sensitivity to house dust mites is seen in 50% of allergic people, whereas for asthmatic children, this rate reaches 80%\[^{9}\].

House dust mites, for which the main nutritional source is skin flakes of human beings and animals, are assumed to be 0.3 mm in size and they are believed to involve 45,000 types, although only 5% of the types could be identified\[^{1,8-10}\]. Their life-cycles generally consist of the stages of egg, larva, protonymph, tritonymph and adult\[^{5,11}\]. Fertilized females can ovulate 1-3 eggs each day for \textit{D. pteronyssinus} during 45 days, and for \textit{D. farinae} during 30 days\[^{1-3}\].

For mites, humidity and temperature constitute important environmental factors that affect the population in a period from the egg stage until the adult stage\[^{5,12}\]. It has been determined by studies that the most convenient temperature for mites to reproduce is 25 - 27 °C, relative humidity need is about 75 - 80%, and they can develop in 19 - 30 days under these conditions\[^{5,13,14}\].

Besides the impact of climate and the structure of environment, house dust mites’ species diversity and population density can also depend on the characteristic features of the house and furniture and the life conditions of the household\[^{6,12}\]. Studies report that house dust mites are mostly found in bed, quilt, pillow, sheet, blanket and carpets\[^{5,13}\]. 70% of house dust mites determined by studies in many countries consisted of \textit{D. pteronyssinus} and \textit{D. farinae} species\[^{2,10}\].

According to the studies made in our country, house dust mites are found at the rate of 18.6% across Turkey and the most common species is reported as \textit{D. Pteronyssinus}\[^{7,9,17,18}\].

There has not been any comprehensive study for the search of house dust mite’s fauna in the province of Hatay, Turkey and investigation of its relationship with allergy. In this study, in which the contribution to control programs is intended by considering the importance of struggling against mites for public health, it is aimed to make the search of house dust mite’s fauna in the province of Hatay, and also to investigate the relationship between house dust mite prevalence and climate, environmental factors, individual habits, dwelling structure and allergic symptoms in individuals.

**MATERIALS AND METHODS**

In this study, 200 samples of house dust in total were collected from 25 different neighborhoods in the province of Hatay in the time period between January-December 2012. One hundred and eighty-nine samples of dust in total were collected from the houses.

The houses were categorized as 60 single-storey houses and 129 apartments. Also, 11 samples of dust in total were collected from 11 different classrooms of a kindergarten. We considered to compare the types of mites in houses and kindergartens. Eighty-nine of the houses constituted a low socioeconomic level, including 60 single-storey houses and 29 apartments. These were chosen from the settlements whose infrastructure problems are not addressed and environmental cleaning is not fully supplied. The remaining 100 houses were chosen from settlements with completed infrastructure and well-provided environmental cleaning. It was observed that hygiene rules were paid attention and the staff was using galoshes and aprons in the kindergarten, which was located in a settlement with good socio-economic level.

The participants were asked about the occurrence of allergic symptoms among individuals of a family and the number of people in whom the symptoms were seen. Allergic symptoms were categorized as coughing, itching, shortness of breath, wheezing, runny and itchy nose, consecutive and frequent sneezing, red eyes and watery eyes in the survey\[^{19,20}\]. In addition, the number of rooms in the houses, insolation conditions of the houses, heating systems of the houses, the frequency of cleaning in the houses, the frequency of the insolation of pillows and quilts in the houses, the frequency and the temperature of washing duvets in the houses, presence or absence of a pet in the houses, type of carpet used in the houses and income level of the houses were learned through surveys.

Dust samples were collected by using a 1200 watt vacuum cleaner and a different dust bag for each house. House dusts were vacuumed from the carpets in bedrooms, living rooms and kids rooms, bed facets and couches by vacuuming for 2 - 3 minutes per 1 square meter. Dust samples collected from each house were placed in plastic bags and labeled. Name-surname, address, date of the collection of dust and time were recorded on the labels. Also, a survey was applied in each household to determine the case of allergy in family members, structure of the house, cleaning habits and socio-economic level of the family. Characteristics of the houses and family members with allergy complaints were determined by the
questionnaires which were filled in completely by an adult in each household. The surveys applied in kindergartens were filled in by responsible teachers.

The analysis of the dust samples collected was initiated in 24 hours, when they were taken to Parasitology Laboratory of Mustafa Kemal University Faculty of Medicine Research Hospital. Coarse particles in the samples were removed with decontamination by dry sieving with plastic sieves. In the sieving process, dust were placed in sieves on top of each sample, and with circular motions fine dust particles were separated and enabled to pass to the container below. Containers with sieved dust were labeled in order to prevent mixing[1,7].

Types of mites detected in house dust were identified according to Coloff's (2009) type identification key[1]. Pearson chi-square and Fisher exact tests were used. Statistical analysis was made with SPSS 19 program.

RESULTS

In the study, a total of 200 dust samples were collected from 25 different neighborhoods in the province of Hatay within the time period between January 2012 and December 2012. Of these, 189 of the dust samples were collected from houses and 11 of them were collected from 11 different classrooms of a kindergarten.

The ones taken from houses were categorized as 60 from single-storey houses and 129 from flats. Mites were found in 115 (57.5%) of the total 200 dust samples (Fig 1), 8 of the 11 different classrooms

![Fig 1: The frequencies of mites in houses](image-url)
in a kindergarten (72.7%) and 107 of the 189 houses (56.6%, p = 0.23), (Table 1). According to the findings, when the possible relevant features of houses in terms of their relationship with the presence of house dust mites were analyzed; there was no significant relationship found between mite prevalence and other criteria except the number of rooms when the ground clearance of houses, the presence of a garden, carpet type, washing temperature and duration of duvets, times of the insolation of pillows and quilts, heating devices, cleaning times, insolation conditions, presence of a pet and the economic situation of the family (p >0.05) (Tables 1 - 6). Mite prevalence was positive for 33 of the 60 single-storey houses (55%), 74 of the 129 apartments (57.4%), and 8 of 11 classrooms (72.7%).

D. pteronyssinus was the most common mite type, which was found in 83 (72.2%) of 115 houses. The prevalence of other mites are as follows: D. farinae 23 (20%), Chortoglyphs arcuratus 8 (7%), Lepidoglyphus destructor 5 (4.4%), Cheyletus spp. 2 (1.7%), Mesostigmata 2 (1.7%), Histiostoma spp. 2 (1.7%), and non-6 (5.2%) (Fig 2). In 12 (10.4%) of the houses, there were two types of house dust mites found, while four types of house dust mite were observed, D. pteronyssinus and D. farinae were found in six (5.2%) of them, D. pteronyssinus and undefined in two (1.7%) of them, D. pteronyssinus and Chortoglyphs arcuratus in two (1.7%) of them, and D. farinae and undefined in one (0.9%) of them. In the house where four species were identified together, D. pteronyssinus, L. destructor, Chortoglyphs arcuratus and undefined were found.

In 84 (73%) of the houses where mites were found, there were one or more individuals with allergic symptoms. House dust mite was detected in 22 (62.9%) of 35 houses with shortness of breath among family members; 11 (57.9%) of 19 houses with

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### Table 2: The presence of mites according to heating type

<table>
<thead>
<tr>
<th>Heating type</th>
<th>Present</th>
<th>Present (%)</th>
<th>Absent</th>
<th>Absent (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stove</td>
<td>60</td>
<td>55.6</td>
<td>48</td>
<td>44.4</td>
<td>108</td>
</tr>
<tr>
<td>Central heating (radiator)</td>
<td>39</td>
<td>58.2</td>
<td>28</td>
<td>41.8</td>
<td>67</td>
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<tr>
<td>Air conditioner</td>
<td>12</td>
<td>70.6</td>
<td>5</td>
<td>29.4</td>
<td>17</td>
</tr>
<tr>
<td>Electric stove</td>
<td>3</td>
<td>75</td>
<td>1</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Natural gas</td>
<td>1</td>
<td>25</td>
<td>3</td>
<td>75</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>57.5</td>
<td>85</td>
<td>42.5</td>
<td>200</td>
</tr>
</tbody>
</table>

---

### Table 3: The presence of mites according to frequency of insolation

<table>
<thead>
<tr>
<th>Mite</th>
<th>Monthly n(%)</th>
<th>Every Six Months n(%)</th>
<th>Annually n(%)</th>
<th>Never n(%)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>53 (59.6)</td>
<td>36 (50)</td>
<td>12 (63.2)</td>
<td>14 (70)</td>
<td>115</td>
<td>0.34</td>
</tr>
<tr>
<td>Absent</td>
<td>36 (40.5)</td>
<td>36 (50)</td>
<td>7 (36.8)</td>
<td>6 (30)</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>89 (44.5)</td>
<td>72 (36)</td>
<td>19 (9.5)</td>
<td>20 (10)</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

---

### Table 4: The presence of mites according to cleaning of duvets

<table>
<thead>
<tr>
<th>Mite</th>
<th>Weekly n(%)</th>
<th>Every two weeks n(%)</th>
<th>Every three weeks n(%)</th>
<th>Never n(%)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>50 (58.1)</td>
<td>51 (60)</td>
<td>6 (33.3)</td>
<td>8 (72.7)</td>
<td>115</td>
<td>0.52</td>
</tr>
<tr>
<td>Absent</td>
<td>36 (41.9)</td>
<td>34 (40)</td>
<td>12 (66.7)</td>
<td>3 (27.3)</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>86 (43)</td>
<td>85 (42.3)</td>
<td>18 (9)</td>
<td>11 (5.5)</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

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Fig 2: Types and numbers of mites observed in the houses
wheezing; 51 (63.8%) of 80 houses with runny nose complaint; 40 (67.8%) of 59 houses with frequent sneezing complaint; 23 (62.2%) of 37 houses with red eyes complaint; 24 (63.2%) of 38 houses with watery eyes complaint; 24 (72.7%) of 33 houses with itching complaint; and 43 (58.9%) of 73 houses with coughing complaint. In total, it was determined that 238 individuals had allergic symptoms in the houses where mites were found (Fig 3).

There was no significant difference observed according to Fishers Exact test made in statistical analysis that mite prevalence is higher in schools compared to households (p = 0.23). When the mite prevalence was examined according to the number of rooms in houses (except school), 23 of the 189 houses had one or two rooms and 166 of them had three or more rooms. Mites were found in 7 (30.4%) of the houses with one or two rooms, whereas in 100 (60.2%) of the houses with three or more rooms. A significant relationship was found between the number of rooms in houses and mite prevalence, when the presence of mites were analyzed with chi-square test according to the number of rooms in houses (p <0.05).

**DISCUSSION**

In many countries across the world, there are several studies about the prevalence of house dust mites and their types. It was reported that house dust mites were found in Europe at the rate of 23 - 94.5%, in North America at the rate of 16.9 - 77.5%, in South America at the rate of 47 - 100% and in the Far East at the rate of 26.4 - 88.1%

Table 5: The presence of mites according to carpet type

<table>
<thead>
<tr>
<th>Mite</th>
<th>Commercial n(%)</th>
<th>Wool n(%)</th>
<th>Wall-To Wall n(%)</th>
<th>Other n(%)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>58 (63.7)</td>
<td>33 (35.9)</td>
<td>18 (50)</td>
<td>6 (42.9)</td>
<td>115</td>
<td>0.31</td>
</tr>
<tr>
<td>Absent</td>
<td>33 (36.3)</td>
<td>26 (44.1)</td>
<td>18 (50)</td>
<td>8 (57.1)</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>91 (45.5)</td>
<td>59 (29.5)</td>
<td>36 (18)</td>
<td>14 (7)</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: The presence of mites according to economic situation

<table>
<thead>
<tr>
<th>Mite</th>
<th>&lt;1000 n(%)</th>
<th>1000 - 1500 n(%)</th>
<th>1500 - 2000 n(%)</th>
<th>&lt; 2000 n(%)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>19 (59.4)</td>
<td>36 (63.2)</td>
<td>40 (52.6)</td>
<td>20 (57.1)</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>13 (40.6)</td>
<td>21 (36.8)</td>
<td>36 (47.4)</td>
<td>15 (42.9)</td>
<td>85</td>
<td>0.67</td>
</tr>
<tr>
<td>Total</td>
<td>32 (16)</td>
<td>57 (28.5)</td>
<td>76 (38)</td>
<td>35 (17.5)</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

Fig 3: The status of mites in the houses where family members have allergic symptoms
was observed as higher. The reason might be linked to a mean temperature of 18.1 °C and humidity of 69%, the neighborhoods where the dust samples collected had low socio-economic level and/or the life style of people.

Regarding the studies made in different provinces in our country, mites were determined by Aygan and Özçelik at the rate of 18% in Sivas, and by Kalpakkloğu et al at the rate of 24.1% in five different regions of Turkey[18,21]. It was stated that mites were found by Aldemir and Baykan at the rate of 57.66% in Konya[18], Akdemir and Gürdal at the rate of 18.05% in Kütahya[17], Gülbahtar et al at the rate of 53.8% in İzmir[22], Gülgeğen et al at the rate of 34.38% in Bursa[7], Akdemir and Yılmaz at the rate of 29.3% again in Kütahya[23], Ertabaklar et al at the rate of 22.72% in Aydn[9], Çiftçi et al at the rate of 23.1% in Western Anatolia in the provinces of Denizli[24], Kütahya, Isparta, Uşak and Afyon, Doğan et al at the rate of 16.67% in Eskişehir[11], and Aykut et al at the rate of 100% in the provinces of Bitlis and Muş[13].

D. pteronyssinus was the most common type of mite which was detected in 83 (72.2%) of 115 houses where mites were found in our study. The other types were D. farinae (20%), C. Arcuatus (7%), L. destructor (4.4%), Cheyletus spp. (1.7%), Mesostigmata (1.7%), Histioctoma spp. (1.7%) and undefined (5.2%). Two types of mites were found in 12 (10.4%) houses and four types were of mites found in one (0.9%) house. In the houses where two types of house dust mites were detected, they were determined as D. pteronyssinus and D. farinae in 6 (5.2%), D. pteronyssinus and undefined in 2 (1.7%), D. pteronyssinus and Chelostigmata in 2 (1.7%), D. pteronyssinus and Cheyletus spp. in 1 (0.9%), D. pteronyssinus and L. destructor in 1 (0.9%) and D. farinae and undefined in 1 (0.9%) of them. Four types which were determined together were identified as D. pteronyssinus, L. destructor, Chelostigmata arcuatus and undefined ones. The most common type of mite according to studies which were done in many countries and throughout Turkey is D. pteronyssinus and our study was found to be compatible with these studies[22,23].

Dust samples collected from kindergarten were taken from the carpets and cushions in the classrooms. D. pteronyssinus was seen in all 8 (72.7%) classrooms in which mites were detected. It was learned that 15 - 20 children study in each classroom, hygiene rules are complied meticulously, galoshes and aprons are being used by all the staff and cleaning is done daily in the schools which are located in the city center, have a high level of income and whose infrastructure problems are addressed compared to the other regions included in the study. In this kindergarten which was included in the study, it was concluded that it is very difficult to fight with the mites which have high ability to adapt to the environment due to the presence of mites at high level despite the precautions taken.

In one dust sample taken from a house where an old lady lives alone, huge amount of D. pteronyssinus and L. destructor types of mites and also one Demodex spp. were detected. It was reported that this person, who is generally at home, has cough, itch, runny nose, itchy nose and red eyes, and loss of eyebrows and eyelashes. The symptoms in this individual, living in a house where the convenient environmental factors for mites to live are formed, were found compliant with house dust mite allergy and Demodex spp. infection.

The most commonly observed types of mites in the world are determined as D. pteronyssinus, D. farinae, E. maynei and B. Tropicalis[6]. According to the studies made in many countries, Dermatophagoides type of mites constitute 70% of house dust mites determined, and D. pteronyssinus forms 88% of this type[16]. In our study, D. pteronyssinus (72.2%) was the most common mite species and coincided with studies done.

Many studies were conducted in our country in pursuit of search of types of house dust mites. Kalpakkloğu et al collected house dust samples from five different regions of Turkey[18]. They stated that D. pteronyssinus, D. farinae and L. destructor were the most common species. Kalpakkloğu et al found D. pteronyssinus (83%) and D. farinae (12%) as the most widespread types in 930 dust samples from 7 geographic regions of Turkey[18]. It was stated by Aldemir and Baykan as D. pteronyssinus (57.66%) in Konya[18], Gülbahtar et al as D. Pteronyssinus (71.4%), D. farinae (23%) in İzmir[22], Gülgeğen et al as D. pteronyssinus (58.34%), Glycyphagus domesticus (16.67%) in Bursa[7], Akdemir and Gürdal as Tyrophagus putrescentiae (43.96%), D. pteronyssinus (31.03%) in Kütahya[17], Çiftçi et al as D. pteronyssinus (23.1%), C. arcuatus (5.2%) in the provinces of Denizli, Kütahya, Isparta, Uşak and Afyon[24], Doğan et al as D. pteronyssinus, Chortoglyphs arcuatus in Eskişehir[11], Aykut et al as D. pteronyssinus (83.2%), L. destructor (6.26%) in the provinces of Bitlis and Muş[13]. The results of our study is compatible with several studies conducted in our country in terms of the finding that D. pteronyssinus (41.5%) and D. farinae (11.5%) are the most common types of mites.

The relationship between mites and asthma and allergic diseases is studied in many countries. It was indicated by Warner et al that mites were found in the houses of 53 of 55 children with asthma in Sweden; Simpson et al that all 19 patients with asthma were sensitive to D. pteronyssinus in England; Mihrshahi et al that house dust mite allergy was at the rate of 26 - 32% among children in Australia; Sharma et al
that mite population was found in 57% of 150 atopic allergic patients at high level and in 17% of them at low level in India, and that there is a proportional relationship between high presence of mites and the frequency and severity of allergy attacks\[^{6,25-27}\].

Regarding the studies conducted in our country, it was stated by Güleğen et al that one study conducted in Bursa showed 66.9% of 127 women with asthma were sensitive to *D. pteronyssinus* and 65.4% of them were sensitive to *D. farinae*, Tamer and Çalışkan that in Kocaeli 25.6% of 1279 patients with allergic symptoms were sensitive to mites\[^{8,28}\]; Öztürk et al that in Düzce 72.5% of 180 patients with allergic rhinitis were sensitive to *D. farinae* and 63.7% of them were sensitive to *D. Pteronyssinus*\[^{29}\]. Koca stated that 45.3% of 527 people with allergic respiratory complaints had house dust allergy in Osmaniye\[^{30}\].

In our research, the possible allergic symptoms (such as asthma, allergic rhinitis) in family members were determined by survey questions. Asthma is a disease usually caused by chronic inflammation of the respiratory tract characterized by allergic origin and persistent or paroxysmal cough, wheezing, shortness of breath and sensation of pressure on the chest\[^{40}\].

Allergic symptoms were categorized as coughing, itching, shortness of breath, wheezing, runny and itchy nose, consecutive and frequent sneezing, red and watery eyes in the survey\[^{19,20}\].

Characteristics of the houses and the family members who have allergic complaints were learned by the questionnaires that were filled completely by an adult in each family. Surveys applied in kindergarten were filled by responsible teachers.

According to the obtained information, one or more individuals with allergic symptoms were found in 84 (73%) of the houses, whereas in 31 (27%) of the houses there was no one with an allergic symptom. According to this study, house dust mites were observed in 22 (62.9%) of 35 houses where there was shortness of breath among family members, 11 (57.9%) of 19 houses where wheezing was found, 51 (63.8%) of 80 houses where runny nose complaints were found, 40 (67.8%) of 59 houses where frequent sneezing complaints were found, 23 (62.2%) of 37 houses where red eyes complaints were found, 24 (63.2%) of 38 houses where watery eyes complaints were found, 24 (72.7%) of 33 houses where itching complaints were found, 43 (58.9%) of 73 houses where coughing complaints were found. In total, it was determined that one or more allergic symptoms was found in 238 people in the houses where mites were detected.

When the mite prevalence was examined according to the number of rooms in houses (except school), 189 houses were defined as 23 of them with one or two rooms and 166 of them with three or more rooms.

Mites were found in 7 (30.4%) of the houses with one or two rooms and 100 (60.2%) of the houses with three or more rooms. A significant relationship was found between the number of rooms in houses and mite prevalence. Ratio of house dust mite rate by number of rooms is statistically meaningful, it is thought that the number of people living in houses which have many rooms may be too large and also that mites may have more living space. According to the findings, when the possible relevant features of houses in terms of their relationship with the presence of house dust mites were analyzed; there was no significant relationship found between mite prevalence and other criteria except the number of rooms when the ground clearance of houses, the presence of a garden, carpet type, washing temperature and duration of duvets, times of the insolation of pillows and quilts, heating devices, cleaning times, insolation conditions, presence of a pet and the economic situation of the family. Yet, the possibility of misinformation due to the concern of the individuals in households not to look unfavourable should not be forgotten in the case of cleaning habits that happened to be unrelated with the presence of mites.

In this study, the search of house dust mite’s fauna in the province of Hatay, its relationship between allergy and the factors which have an impact on mite population in houses were aimed. The purpose was to make a contribution to protection and control programs since this study is the most comprehensive one conducted in our province.

**CONCLUSION**

The house dust mites were found widespread in the province of Hatay. Carpets in houses should be removed, ventilation of the house should be paid attention due to decrease humidity rate, pillows and quilts should be isolated frequently in order to keep house dust mite populations under control as they are one of the major risk factors in terms of allergic illnesses. Furthermore, doctors should inform the patients, especially the ones with allergic complaints, about house dust mites and the ways of protection.

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Case Report

Hemophagocytic lymphohistiocytosis associated with visceral Leishmaniasis in a patient with cirrhosis of HCV: diagnostic challenge

Tolga Duzenli, Harun Aslan, Taner Akyol

1Department of Gastroenterology, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey
2Department of Internal Medicine, Koc University Hospital, Istanbul, Turkey
3Department of Gastroenterology, Samsun Gazi State Hospital, Samsun, Turkey

ABSTRACT

Leishmania infection associated hemophagocytic syndrome is very rare. Moreover, visceral leishmaniasis related hemophagocytic lymphohistiocytosis in a patient with liver cirrhosis will be very difficult to recognize because of the overlapping clinical features and negative marrow evaluation at onset. In this report, we present a 53-year-old male patient diagnosed with visceral leishmaniasis related hemophagocytic lymphohistiocytosis who had referred to our clinic for further evaluation of decompensated cirrhosis due to hepatitis C virus. Although the correct diagnosis was made, the patient did not improve due to co-morbidities.

KEYWORDS: cirrhosis, HCV, hemophagocytic, leishmaniasis, lymphohistiocytosis

INTRODUCTION

Visceral leishmaniasis (VL) is a systemic disease caused by dissemination of protozoan parasite Leishmania throughout the reticuloendothelial system. It may mimic or lead to several types of hematological disorders including hemophagocytosis. Infection associated hemophagocytic syndrome implicating Leishmania is very rare and often difficult to diagnose\(^1\).

Clinical features lacked discriminating value to recognize VL as the inciting etiology. Bone marrow aspiration establishes the diagnosis in about 80% of cases but is often negative at onset of the syndrome due to the pauci-microbial nature of the disease and patchy involvement. Repeated marrow aspiration, liver biopsy, blood cultures and serology may be required to establish the diagnosis.

VL related hemophagocytic lymphohistiocytosis (HLH) in a patient with liver cirrhosis is often under-recognized because of the overlapping clinical features and negative marrow evaluation at onset, leading to high mortality rates\(^2\).

In this study, we report a patient with hepatitis C virus (HCV)-associated liver cirrhosis who suffered complications of HLH secondary to VL.

CASE REPORT

A 53-year-old male patient referred to our clinic for the treatment of decompensated cirrhosis due to HCV. In his past medical history, he had partial gastrectomy due to upper gastrointestinal bleeding. Apart from these, he had no remarkable past medical history. His complaints were fever and night sweat lasting for four months. He had referred to a local hospital, and was hospitalized because of pancytopenia. At that time, bone marrow aspiration was obtained which had revealed dysmyelopoiesis, dysmegakaryopoiesis and dyserythropoiesis. Neither hematologic nor any other malign infiltration was detected. In abdominal ultrasonography, hepatomegaly and splenomegaly had been reported. Anti-HCV antibody and HCV-RNA was positive. The patient was diagnosed with chronic HCV infection while no proper explanation was suggested regarding the origin of the fever. Meanwhile, the
patient experienced upper gastrointestinal bleeding that could not be controlled by medical or endoscopic interventions. Eventually the patient underwent distal gastrectomy. A liver wedge biopsy was obtained during the procedure which demonstrated hepatitis and cirrhosis. During the early postoperative phase, the patient had developed ascites and became decompensated while the fever was continuing. After two months of in-patient investigation and treatment, the patient was discharged and referred to our clinic for further evaluation and liver transplantation.

At admission, the patient had fever, fatigue and abdominal distention. His fever had lasted for almost 4 months with sustained pattern, consistently elevated unless intervened with antipyretics. In physical examination, his general condition was very poor, looking cachectic with loose skin folds. Besides, dryness of the skin and mucosa, and massive ascites and splenomegaly were detected. Initial laboratory investigation revealed pancytopenia (Table 1). Since the patient had ascites and fever, we performed paracentesis and drained 2250 ml transudate ascites. In the cell count of fluid, WBC was 75/mm³ with 35% neutrophils. Therefore, spontaneous bacterial peritonitis was excluded. Along with the culture of ascites, the blood and urine cultures were also obtained, results of which were all negative. However, empirical antibiotic treatment was begun according to the febrile neutropenia protocol. All viral markers were negative with the exception of anti-HCV antibody and HCV-RNA (5x10⁶ copy/ml). To detect a focus of infection, we performed abdominal ultrasonography and thoracoabdominal computed tomography (Figure 1). The appearance of liver was consistent with cirrhosis, and splenomegaly was detected (longitudinal axis was 192 mm) while there was no sign of infection. Upper gastrointestinal endoscopy was performed, and there were no esophageal varices.

**Table 1: Laboratory data of the patient**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range*</th>
<th>On presentation</th>
<th>3rd day of treatment</th>
</tr>
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<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.6–17.2</td>
<td>8.7</td>
<td>8.9</td>
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<tr>
<td>Hematocrit (%)</td>
<td>39.5–50.3</td>
<td>26.5</td>
<td>26.9</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4300–10300</td>
<td>700</td>
<td>2900</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>156000–373000</td>
<td>33000</td>
<td>560000</td>
</tr>
<tr>
<td>Neutrophils (per mm³)</td>
<td>2100–6100</td>
<td>450</td>
<td>1770</td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
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<td>124</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
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<td>3.87</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
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<td>18</td>
<td>42</td>
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<tr>
<td>Creatinine (mg/dl)</td>
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<td>0.69</td>
<td>1.03</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
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<td>99</td>
<td>57</td>
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<td>Albumin (g/dl)</td>
<td>3.3–5.0</td>
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<tr>
<td>Lactate dehydrogenase (U/liter)</td>
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<td>3676</td>
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<td>Amylase (U/liter)</td>
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<td>Alanine aminotransferase (U/liter)</td>
<td>10–40</td>
<td>16</td>
<td>102</td>
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<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>10–40</td>
<td>74</td>
<td>425</td>
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<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>38–155</td>
<td>331</td>
<td>452</td>
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<tr>
<td>Gamma glutamyl transferase (U/liter)</td>
<td>10–55</td>
<td>72</td>
<td>90</td>
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<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.2–1.0</td>
<td>1.18</td>
<td>8.12</td>
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<td>Direct bilirubin (mg/dl)</td>
<td>&lt;0.2</td>
<td>0.47</td>
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<td>Ferritin (ng/ml)</td>
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<tr>
<td>Fibrinogen (mg/dl)</td>
<td>200–500</td>
<td>68</td>
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<tr>
<td>Leishmania rK-39 dipstick</td>
<td>negative</td>
<td>positive</td>
<td></td>
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<tr>
<td>Leishmania IFA&amp;ELISA Ig G</td>
<td>negative</td>
<td>positive</td>
<td></td>
</tr>
</tbody>
</table>

* Reference ranges are Gulhane hospital’s values. These ranges are affected by the patient population and the laboratory methods used. They may therefore not be appropriate for all patients.

**Fig 1:** CT screening of the patient. Cirrhotic liver (blue arrow) and splenomegaly (black arrow).
For the investigation of anemia, ferritin levels were analyzed and these revealed very significant hyperferritinemia (12096 ng/ml, ranges 22 - 322 ng/ml). Serum ferritin was repeated for confirmation, which was much higher (15409 ng/ml). Autoantibodies and markers of vasculitis were negative. Given the fever that was not responding to antibiotics, marked hyperferritinemia and splenomegaly, adult onset Still disease and HLH were considered. Additionally, while the fever, massive splenomegaly and the geographic region where the patient came from (Adana, Türkiye, an endemic area for leishmaniasis) was taken into account, VL was also added to the list of differential diagnosis. At this stage, bone marrow aspiration and biopsy were performed to investigate hematologic malignancies, HLH and leishmaniasis. While the level of fasting triglycerides were normal and hemophagocytosis could not be demonstrated in bone marrow aspirate, given the clinical and laboratory findings of the patient including pancytopenia, fever, splenomegaly, hypofibrinogenemia (68 mg/dl; reference value: 200-500 mg/dl), hyperferritinemia and hepatitis, the diagnosis of HLH was made. As an underlying cause, the patient was examined for leishmaniasis. Serum leishmania Ig G test was positive. The aspirated bone marrow material was inoculated into NNN culture and examined in a Giemsa stained smear. Amastigotes were visualized on the smear (Figure 2), ELISA and IFA tests for rK-39 antigen found positive, therefore diagnosis of VL was also made. The diagnosis of HLH was considered as associated with VL. Treatment protocol was targeted to the causative disease, and liposomal amphotericin B was commenced for the Leishmaniasis. Due to the high HCV viral load, steroid or immunosuppressant treatments were postponed to see the response to amphotericin, and intravenous immunoglobulin was also added to the treatment protocol.

On the third day of treatment, the patient’s complete blood count improved dramatically. On the second day, WBC: 1200/mm^3; neutrophils 640/mm^3; hemoglobin: 7.31 gr/dl and platelets: 4000/mm^3; whereas on the third day WBC: 2900/mm^3; neutrophils: 1770/mm^3; hemoglobin: 8.9 gr/dl and platelets: 56000/mm^3. However, liver function tests worsened and at the third day of the initiation of treatment for VL, the patient developed confusion and dyspnea. He was transferred to the intensive care unit. An infiltration was detected on chest x-ray. Subsequently, anuria and hypotension developed, his mental status worsened. Despite intensive care and mechanical ventilation support, the patient could not be recovered.

**DISCUSSION**

VL presents a sub-acute or chronic course and if not treated with a specific therapy, the disease almost invariably leads to death. Our case was interesting because a number of considerations can be made. First of all, the presence of anti-HCV positivity, together with liver dysfunction and hepatosplenomegaly, may lead to the diagnosis of HCV-related liver cirrhosis. This was the case in our patient whose HCV-RNA was also positive. Although he has a biopsy-proven cirrhosis, the possibility of leishmaniasis as the cause of decompensation of the liver disease, is more likely. A similar case describing a patient with leishmaniasis and misdiagnosed as chronic liver disease has been reported[3]. In that report, presence of the anti-HCV positivity contributed to the delay in the true diagnosis. The authors stated that the diagnosis of VL was made by chance. The liver and spleen were much larger than the volume expected in HCV-associated liver cirrhosis, and initial suspicion was a possible lymphoproliferative disorder.

Prakash et al have presented a patient with clinical and biochemical features of liver cirrhosis in whom a correct diagnosis of VL was made after liver biopsy, in which parasite in the Kupffer cells were demonstrated. Unfortunately, the patient died after commencing therapy with sodium antimony stibogluconate[4]. In addition to the chronic liver disease, manifestation of VL can also mimic acute hepatitis, as reported by Hervas et al[5]. In our case, since HCV-RNA was also positive in addition to anti-HCV antibody, the diagnosis HCV infection seems to be correct. The
patient was investigated for the presence of an infection without any positive results. The fever and markedly elevated ferritin levels directed us to HLH. After determining the patient was fulfilling the diagnostic criteria suggested for HLH, we looked for a triggering etiology. Because of the patient’s hometown, which was endemic for leishmaniasis, and consistent clinical findings, VL had a high probability. Consequently, the diagnosis was confirmed with serological tests. It can be speculated that our patient had no HLH since hemophagocytosis could not be demonstrated in bone marrow aspiration. However, it should be kept in mind that in approximately 20% of patients with HLH, detecting hemophagocytosis on the first bone marrow specimen is quite difficult, perhaps even impossible\(^6\). Moreover, it had been recommended that not demonstrating hemophagocytosis on the first attempt, as long as the patient fulfilled the suggested criteria, should not delay timely initiation of treatment\(^7\).

The other criteria of HLH, low or absent natural cell activity and soluble CD-25 value, could not be tested because of the technical insufficiency of our laboratory. Actually, we could not exactly determine whether the hepatitis was associated with HCV or HLH. Presumably, it could not be differentiated in such a complicated case but co-existence of both may have been the case in our patient.

**CONCLUSION**

This is the first case of HLH secondary to VL in a patient with HCV cirrhosis to the best of our knowledge. Since most of the clinical findings are similar, making a correct diagnosis remains a challenge. However, we expect that this case will help to raise awareness of this rare entity and keep clinicians suspicious for exploring all clinical and laboratory abnormalities which are inconsistent with the diagnosis made.

**ACKNOWLEDGMENT**

**Author Conflict of Interest/Study Support:** None to declare

**Financial support:** None to declare

**Acknowledgments:** None to declare

Informed consent is obtained from the patient for the publication of his information and imaging.

**REFERENCES**

ABSTRACT

Disseminated cysticercosis (DCC) is a very rare, infectious form of cysticercosis in which the cysticerci spread throughout the body. There are myriad clinical manifestations and imaging findings depending on the immune response mounted by the host on the parasite, site of larval encystment, stage and mass effect of the parasite. A 31-year-old immunocompetent male presented with symptoms of multiple palpable nodules and recurrent generalized seizures. After radiological assessment from whole body radiographs, ultrasound examination, MRI and pathologic biopsy, he was diagnosed as having disseminated cysticercosis involving the brain, lungs, eyes, skeletal muscles and subcutaneous tissue through the whole body. The patient was treated with a combination of antiepileptic medication and steroids. Follow-up imaging showed improvement, and the patient was asymptomatic 3 months after treatment. In this case report, we discuss and illustrate DCC in terms of epidemiologic features, disease course, pathophysiologic features, clinical presentation, diagnosis and radiologic findings, and treatment.

KEYWORDS: cysticercosis, disseminated cysticercosis, magnetic resonance imaging, neurocysticercosis, taenia solium

INTRODUCTION

Cysticercosis is a zoonotic disease seen in tropical countries which is caused by Cysticercus cellulosae, which is the larval form of the pork tapeworm, Taenia solium. It most commonly affects the central nervous system (subarachnoid space, ventricles, or spinal cord), subcutaneous tissues, lungs, eyes, liver, skeletal muscles, and occasionally the pancreas, thyroid, and heart[1]. Transmitted by the fecal-oral route, this disease is not only limited to the endemic zone; it has now spread worldwide due to globalization. One of the rare complications and uncommon manifestations of cysticercosis is its disseminated form. Diagnosis of disseminated cysticercosis (DCC) can be considered to be confirmed if there are multiple vesicular cystic lesions present in the brain and cysts are demonstrated in at least two other body parts[2]. However, widespread massive dissemination of the cysticercal infestation can result in the involvement of any organ in the body[3]. The main features of DCC include dementia, confusion, intractable epilepsy, enlargement of the subcutaneous and lingual nodules, muscle hypertrophy and a relative absence of focal neurological signs or obvious raised intracranial pressure, at least until late in the disease. Painless diffuse enlargement of all muscle groups (muscular pseudohypertrophy), a rare presentation, gives the patient a ‘Herculean appearance’[1]. Fewer than 50 cases of DCC have been reported worldwide, the majority being from India.

We report here an unusual rare case of DCC involving diffuse involvement of the brain, subcutaneous tissue and multiple organ systems accompanied by widespread muscle hypertrophy, treated with symptomatic management and antiepileptic medication.

CASE REPORT

Clinical presentation

A 31-year-old immunocompetent male, non-vegetarian, presented with a 2-month history of headache, vomiting and recurrent episodes of convulsions. He also complained of multiple palpable...
nodular lesions all over the body, progressive loss of memory and judgment for three months. A physical examination revealed several firm, well-circumscribed, non-tender subcutaneous nodules all over the body, predominantly seen over the neck, chest, back region, abdominal wall and extremities. The nodular lesions were well defined and varying in size from 0.5 to 3 cm. The typical “Herculean” appearance, associated with muscular pseudohypertrophy, was seen in all extremities. Neck rigidity and exophthalmos was also observed. He had stable vital signs and no focal neurological deficit was noted.

Routine hematological investigations showed hemoglobin to be 11.5 g/dl and the total leukocyte count was within normal limits. The differential leukocyte count showed borderline eosinophilia (6%). Human immunodeficiency virus, hepatitis B surface antigen and hepatitis C virus testing were non-reactive. All other investigations were within normal limits.

**Diagnostic work-up**

Plain radiographs showed typical ‘rice-grain’ shaped or cigar-shaped calcifications in the soft tissue of shoulder, chest, abdomen, gluteal and iliopsoas muscle regions. Fig 1c: Lower pelvic and limb X-ray showing similar calcified lesions, lying parallel to muscle fibres, in gluteal, pelvic, and limb muscles.

Fig 1a: Disseminated cystercosis—anteroposterior view of right shoulder and posteroanterior view of abdominal X-Ray film (Fig 1b) revealing multiple rice grain or cigar-shaped calcifications in the soft tissue of shoulder, chest, abdomen, gluteal and iliopsoas muscle regions. Fig 1c: Lower pelvic and limb X-ray showing similar calcified lesions, lying parallel to muscle fibres, in gluteal, pelvic, and limb muscles.

of 8 to 10 mm with eccentric echogenic intraleisonal focus, representing scolex. These lesions were diffusely dispersed in subcutaneous tissue, superficial muscular plane of face and neck, chest, back and all extremities (Fig 2). Magnetic resonance imaging (MRI) of the brain revealed diffuse hyperintense cystic lesions with eccentric hypointense scolex in the parenchymal, scalp tissue and retroocular regions. T2W axial images showed multiple cystic lesions with hypointense foci within both cerebral hemispheres, cerebellum, extracranial muscles and soft tissues of the neck. These lesions had a “cyst with dot sign

Fig 2: Ultrasound reveals a cystic lesion (white arrow) with hyperechoic scolex (black arrow) in the left calf region.
(starry sky)” appearance, or eccentric scolex (Fig 3a, b). There was evidence of mild hydrocephalus, brain edema and signs of raised intracranial tension (Fig 3c). The bilateral brain parenchyma, extraocular, facial and tongue muscles were involved (Fig 3 d, e). These imaging features, along with patient’s history of intractable epilepsy, are characteristic of encephalitic form of neurocysticercosis.

Similar numerous hyperintense lesions with longitudinal orientation along the muscle fibers were distributed in the limb muscles and adjacent subcutaneous tissues of the neck, chest wall, forearms and arms, back, abdominal wall, thighs, calves, gluteal, pelvic as well as the paraspinal muscles, suggestive of DCC (Fig 4). A cystic lesion was seen in right lung (Fig 5). The solid abdominal organs and cardiac muscles were normal. Perimetry and fundus examination were also within normal limits.
Antibodies to cysticerci were detected in the serum and cerebrospinal fluid by means of an enzyme-linked immunosorbent assay. Other cerebrospinal fluid (CSF) findings include glucose: 42 mg/dl, 10 leucocytes per cu.mm, and protein: 96 mg/dl.

**Histopathological examination**

An oval translucent cyst was resected from the deltoid muscle, and histopathological examination of the cyst was consistent with the diagnosis of cysticercosis.

**Treatment**

This patient was symptomatically managed with mannitol and glucocorticoids to decrease edema and inflammation. Antiepileptics were continued. Follow-up imaging showed improvement, and the patient was asymptomatic 3 months after treatment.

**DISCUSSION**

Human cysticercosis is a tissue infection which occurs due to infestation by the encysted larval stage of the pork tapeworm, *Taenia solium*. With regard to clinical manifestation, the disease can present in two forms: taeniasis and cysticercosis. Taeniasis is acquired through the consumption of cyst-infected pork. In contrast, cysticercosis is developed through the ingestion of eggs from the feces of a tapeworm carrier, with little evidence of other forms of contamination (e.g., through the agency of air, water, or flies)[4]. Infective embryos (hatched from the ingested eggs) disseminate through the systemic circulation after actively crossing the intestinal mucosa. Some cysts are cleared by the liver. Lodged cysts in capillaries (mostly

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**Fig 4:** Whole Body Coronal STIR image shows innumerable intramuscular and few subcutaneous hyperintense foci throughout the body (multiple cysticerci involving almost all muscles of the axial and appendicular skeleton) suggestive of disseminated cysticercosis.

**Fig 5:** Coronal STIR scan at the level of cervical spine and chest display cysticerci in the right lung upper lobe (see arrow). Chest wall muscles are also involved.
in muscle and brain tissue) develop into immature cysts and later into larval cysts, taking up to 3 months to reach this stage[6]. When the parasite dies by natural processes or as a result of antihelminthic therapy, an inflammatory response with perilesional edema and focal enhancement ensues, followed by calcification[8]. DCC was reported as early as 1912 by the British Army medical officers stationed in India[3].

The clinical presentation of patients with DCC syndrome is highly variable and nonspecific and depends on the location, number, size, and stage of the parasites, as well as the degree of the host reaction[7]. Furthermore, individual responses to the parasite differ. Our patient was characterized by seizures, abnormal mentation, palpable subcutaneous nodules and pseudomuscular hypertrophy. These symptoms are typical for DCC.

The diagnosis of cysticercosis is based on a constellation of (a) clinical findings; (b) the cysticercus-specific IgG antibody level as determined with an enzyme-linked immunoassay; (c) an enzyme-linked immunosorbent assay in either serum or CSF, with a specificity and sensitivity of 100% and 98%, respectively[8]; and (d) noninvasive imaging findings (CT and MRI)[6].

CT and MRI findings are better in diagnosing this entity as they demonstrate the number, anatomical localization and topography of lesions, their stage of involution, and the degree of inflammatory reaction of the host against the parasites and have largely replaced previous radiological procedures such as plain roentgenograms, pneumoencephalograms, cerebral angiography and myelography[9]. High resolution ultrasound is useful in noninvasively demonstrating subretinal cysticercosis and cysticercal cysts at other unusual sites. In our patient, ultrasonography of the eyes, color Doppler and MR studies revealed cystic lesions in both the orbits, diagnosing ocular cysticercosis.

In general, MR is superior to CT imaging in better image detection, higher resolution and definition, which makes for better lesion conspicuity. This higher contrast resolution is particularly helpful in the detection of inflammatory changes and the evaluation of ventricular involvement. However, its sensitivity for the detection of calcified lesions is poor. MRI is the imaging modality of choice for the evaluation of patients with brainstem cysts, intraventricular cysticercosis, small cysts located over the convexity of cerebral hemispheres, and in the follow-up of such patients whereas CT remains the best screening neuroimaging procedure for patients with suspected neurocysticercosis and small calcifications[1].

DCC is not a single disease entity that can be managed uniformly. Treatment of DCC is controversial and depends on the location and cyst burden, the symptoms, and associated complications[10]. Furthermore, cysticidal agents, such as albendazole and praziquantel, may complicate the treatment as they themselves initiate a host inflammatory response that may result in raised intracranial tension and more symptoms. In general, management of DCC is symptomatic (antiepileptics and steroids) and cysticidal (i.e., albendazole and praziquantel). Although surgical intervention (i.e., shunt placement or emergency decompression with parasite removal) may eventually become necessary, it is rarely used nowadays because the diagnosis is being made at earlier stages and pharmacologic therapy is usually sufficient[11,12]. The role of cysticidal drugs is controversial. Wilson et al recommended that all patients with multiple cysts should receive treatment with cysticidal drugs[13]. However, these drugs hasten the death of the cysticerci cysts, which may occur even in the absence of such treatment. Cysticidal therapy may be associated with a generalized anaphylactic reaction, which may be due to the demise of cyst and massive release of antigens. Hence, these therapies should be advised with high degree of caution and should be individualized. Cysticidal drugs have no role in the presence of inactive calcified cysts, because the parasites are already dead[14]. Our patient, a case of encephalitic form of disseminated cysticercosis, was well managed by antiepileptics and steroids. He did not receive albendazole and/or praziquantel, and was asymptomatic since last 3 months.

Recently, a combination of albendazole and praziquantel was found to be effective in comparison to a single drug therapy in patients with parenchymal brain cysticercosis with ≤ 20 viable cysts. Complete cyst clearance was seen in 75% (12 of 16) of the patients with a combination therapy whereas only 25% (4 of 16) patients had complete cyst clearance in the subgroup of patients who received only albendazole. The role of albendazole and praziquantel combination therapy is worth trying in patients with massively infected disseminated cysticercosis[15]. A randomized controlled study is urgently needed to assess the efficacy of the combination therapy and currently available drugs. The role of repeated courses of antiparasitic drugs also needs to be evaluated.

CONCLUSION

In DCC, diagnostic approach, treatment, and prognosis differ widely depending on the type of infection. It is important to recognize this pleomorphic disease clinically; early radiological evaluation is warranted in cases of disseminated condition. In most of the patients with disseminated cisticercosis, quality of life is often poor with sinister prognosis.
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A case of malignant solitary fibrous tumor arising from the palatine tonsil: case report and review of literature

Baeth Al-Rawashdeh1, Sana Batarseh2, Mohammad Alkhoujah3
1Department of Otorhinolaryngology, Jordan University Hospital, University of Jordan, Amman, Jordan
2Department of Otorhinolaryngology, Albasheer Hospital, Amman, Jordan
3Royal medical services, Amman, Jordan

ABSTRACT

A solitary fibrous tumor (SFT) is an uncommon, generally benign, mesenchymal spindle cell neoplasm. It’s a rare, well-recognized entity of soft tissue tumors that was originally found in pleural tissue. Klemperer and Rabin first described it in 1931 from five primary tumors of the pleura. On searching the literature available till date, we could find only two reported cases of malignant SFT in the palatine tonsils of a 62-year-old male patient in Brazil and a 17-year-old male patient in Turkey; and one reported case of a benign SFT arising from the palatine tonsil in a 66-year-old Japanese woman. We are reporting here another case of malignant SFT in the palatine tonsils of a 49-year-old previously healthy lady that was treated by wide local surgical excision. Immunohistochemical studies showed the tumor cells being strongly positive for CD34 and BCL-2, which was highly suggestive of SFT. Up to date and after 12 months of follow up, there are no signs of local recurrence or distant metastases.

KEY WORDS: CD34, computed tomography, BCL-2

INTRODUCTION

A solitary fibrous tumour (SFT), which is also called a localized fibrous mesothelioma or submesothelial fibroma, is a neoplasm which essentially originates in the mesothelium-covered surfaces, such as the pleura and peritoneum[1]. The reported incidence of this tumor, whether benign or malignant is 0.00025%[2]. It usually occurs in the elderly ages (6th and 7th decades), and often causes large masses (>8 cm)[2,3]. They occur equally in both sexes. The vast majority of cases are morphologically and clinically benign, with only 5% of cases showing malignant behaviour such as recurrent or metastatic disease[4]. Metastases occur usually by haematogenous dissemination to the lung, liver, central nervous system, spleen, peritoneum, adrenal gland, gastrointestinal tract, kidney and bone listed in the order of frequency[5]. While previously considered to be of serosal origin and solely limited to the pleural cavity, more recently the tumor has been described in other locations, including the head and neck, supporting the theory that solitary fibrous tumors originate from widespread primitive mesenchymal cells and are not restricted to the serosal surfaces. These tumors can occur in intrapulmonary parenchyma, meninges, eye, nasal cavity and paranasal sinuses, parapharyngeal space, salivary glands, thyroid, peritoneum and retroperitoneum, thymus, liver, spermatic cord, bladder and prostate, kidney, adrenal gland, medulla spinalis, periosteum, pericardium, mediastinum, and soft tissue[6,7].

CASE REPORT

A 49-year-old lady who was previously healthy presented to our department with a two month history of throat discomfort and foreign body sensation in the throat that disturbed her sleep on many occasions. She had no past history of smoking or drinking alcohol. Clinical examination revealed prominent left palatine tonsil and left peritonsillar swelling. Regional examination was unremarkable. Full blood
count showed normal parameters of leukocytes and erythrocytes. Erythrocyte sedimentation rate was within its normal range. A primary clinical suspicion of lymphoma versus squamous cell carcinoma was raised. Computed tomography scan with contrast of the neck (Fig 1) showed strongly enhancing well defined soft tissue lesion noted in the left tonsil extending to the parapharyngeal region, and no lymph node enlargement was seen. Differential diagnosis from the radiologist’s point of view was lymphoma and less likely neurogenic tumor. Chest, abdomen and pelvis CT scans were done and were within the normal limits. Left tonsillectomy was done for diagnostic purposes (the operation was started by local infiltration with diluted adrenaline of the anterior pillars, followed by sharp dissection and completed by blunt dissection using the finger trying to include the tumor capsule).

The specimen was sent for histopathology and immunohistochemical evaluation. The pathology report stated: “macroscopically the specimen was an oval piece of grayish tissue measuring 4.3 x 2.5 x 1.5 cm”. Histological examination of the specimen showing a well-circumscribed mass composed of proliferation of spindle cells with oval nuclei (Fig 2) with significant mitotic index (> 4/10HPF) (Fig 3). These cells were arranged in hemangiopericytoma like pattern. No necrosis was seen. Surgical margins were free of tumor, and although the tumor cells were seen reaching the capsule margin, they did not penetrate it. Differential diagnosis was synovial carcinoma, vascular tumor, smooth muscle tumor and schwannoma. Immunohistochemical studies showed the tumor cells being strongly positive for CD34 (Fig 4) and BCL-2 (Fig 5) which was highly suggestive of SFT, negative for CD31 (Fig 6), and negative for smooth
muscle actin (Fig 7), which ruled out the probability of smooth muscle tumor. The neoplastic cells were also focally positive for Desmin (Fig 8), negative for S100 protein (Fig 9) and cytokeratin (Fig 10) and finally faintly focally positive for CD99 (Fig 11).

Based on this analysis, the diagnosis of malignant SFT in the palatine tonsil was established. No further treatment was performed and the patient was followed...
up for about 12 months with no relapse or metastases till now. Consent was obtained from the patient to publish this case.

DISCUSSION
The histogenesis of the SFT has been debated as to whether it’s a tumor of mesothelial or mesenchymal cell origin and the latter is now the favored one[8]. As cellular areas of SFT overlap histologically with hemangiopericytoma and the immunoprofile of these entities is similar, they are considered closely related, if not a spectrum of the same entity according to the recent WHO classification of soft tissue tumors[9]. SFT was originally thought to occur exclusively in the pleura, but various extrapleural intrathoracic as well as extrathoracic SFT have been reported in numerous sites[10], such as peritoneum[11], kidney[12], spinal cord[13], meninges and cerebral cortex[14,15] and extremities[16].

Particularly in the head and neck, SFT has been reported in the nose, paranasal sinuses, nasopharynx[17,18], larynx[19], orbit[20], oral cavity[21,22], tongue[7], buccal space[23] which is the most common site in the oral cavity, floor of the mouth[24], palatine tonsils[25,26], thyroid gland[27], salivary glands[28,29], parotid[30] and the carotid sheath[31].

Benign and malignant forms of the tumor do occur, with the benign variant being 3 to 4 times more common. Various series of extrapleural SFT showed almost equal distribution of the incidence for male and female, with patient’s ages ranging from the third to the eighth or ninth decade[32].

Usually it has a benign behavior with no local recurrence or metastasis, but malignant variants have also been described, and local recurrences[19] as well as metastases may occur. The risk of local recurrence and metastasis correlates to the tumor size and histological status of surgical resection margins and may reach up to 10% even in so-called “benign” tumors[33].

The literature contains <50 reported cases of SFT of the oral cavity[24], with the most common site being the buccal mucosa (56.8%), followed by the tongue (16.2%) and the lip. Patients with SFT of the oral cavity typically present with a slowly growing non-tender mass, many of them are asymptomatic, but when symptoms do occur, they vary according to the site and the size of the lesion. Extra-thoracic SFT is difficult to diagnose histopathologically because of its histological variability.

Paraneoplastic syndrome is rarely seen in these tumors and mainly occurs in the case of large SFTs[6]. Hypoglycemia occurs in 2 - 4% of cases. Doege and Potter described the hypoglycemia seen in the cases of SFT independently in 1930. This condition was named Doege-Potter syndrome and although rare, must be considered in cases of refractory hypoglycemia[34].

Characteristic microscopic features are described as a ‘pattern-less’ growth pattern, with bland spindle cell cytology, alternating hyper and hypocellular areas, keloid-like hyalinization, neural-type palisading and a frequently prominent branching vasculature often described as ‘Hemangiopericytoma-like’ pattern[35].

Irrespective of anatomic location, most SFTs exhibit diffuse and moderate to strong positivity for CD34, BCL-2 and CD99[36]. In the current case, CD34 and BCL-2 were both strongly positive, whereas CD99 was focally positive. Complete surgical removal in order to obtain clear margins is curative in most cases. Because of the possible local recurrence and distant metastases and the difficulty in prediction of the tumor behavior, which depends mainly on histological features, a long term follow up is advisable for patients with extrapleural SFT[37].

CONCLUSION
After review of the literature, we found that malignant solitary fibrous tumor occurring in the palatine tonsils is a very rare tumor. This case is presented as the third malignant tonsillar SFT in the literature.

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REFERENCES


Bloody diarrhoea in neonates - Surprising reasons of mucoid and bloody diarrhoea in the neonates

Gokce Celep¹, Yalciner Erdogan¹, Seviye Akpinar¹, Cetin Kilinc²
¹Amasya University Medical Faculty, Sabuncuoğlu Şerefeddin Education and Research Hospital, Department of Paediatrics, Amasya, Turkey
²Department of Microbiology, Kastamonu State Hospital, Kastamonu, Turkey

ABSTRACT

Mucoid and bloody diarrhoea is a rare and difficult clinical problem to be solved in neonates. It has many reasons and evaluation needs broad perspective from the clinicians. The bleeding breast of the mother, infections, anal fissure or surgical problems can be seen in full term neonates, but sometimes we can meet unexpected diagnosis.

Entamoeba histolytica (E. histolytica), is a common intestinal parasite widely spread throughout the world. The infection may cause dehydration, fever, vomiting, diarrhoea, feeding problems, morbidity and mortality in infants. The diagnosis is based on clinical, epidemiological findings, stool microscopy supported with antigenic or molecular genetic tests. The treatment contains antiamoebic agents, hydration, and supportive treatment. Breastfeeding is important for protection. Here, we present six hospitalized neonates because of mucoid and bloody diarrhoea with dehydration and bad clinical status. The clinical signs pointed to amoebiasis and were treated well with metronidazole with a surprising exception.

KEY WORDS: amoebic enterocolitis, invasive diarrhoea, neonates

INTRODUCTION

Amoebiasis, caused by Entamoeba histolytica (E. histolytica), is a common parasitic infection widely spread throughout the world. It is estimated that approximately 500 million people are infected with E. histolytica, but just 10% of them are symptomatic with signs such as colitis, amoebic dysentery, and visceral abscesses. Invasive amoebiasis may be mortal, especially in young infants, malnourished children and immunosuppressed people[4-6]. The contamination of water and food with four nucleated cysts discarded by the infected individuals plays an important role in the transmission chain. The infection rate is high in low socioeconomic and crowded societies due to poor personal hygiene[2,3]. Due to the method of transmission, amoebiasis is a rare clinical problem in neonates and has different features[4-6]. The bleeding breast of the mother, infections, anal fissure or surgical problems can be the reasons for bloody stool, mimicking necrotizing enterocolitis in full term neonates, but sometimes we can meet an unexpected diagnosis. In this brief report, we present six neonates who were hospitalized because of mucoid and bloody diarrhoea with regard to age at onset, other clinical findings, diagnostic procedures, response to treatment and epidemiological features.

This brief report is approved by the local committee of the Education and Research Hospital with the decision number 6938/75281285-2018

SUBJECTS AND METHODS

This case report was performed in the neonatal intensive care unit (NICU) of Amasya Sabuncuoğlu Şerefeddin Education and Research Hospital, in the north of Turkey. All patients were hospitalized at different times, from September 2011 to December 2017. The records of patients diagnosed with “amoebic gastroenteritis” were obtained from the hospital data system and the patients’ files were studied retrospectively. All patients underwent

Address correspondence to:
Dr. Gokce Celep, Sabuncuoğlu Şerefeddin Education and Research Hospital, Merkez, Amasya, Turkey. Tel: +90 532 608 25 77; Fax:+90 358 212 00 01
E-mail: gokce4celep@yahoo.com
physical examination and laboratory analyses including hemogram, C-reactive protein (CRP), renal and hepatic functions, electrolytes and coagulation parameters. Microbiological studies were performed with blood, urine, stool cultures, occult blood and direct microscopy of fresh stool samples within 20-30 minutes. For microscopic examinations of stool, approximately 2 g of stool sample was stained with saline solution and Lugol’s iodine stain. Preparations were investigated with 10X and 40X lenses. When available, *E. histolytica* antigen specific adhesin enzyme-linked immunosorbent assay (ELISA) test (a second generation monoclonal antibody-based ELISA, TECHLAB Blacksburg; VA, USA) was studied from these samples according to the manufacturer’s instructions and recommendations. All data of the cases were collected from the hospital record system and patients’ files were studied retrospectively.

### RESULTS

All patients were hospitalized at different times, from September 2011 to December 2017 in the NICU. Their ages varied between 12 - 24 days old. Three of them were born by spontaneous vaginal delivery and three by caesarean section, all following uncomplicated full term pregnancies. Their birth weights were appropriate with their gestational age and all were breastfed. The mothers had no breast problems causing bleeding.

All patients had feeding difficulties and diarrhea for more than five times a day with mucoid, greenish, sometimes bloody stool for at least three days before admission. Two patients had been given tap water with sugar soon after the birth because of false belief in traditional jaundice treatment. All were lethargic and had fever with dehydration. On physical examination, vital signs were stable with abdominal distension and increased bowel sounds. No organomegaly and anal fissure was detected. The evaluations of cardiovascular, nervous and respiratory systems were unremarkable. Sera laboratory investigations and coagulation parameters were nonspecific, except for CRP positivity (Table 1). Blood, urine and stool cultures showed no pathogenic organisms. Stool microscopy was performed by an experienced microbiologist for all the patients. Five of the specimens contained...

### Table 1: Features of the patients

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (days)</th>
<th>Gender</th>
<th>Clinical findings</th>
<th>Laboratory findings</th>
<th>Stool microscopy</th>
<th>Adhesine antigen</th>
<th>Epidemiologic features</th>
<th>Response to metronidazole</th>
<th>Clinical follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Female</td>
<td>Mucoid diarrhea, jaundice</td>
<td>CRP (-), no electrolyte imbalance, no anaemia</td>
<td>Leukocyte + Erythrocyte + Cyst, Occult blood (+)</td>
<td>Positive</td>
<td>Not defined</td>
<td>Yes</td>
<td>Discharged with oral metronidazole</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>Female</td>
<td>Fever, mucoid diarrhea, lethargy, poor weight gain</td>
<td>CRP (-), no electrolyte imbalance, no anaemia</td>
<td>Leukocyte + Erythrocyte + Cyst</td>
<td>Positive</td>
<td>Not defined</td>
<td>Yes</td>
<td>Discharged with oral metronidazole</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>Female</td>
<td>Mucoid diarrhea, vomiting, fever</td>
<td>CRP (-), no electrolyte imbalance, no anaemia</td>
<td>Leukocyte + Erythrocyte + Cyst</td>
<td>Positive</td>
<td>Not defined</td>
<td>Yes</td>
<td>Discharged with oral metronidazole</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>Male</td>
<td>Mucoid, bloody diarrhea, vomiting, jaundice</td>
<td>CRP (+), no electrolyte imbalance, no anaemia</td>
<td>Leukocyte + Erythrocyte + Cyst, Occult blood (+)</td>
<td>Not available</td>
<td>8 year old brother, under Metronidazole treatment because of amebic colitis</td>
<td>Yes</td>
<td>Discharged with oral metronidazole</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>Male</td>
<td>Mucoid, bloody diarrhea, vomiting, jaundice, dehydration</td>
<td>CRP (+), no electrolyte imbalance, no anaemia</td>
<td>Leukocyte + Erythrocyte + Cyst</td>
<td>Not available</td>
<td>9 years old sister, hospitalized because of amebic colitis at the same time</td>
<td>Yes</td>
<td>Discharged with oral metronidazole</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>Female</td>
<td>Mucoid, bloody diarrhea, vomiting, colic, restlessness</td>
<td>CRP (-), no electrolyte imbalance, mild anaemia</td>
<td>Leukocyte + Erythrocyte + Cyst</td>
<td>Not available</td>
<td>Not defined</td>
<td>No</td>
<td>Diagnosed as food allergy (cow’s milk); after diet application clinical and stool problems were solved.</td>
</tr>
</tbody>
</table>
DISCUSSION

Here, six neonates with bloody gastroenteritis are presented with rare diagnosis at the neonatal period: amoebic gastroenteritis and cow’s milk protein allergy. Most of the E. histolytica infections (85 - 95%) are asymptomatic, but the World Health Organization recommends treatment for E. histolytica when detected by antigenic tests or molecular methods, whether the infection is symptomatic or asymptomatic, for breaking the transmission chain[7]. It is prevalent in developing countries in temperate and tropical regions. Prevalence is reported as 4% in high risk groups in developed countries[7,8]. The prevalence in Turkey is estimated to be 0.4 - 18.4%[8,10]. Direct microscopy (with SF and/or lugol), trichrome staining, antigen (ELISA) tests, enzymatic tests, culture, polymerase chain reaction in faeces, and antibody tests in serum are used for detection and identification of Entamoeba species[2,3]. Amoebiasis is a rare problem in neonates. The knowledge and experience are limited with case reports. Water supply, poor hygienic status and immunosuppression are the main risk factors for infection[8,9].

There are many species in the genus Entamoeba and at least 8 of them infect humans: E. histolytica, E. dispar, E. coli, E. moshkovskii, E. hartmanni, E. polecki, E. gingivalis, and E. bangladeshi. E. polecki, E. coli, E. hartmanni, and E. gingivalis do not pose a problem for morphologic identification[3]. E. histolytica is morphologically indistinguishable from the others[3]. E. dispar is commensally non-pathogenic, but recent reports have shown E. moshkovskii and E. bangladeshi as susceptible pathogens causing diarrhoea[3]. Only E. histolytica is known as the cause of amoebiasis in humans[3]. Direct microscopy of the wet mount is the most common method for detecting amoeba. Necessity of experienced healthcare professionals is important because confusion of amoebic cysts with other non-pathogenic Entamoeba species and macrophages, leukocytes is possible. If the mount is fresh enough, detecting trophozoites can make diagnostic confirmation better. This is the reason behind a sensitivity of 10 - 60%, and specificity of 85 - 90%, and these may be improved by repeating tests, since false negativity is more common. Molecular genetic testing provides the most reliable results; but they are expensive and not practical. Antigenic tests seem to be more convenient and reliable to use[8-10]. In our study, we evaluated three patients with antigenic tests due to technical problems. For the other three, repeating stool microscopy, clinical and epidemiological clues, and response to treatment guided us.

CONCLUSION

Amoebiasis is a common public health problem all around the world, but rare in neonates. Knowledge and experience are limited with case reports in the neonatal period. Water supply, poor hygienic status and immunosuppression are related with transmission and symptomatic infection in all age groups. The diagnosis should be in consideration when there is complicated, invasive, resistant diarrhoea in the newborn in epidemic areas. Stool microscopy must be confirmed with antigenic or genetic tests to prevent false negativity or positivity. When confirmation tests are not available, repeating stool microscopy, negative stool culture, and
following epidemiological and clinical clues will be useful for treatment decision. If the clinical outcome to treatment is poor, other differential diagnosis must be thought of, such as invasive gastroenteritis, cow’s milk protein allergy, anal fissure, and poliposis. Breastfeeding seems to be the best way of protection; neonates should be avoided other liquids, including tap water. Personal hygienic rules and washing hands effectively are more important to prevent transmission.

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Author contributions: Gökce Celep was involved in concept, design, supervision, materials, data collection, literature search, and writing the manuscript. Yalçiner Erdoğan was involved in concept, design, supervision, materials, data collection, literature search and critical reviews. Seviye Akpınar was involved with concept, design, data collection and literature search. Çetin Kılınç was involved in concept, design, materials, data collection and processing, analysis and interpretation.

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High-resolution fingerprinting of Candida parapsilosis isolates suggests persistence and transmission of infections among neonatal intensive care unit patients in Kuwait

Asadzadeh M1, Ahmad S1, Al-Sweih N1, Hagen F2,3, Meis JF2,3, Khan Z5
1Department of Microbiology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait
2Department of Medical Mycology, Westerdijk Fungal Biodiversity Institute, Utrecht, Netherlands
3Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital (CWZ), Nijmegen, Netherlands
4Centre of Expertise in Mycology, Radboudumc/CWZ, Nijmegen, Netherlands
5Department of Microbiology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait. zkhan@hsc.edu.kw.


Candida parapsilosis causes ∼35% of all candidemia cases in neonates. High-resolution fingerprinting of C. parapsilosis isolates from neonatal intensive care unit (NICU) patients in Maternity Hospital (MH) was performed to identify epidemiologically related strains. Sixty-eight bloodstream/colonizing strains isolated from 59 NICU patients, two isolates from health care workers (HCWs) from MH and 18 bloodstream isolates from two other hospitals were used. Six microsatellite markers were employed, isolates were assigned a numerical microsatellite genotype (MSG), dendrogram was constructed and similarities between genotypes were visualized by minimum spanning tree. Fifty bloodstream isolates from MH yielded 37 MSGs with 20 isolates clustering in 7 MSGs. Duplicate isolates and colonizing strains yielded same/highly similar MSG as bloodstream isolates. Colonizing strains from two non-candidemia patients yielded unique MSGs while others belonged to a cluster. All isolates from HCWs and from two other hospitals belonged to unique MSGs. Cluster isolates came from patients in NICU-1 or from neonates in NICU-1 and other NICUs. Clonal complexes comprising closely related genotypes indicative of microevolution were also detected. Our data show that some C. parapsilosis strains have persisted in MH environment over several years and these endemic genotypes were transmitted to other patients in NICU-1 and/or other nearby NICUs.

Effect of Causative Micro-organisms on Patterns of Labeled White Blood Cells in Osteomyelitis

Dannoon SF1, Al-Fouzan W2,3, Alenezi SA1, Alosaimi A3, Alhusain M4, Elgazzar AH1
1Department of Nuclear Medicine, Faculty of Medicine, Kuwait University, Kuwait
2Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait
3Department of Laboratories, Microbiology Unit, Farwania Hospital, Kuwait
4Department of Medicine, Farwania Hospital, Kuwait


OBJECTIVE
The aim of this study is to investigate the effect of microbiological characteristics of causative organisms on the scintigraphic patterns of labeled-white blood cells (WBC) scan in cases of proven osteomyelitis.
MATERIALS AND METHODS
Retrospective analysis of 25 patients referred with suspected osteomyelitis and had both bone and labeled-WBC scans performed and complete records of the microbiological culture of the causative organism. The bone and labeled-WBC scans were retrieved and reviewed by two nuclear medicine physicians. Any definite focal accumulation of labeled WBCs within the bone was considered positive for osteomyelitis. Diagnosis of osteomyelitis in the discharge summary was considered the reference standard and was based on a combination of the clinical scenario, imaging, and laboratory findings including microbiology. Correlation of the pattern of labeled WBC and the type of microorganisms was done.

RESULTS
A total of 16 patients were included in this study, seven females and nine males. Of these, seven patients had Gram-positive whereas nine patients had Gram-negative organisms. The majority (85.7%) of Gram-positive organisms showed increased accumulation of labeled WBCs, whereas only one-third (33.3%) of patients with Gram-negative organisms had such finding.

CONCLUSION
The pattern observed in this study shows that the false-negative results of labeled-WBC scans were mainly noted in patients with Gram-negative as opposed to Gram-positive infections. This confirms the experimental animal study findings that the secretion of anti-chemotactic factors by Gram-negative organisms, seems to be inhibiting the migration of labeled WBCs to the site of infection. The inhabitation is decreasing the accumulation of labeled WBCs and consequently resulting in a false-negative finding. The study adds to evidence that microbiological characteristics of the causative organisms are another explanation for the false-negative WBC in proven osteomyelitis.

Distinctive vasculopathy with systemic involvement due to levamisole long-term therapy: a case report
Aoun B1, Alali M2, Degheili JA3, Sanjad S1, Vaquin C4, Donadiou J5, Ulinski T6, Termos S7
1Division of Pediatric Nephrology, Department of Pediatrics, American University of Beirut, Beirut, Lebanon
2Hepatobiliary and Transplant Unit, Department of Surgery, Al-Amiri Hospital, Kuwait City, Kuwait
3Division of Urology, Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon
4Division of Pediatric Dermatology, Armand Trousseau Hospital, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France
5Division of Pediatric Hematology, Armand Trousseau hospital (APHP), Paris, France
6Division of Pediatric Nephrology, Armand Trousseau Hospital, Assistance Publique - Hôpitaux de Paris (APHP), Paris, France
7Hepatobiliary and Transplant Unit, Department of Surgery, Al-Amiri Hospital, Kuwait City, Kuwait. dr.termos@hotmail.com.


BACKGROUND
Levamisole belongs to the antihelminthic class of drugs that are sometimes administered to patients with frequently relapsing or steroid-dependent nephrotic syndrome, owing to its steroid-sparing effects. Neutropenia and skin lesions, compatible with vasculitis, have been reported as drug complications, but they are rarely associated with any systemic involvement.

CASE PRESENTATION
We report a case of a 9-year-old Arab boy with steroid-dependent nephrotic syndrome who was treated with levamisole after his third relapse. The drug was initially well tolerated, but mild isolated neutropenia occurred 6 months after levamisole administration. This was followed by cutaneous vasculitis of both
ears and the left cheek. The patient also developed hepatosplenomegaly and anemia. Levamisole was discontinued, and his disease remained in remission. All the systemic manifestations disappeared gradually over the course of 1 month. The patient remained in remission until 1 year after levamisole withdrawal, when clinical nephrosis recurred.

CONCLUSIONS
Despite levamisole’s being a useful drug for maintaining remission in steroid-dependent nephrotic syndrome, patients on long-term levamisole therapy should be monitored closely to prevent serious complications that can easily be resolved by simple drug withdrawal.

Comprehensive Genetic Results for Primary Immunodeficiency Disorders in a Highly Consanguineous Population

Al-Herz W1,2, Chou J3, Delmonte OM4, Massaad MJ5, Bainter W3, Castagnoli R6, Klein C7, Bryceson YT8, Geha RS3, Notarangelo LD4

1Department of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
2Allergy and Clinical Immunology Unit, Pediatric Department, Al-Sabah Hospital, Kuwait City, Kuwait
3Division of Immunology, Department of Pediatrics, Children’s Hospital, Harvard Medical School, Boston, MA, United States
4Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States
5Department of Experimental Pathology, Immunology, and Microbiology, Pediatrics and Adolescent Medicine, Faculty of Medicine, American University of Beirut, Beirut, Lebanon
6Department of Pediatrics, University of Pavia, Foundation IRCCS Policlinico San Matteo, Pavia, Italy
7Department of Pediatrics, Dr. von Hauner Children’s Hospital, University Hospital, LMU, Munich, Germany
8Department of Medicine, Centre for Hematology and Regenerative Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden


OBJECTIVE
To present the genetic causes of patients with primary immune deficiencies (PIDs) in Kuwait between 2004 and 2017.

METHODS
The data was obtained from the Kuwait National Primary Immunodeficiency Disorders Registry. Genomic DNA from patients with clinical and immunological features of PID was sequenced using Sanger sequencing (SS), next generation sequencing (NGS) of targeted genes, whole exome sequencing (WES), and/or whole genome sequencing (WGS). Functional assays were utilized to assess the biologic effect of identified variants. Fluorescence in situ hybridization (FISH) for 22q11.2 deletion and genomic hybridizations arrays were performed when thymic defects were suspected.

RESULTS
A total of 264 patients were registered during the study period with predominance of patients with immunodeficiencies affecting cellular and humoral immunity (35.2%), followed by combined immunodeficiencies with associated syndromic features (24%). Parental consanguinity and family history suggestive of PID were reported in 213 (81%) and 145 patients (55%), respectively. Genetic testing of 206 patients resulted in a diagnostic yield of 70%. Mutations were identified in 46 different genes and more than 90% of the reported genetic defects were transmitted by an autosomal recessive pattern. The majority of the mutations were missense mutations (57%) followed by deletions and frame shift mutations. Five novel disease-causing genes were discovered.
**Conclusions:** Genetic testing should be an integral part in the management of primary immunodeficiency patients. This will help the delivery of precision medicine and facilitate proper genetic counseling. Studying inbred populations using sophisticated diagnostic methods can allow better understanding of the genetics of primary immunodeficiency disorders.

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**Knowledge, attitudes, behaviours and practices towards diabetes mellitus in Kuwait**

Carballo M1,2, Mohammad A1, Maclean EC2, Khatoon N1, Waheedi M3, Abraham S1.

1Dasman Diabetes Institute, Kuwait
2International Centre for Migration, Health and Development, Geneva, Switzerland
3Department of Pharmacy Practice, Kuwait University, Kuwait


**BACKGROUND**
Rates of diabetes in Kuwait are among the highest in the world.

**AIMS**
To inform prevention initiatives, this study assessed diabetes knowledge, attitudes towards it, and personal behaviour relating to risk factors among the Kuwaiti population.

**METHODS**
A cross-sectional knowledge, attitudes, beliefs and practices survey of 1124 people was performed between July and September 2015. Descriptive analysis and χ2 tests were performed.

**RESULTS**
Although most participants (94%) had heard of diabetes and 87% believed type 2 diabetes to be preventable, knowledge of risk factors was poor [family history (87%), age (44%), low exercise (10%), obesity (4%), diet (0%) and stress (0%)]. Dietary patterns in Kuwait were variable and, of concern, 42% of those with diabetes had been eating more since diagnosis. Lifestyle, particularly among Kuwaitis and people with diabetes, was sedentary - 47% of participants walked < 20 minutes per day.

**CONCLUSIONS**
Despite the importance of diet and exercise for diabetes prevention, significant gaps in public education clearly exist. At a policy level, much remains to be done and intensified intersectoral programmes are required to improve public awareness.
Forthcoming Conferences and Meetings

Compiled and edited by

Vineetha Elizabeth Mammen

Kuwait Medical Journal 2019; 51 (1): 110 - 115

5th Annual Congress and Medicare Expo on **Trauma & Critical Care**
Mar 5 - 6, 2019
*Netherlands* / Amsterdam
Email: trauma2019@europemeet.com

7th International Conference on **Bacteriology and Infectious Diseases**
Mar 7 - 8, 2019
*Netherlands* / Amsterdam
Email: bacteriology@europemeet.com

Updates in **Internal Medicine 2019 Conference**
Mar 7 - 9, 2019
*Kuwait* / Kuwait City, Millennium Hotel and Convention Center
Contact: +965 2487 8168
Email: info@imupdateskw.com

First GCC **Rheumatology Conference**
Mar 8 - 9, 2019
*Kuwait* / Symphony Style Hotel
Contact: karkwt.org/gccrc

2nd Kuwait Medical Laboratory and **OB/GYN Conference**, Farwaniya Hospital Laboratory
Mar 13 - 14, 2019
*Kuwait* / Millennium Hotel
Email: contact@flhk.com

25th World Congress on **Dentistry and Oral Health**
Mar 14 - 15, 2019
*United Kingdom* / London
Venue: Park Inn by Radisson Hotel & Conference Centre, London, Heathrow
Email: dentistrycongress@dentistyspeakerexperts.org

23rd International Conference on **Neurology & Neurophysiology**
Mar 18 - 19, 2019
*Scotland* / Edinburgh
Email: neurophysiology@neurologyspeakerexperts.org

7th International Conference on **HIV/AIDS, STDs and STIs**
Mar 18 - 19, 2019
*United States* / New York
Email: std@americameetings.net

33rd Annual **Vaccines & Vaccination Congress**
Mar 18 - 19, 2019
*United States* / New York
Email: vaccinescongress@americameetings.net

International Conference on **Biomaterials for Bone Tissue Engineering**
Mar 18 - 19, 2019
*United Arab Emirates* / Dubai
Email: biomaterials@meeconferences.org

4th International Conference on **Food Microbiology** and Food Market
Mar 20 - 21, 2019
*United States* / New York
Email: foodmicrobiology2019@aol.com

25th International Conference on **Human Metabolic Health**: Diabetes, Obesity & Metabolism
Mar 21 - 22, 2019
*United Arab Emirates* / Dubai
Email: humanmetabolism@meeconferences.com

2nd Annual Congress on **Diabetes and its Complications**
Mar 25 - 26, 2019
*Hong Kong* / Hong Kong
Email: diabetic@worldmeet.net

5th International Conference on **Clinical Pharmacy** and **Health Care**
Mar 27 - 28, 2019
*United States* / San Antonio, Texas
Email: clinicalpharmacy@annualamericacongress.com

1st Kuwait **Gastroenterology Association Conference**
Mar 29 – 30, 2019
*Kuwait* / Radisson Blu Hotel, Hashemi Ballroom
Contact: www.kgaconf.com

International Conference on **Clinical Case Reports**
Apr 4 - 6, 2019
*France* / Paris
Email: casestudy@europemeet.com
13th International Conference on **Endocrinology, Diabetes and Metabolism**  
Apr 8 - 9, 2019  
New Zealand / Wellington  
Email: endocrinologysummit@endocrineconferences.com

7th International Conference and Expo on **Acupuncture and Alternative Medicine**  
Apr 8 - 9, 2019  
United States / Florida  
Email: acupuncture@conferenceseries.net

3rd International Conference on **Influenza and Emerging Infectious Diseases**  
Apr 10 - 11, 2019  
Canada / Toronto, Ontario  
Email: fluinfectious@americanevent.org

4th World Congress on **Nursing Education & Research**  
Apr 12 - 13, 2019  
Canada / Toronto  
Email: nursingseducationcongress@outlook.com

Annual Neurochemistry and **Neuropharmacology Congress**  
Apr 17 - 18, 2019  
Canada / Montreal  
Email: neuropharma@conferencesamerica.org

4th International Conference on **Pediatrics and Pediatric Surgery**  
Apr 23 - 24, 2019  
United Kingdom / London  
Email: pediatricssurgery@pediatricsspeakerexperts.org

International Conference on **Gastroenterology and Hepatology**  
Apr 24 - 25, 2019  
Hungary / Budapest  
Email: gastroenterology@europemeet.com

3rd World Conference on **Advanced Nursing & Healthcare Simulation**  
Apr 24 - 25, 2019  
United States / Houston, Texas  
Email: americanadvancednursing@gmail.com

9th World Congress on **Breast Cancer**  
Apr 25 - 26, 2019  
United Kingdom / London  
Email: breastcancer@oncologyseries.com

6th International Congress on **Emergency and Trauma Nursing**  
Apr 25 - 26, 2019  
United Kingdom / London  
Email: trauma@meetingsfinder.org

17th International Conference on **Pharmaceutical Microbiology and Biotechnology**  
Apr 29 - 30, 2019  
United Kingdom / London  
Email: pharmamicrobiology@microbiologyspeakerexperts.org

11th World Congress on **Neuropharmacology**  
May 6 - 7, 2019  
Czech Republic / Prague  
Email: neuropharmacology@europemeet.com

International Conference on **E-Health and Healthcare Innovations**  
May 8 - 9, 2019  
Netherlands / Amsterdam  
Email: ehealth@europemeet.com

International Conference on **Internal Medicine and Hospital Medicine**  
May 8 - 9, 2019  
France / Paris  
Email: contact@europemeet.com

8th World Congress on **Addictive Disorders & Addiction Therapy**  
May 9 - 10, 2019  
United Kingdom / London  
Email: addiction@neuroconferences.com

13th International Conference on **Proteomics, Genomics and Bioinformatics**  
May 10 - 11, 2019  
Japan / Tokyo, Radisson Hotel Narita  
Email: proteomicsasia@biochemconferences.org

4th Global **Food Security, Food Safety & Sustainability Conference**  
May 10 -11, 2019  
Canada / Montreal  
Email: oliviacarisella999@yahoo.com

6th World Congress on **Synthetic Biology** and Advanced Biomaterials  
May 13 - 14, 2019  
Australia / Melbourne, Mercure Albert Park  
Email: syntheticbiomaterials@conferenceint.com
12th World Congress on Endocrinology and Metabolic Disorders  
May 13 - 14, 2019  
Japan / Osaka  
Email: endocrinology@worldmeet.net

2nd International Conference on Anatomy and Physiology  
May 17 - 18, 2019  
Singapore / Singapore, Holiday Inn  
Email: anatomy@conferencesseries.org

2nd Global Experts Meeting on Diabetes, Hypertension & Metabolic Syndrome  
May 17 - 18, 2019  
Singapore / Holiday Inn Singapore Atrium  
Email: diabetesmeet@conferenceint.com

2nd Global Meeting on Diabetes and Endocrinology  
May 30 - 31, 2019  
Turkey / Istanbul  
Email: endocrinology@mehealthevents.org

20th Global Nephrologists Annual Meeting  
Jun 3 - 4, 2019  
United Kingdom / London  
Email: nephrologists@nephrospeakerexperts.org

6th World Congress and Exhibition on Antibiotics and Antibiotic Resistance  
Jun 3 - 4, 2019  
United Kingdom / London  
Email: antibiotics@expertsgathering.org

21st Asia Pacific Diabetes Conference  
Jun 10 - 11, 2019  
Australia / Perth  
Email: diabetesasiapacific@endocrineconferences.org

22nd Canada Meetings on Radiology & Novel Cancer Therapies  
Jun 12 - 13, 2019  
Canada / Montreal, Quebec  
Email: radiocancer@americameetings.net

2nd Global Physicians and HealthCare Congress  
Jun 13 - 14, 2019  
Finland / Helsinki  
Email: physicians@memeetings.com

13th World Drug Delivery Summit  
Jun 14 - 15, 2019  
Canada / Montreal  
Email: drugdelivery@annualamericacongress.org

18th Annual World Congress on Neonatology  
Jun 14 - 15, 2019  
Canada / Montreal  
Email: neonatal@pediatricsconferences.com

12th International Conference on Optics, Photonics & Lasers  
Jun 17 - 18, 2019  
United Kingdom / London  
Email: eurooptics@expertsgathering.net

15th Euro Obesity and Endocrinology Congress  
Jun 17 - 18, 2019  
United Kingdom / London  
Email: euroobesity@obesityconference.org

6th International Conference on Otolaryngology, Rhinology and Laryngology  
Jun 20 - 21, 2019  
United Arab Emirates / Dubai  
Email: otorhinolaryngology@meconferences.org

4th International Conference & Exhibition on Metabolic Syndrome  
Jun 20 - 21, 2019  
France / Paris  
Email: metabolicsyndromes@conferencesseries.net

18th Global Conference on Diabetes & Nursing Care  
Jun 27 - 28, 2019  
Amsterdam, Netherlands  
Email: diabetes@europemeet.com

Annual Ophthalmologists Meeting  
Jul 5 - 6, 2019  
United States / Columbus  
Email: ophthalmology@americanevent.org

39th International Conference on Nursing & Healthcare  
Jul 5 - 6, 2019  
United States / Columbus, Ohio  
Email: nursingcongressottawa@gmail.com

World Congress on Insulin Resistance Diabetes, Endocrinology Metabolism and Nursing  
Jul 5 - 6, 2019  
United States / Columbus  
Email: diabetesmedicare@annualamericacongress.com

15th International Congress on Advances in Natural Medicines, Nutraceuticals & Neurocognition  
Jul 8 - 9, 2019  
Germany / Berlin  
Email: nutraceuticals@nutritionalconference.com
28th European Diabetes Congress
Jul 17 - 18, 2019
Scotland / Edinburgh
Email: eurodiabetes@diabetesspeakerexperts.org

27th International Diabetes and Healthcare Conference
Jul 18 - 19, 2019
United Arab Emirates / Abu Dhabi
Email: diabetes@mehealthevents.org

2nd International Conference on Pediatric Pathology and Nursing Care
Jul 19 - 20, 2019
United States / Atlanta
Email: pediatricpharma@annualamericacongress.org

8th International Conference on Clinical Trials
Jul 19 - 20, 2019
United States / Atlanta
Email: christopher@pharmaceuticalconferences.org

Women Oncology & Nursing Care
Jul 19 - 20, 2019
United States / Atlanta
Email: womenoncology@americameetings.com

14th World Congress on Healthcare & Technologies
Jul 22 - 23, 2019
United Kingdom / London
Email: globalhealthcare@healthconferences.org

32nd European Neurology Congress
Jul 22 - 24, 2019
United Kingdom / London
Email: euroneurology@neuroconferences.com

14th International Conference on Laboratory Medicine & Pathology
Jul 22 - 23, 2019
United Kingdom / London
Email: laboratorymedicine@pathologyspeakerexperts.org

5th International Conference on Palliative Care, Medicine and Hospice Nursing
Jul 24 - 25, 2019
Canada / Vancouver
Email: palliativecare@americameetings.org

2nd World Summit on Psychiatry, Mental Health Nursing and Healthcare
Jul 24 - 25, 2019
Canada / Vancouver
Email: psychiatricnursing@americameetings.com

2nd World Congress on Fetal and Maternal Medicine
Jul 24 - 25, 2019
Japan / Kyoto
Email: fetal@worldmeet.net

29th World Diabetes & Heart Congress
Jul 24 - 25, 2019
Australia / Melbourne
Email: diabetesexperts@conferenceint.com

2nd Annual Congress on Medicine
Jul 24 - 25, 2019
Japan / Kyoto
Email: medicine@worldhealthsummit.net

17th International Conference on Cytopathology and Histopathology
Jul 26 - 27, 2019
Canada / Vancouver
Email: cytology@americameetings.net

Future of Aging and Gerontology
Aug 2 - 3, 2019
United States / Chicago
Email: aging@annualamericacongress.com

31st International Conference on Pediatric and Adolescent Diabetes
Aug 12 - 13, 2019
Japan / Tokyo
Email: adolescentdiabetes@conferencesseries.org

28th International Conference on Pediatrics Health
Aug 12 - 14, 2019
Italy / Rome
Email: pediatrichealth@diabetesspeakerexperts.org

2nd International Conference on Emergency & Acute Care Medicine
Aug 14 - 15, 2019
Japan / Tokyo, Radisson Hotel Narita
Email: emergencymedicine@conferenceint.com

11th World Congress on Precision and Personalized Medicine
Aug 14 - 15, 2019
New Zealand / Auckland
Email: personalizedmedicine@conferencesworld.org

6th World Summit on Trauma, Critical Care and Reconstructive Surgery
Aug 14 - 15, 2019
Japan / Tokyo
Email: trauma@conferenceint.com
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<td><em>Singapore, Holiday Inn Atrium</em></td>
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<td><em>Canada / Toronto</em></td>
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Euro Diabetes Congress & Expo  
Oct 3 - 4, 2019  
France / Paris  
Email: rajeshguru@conferenceseries.com

4th International Conference on Molecular Biology & Nucleic Acids  
Oct 7 - 8, 2019  
United States / Chicago / Illinois  
Email: molecularbiology@americameetings.net

18th International Conference on Structural Biology  
Oct 14 - 16, 2019  
United Kingdom / London  
Email: structuralbiology@expertsmeetings.org

8th International Conference and Exhibition on Pain Research and Management  
Oct 17 - 18, 2019  
United Kingdom / London  
Email: painmanagement@chemistryspeakerexperts.org

25th Biotechnology Congress: Research & Innovations  
Oct 18 - 19, 2019  
United States / Dallas  
Email: bioamerica@americameetings.net

30th International Congress on Prevention of Diabetes and Complications  
Oct 21 - 22, 2019  
Switzerland / Zurich  
Email: diabetesmeet@diabetesspeakerexperts.org

7th International Conference on Family Medicine: An Evidence-Based Approach to Patient Care  
Oct 21 - 22, 2019  
Australia / Melbourne  
Email: familymedicine@conferenceseries.org

5th International Conference on Complementary & Alternative Medicine  
Oct 25 - 26, 2019  
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Email: cam@americanevent.org

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Email: internalmedicinecongress@gmail.com

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11th International Chronic Obstructive Pulmonary Disease Conference  
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Email: copdconference@expertsconferences.org

33rd International Conference on Neonatology and Perinatology  
Nov 18 - 19, 2019  
United Kingdom / London  
Email: neonatology@pediatricsspeakerexperts.org

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United Arab Emirates / Dubai  
Email: vaccine@mehealthevents.org

International Conference on Diabetes and Cholesterol Metabolism  
Nov 25 - 26, 2019  
United Arab Emirates / Dubai  
Email: metabolicdiseases@memeetings.net

2nd Head and Neck Conference: The Multidisciplinary Approach  
Dec 5 - 6, 2019  
United Arab Emirates / Abu Dhabi  
Email: headneck@mehealthevents.org
WHO-Facts Sheet

1. Electromagnetic fields and public health
2. Mycotoxins
3. Nipah virus
4. Physical activity
5. Taeniasis / Cysticercosis

Compiled and edited by
Vineetha E Mammen

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1. ELECTROMAGNETIC FIELDS AND PUBLIC HEALTH: MOBILE PHONES

KEY FACTS
- Mobile phone use is ubiquitous with an estimated 6.9 billion subscriptions globally
- The electromagnetic fields produced by mobile phones are classified by the International Agency for Research on Cancer as possibly carcinogenic to humans.
- Studies are ongoing to more fully assess potential long-term effects of mobile phone use.
- WHO will conduct a formal risk assessment of all studied health outcomes from radiofrequency fields exposure by 2016.

Mobile or cellular phones are now an integral part of modern telecommunications. In many countries, over half the population use mobile phones and the market is growing rapidly. In 2014, there is an estimated 6.9 billion subscriptions globally. In some parts of the world, mobile phones are the most reliable or the only phones available.

Given the large number of mobile phone users, it is important to investigate, understand and monitor any potential public health impact.

Mobile phones communicate by transmitting radio waves through a network of fixed antennas called base stations. Radiofrequency waves are electromagnetic fields, and unlike ionizing radiation such as X-rays or gamma rays, can neither break chemical bonds nor cause ionization in the human body.

Exposure levels
Mobile phones are low-powered radiofrequency transmitters, operating at frequencies between 450 and 2700 MHz with peak powers in the range of 0.1 to 2 watts. The handset only transmits power when it is turned on. The power (and hence the radiofrequency exposure to a user) falls off rapidly with increasing distance from the handset. A person using a mobile phone 30–40 cm away from their body – for example when text messaging, accessing the Internet, or using a “hands free” device – will therefore have a much lower exposure to radiofrequency fields than someone holding the handset against their head.

In addition to using “hands-free” devices, which keep mobile phones away from the head and body during phone calls, exposure is also reduced by limiting the number and length of calls. Using the phone in areas of good reception also decreases exposure as it allows the phone to transmit at reduced power. The use of commercial devices for reducing radiofrequency field exposure has not been shown to be effective.

Mobile phones are often prohibited in hospitals and on airplanes, as the radiofrequency signals may interfere with certain electro-medical devices and navigation systems.

Are there any health effects?
A large number of studies have been performed over the last two decades to assess whether mobile phones pose a potential health risk. To date, no adverse health effects have been established as being caused by mobile phone use.

Short-term effects
Tissue heating is the principal mechanism of interaction between radiofrequency energy and the human body. At the frequencies used by mobile phones, most of the energy is absorbed by the skin.
and other superficial tissues, resulting in negligible temperature rise in the brain or any other organs of the body.

A number of studies have investigated the effects of radiofrequency fields on brain electrical activity, cognitive function, sleep, heart rate and blood pressure in volunteers. To date, research does not suggest any consistent evidence of adverse health effects from exposure to radiofrequency fields at levels below those that cause tissue heating. Further, research has not been able to provide support for a causal relationship between exposure to electromagnetic fields and self-reported symptoms, or “electromagnetic hypersensitivity”.

Long-term effects

Epidemiological research examining potential long-term risks from radiofrequency exposure has mostly looked for an association between brain tumours and mobile phone use. However, because many cancers are not detectable until many years after the interactions that led to the tumour, and since mobile phones were not widely used until the early 1990s, epidemiological studies at present can only assess those cancers that become evident within shorter time periods. However, results of animal studies consistently show no increased cancer risk for long-term exposure to radiofrequency fields.

Several large multinational epidemiological studies have been completed or are ongoing, including case-control studies and prospective cohort studies examining a number of health endpoints in adults. The largest retrospective case-control study to date on adults, Interphone, coordinated by the International Agency for Research on Cancer (IARC), was designed to determine whether there are links between use of mobile phones and head and neck cancers in adults.

The international pooled analysis of data gathered from 13 participating countries found no increased risk of glioma or meningioma with mobile phone use of more than 10 years. There are some indications of an increased risk of glioma for those who reported the highest 10% of cumulative hours of cell phone use, although there was no consistent trend of increasing risk with greater duration of use. The researchers concluded that biases and errors limit the strength of these conclusions and prevent a causal interpretation.

Based largely on these data, IARC has classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B), a category used when a causal association is considered credible, but when chance, bias or confounding cannot be ruled out with reasonable confidence.

While an increased risk of brain tumors is not established, the increasing use of mobile phones and the lack of data for mobile phone use over time periods longer than 15 years warrant further research of mobile phone use and brain cancer risk. In particular, with the recent popularity of mobile phone use among younger people, and therefore a potentially longer lifetime of exposure, WHO has promoted further research on this group. Several studies investigating potential health effects in children and adolescents are underway.

Exposure limit guidelines

Radiofrequency exposure limits for mobile phone users are given in terms of Specific Absorption Rate (SAR) – the rate of radiofrequency energy absorption per unit mass of the body. Currently, two international bodies1, 2 have developed exposure guidelines for workers and for the general public, except patients undergoing medical diagnosis or treatment. These guidelines are based on a detailed assessment of the available scientific evidence.

WHO response

In response to public and governmental concern, WHO established the International Electromagnetic Fields (EMF) Project in 1996 to assess the scientific evidence of possible adverse health effects from electromagnetic fields. WHO will conduct a formal risk assessment of all studied health outcomes from radiofrequency fields exposure by 2016. In addition, and as noted above, the International Agency for Research on Cancer (IARC), a WHO specialized agency, has reviewed the carcinogenic potential of radiofrequency fields, as from mobile phones in May 2011.

WHO also identifies and promotes research priorities for radiofrequency fields and health to fill gaps in knowledge through its research agendas.

WHO develops public information materials and promotes dialogue among scientists, governments, industry and the public to raise the level of understanding about potential adverse health risks of mobile phones.

2. Institute of Electrical and Electronics Engineers (IEEE). IEEE standard for safety levels with respect to human exposure to radio frequency electromagnetic fields, 3 kHz to 300 GHz, IEEE Std C95.1, 2005.
2. MYCOTOXINS

KEY FACTS

- Mycotoxins are naturally occurring toxins produced by certain moulds (fungi) and can be found in food.
- The moulds grow on a variety of different crops and foodstuffs including cereals, nuts, spices, dried fruits, apples and coffee beans, often under warm and humid conditions.
- Mycotoxins can cause a variety of adverse health effects and pose a serious health threat to both humans and livestock.
- The adverse health effects of mycotoxins range from acute poisoning to long-term effects such as immune deficiency and cancer.
- A scientific expert committee jointly convened by WHO and the Food and Agriculture Organization of the United Nations (FAO) – called JECFA – is the international body responsible for evaluating the health risk from natural toxins including mycotoxins.
- International standards and codes of practice to limit exposure to mycotoxins from certain foods are established by the Codex Alimentarius Commission based on JECFA assessments.

What are mycotoxins?

Mycotoxins are toxic compounds that are naturally produced by certain types of moulds (fungi). Moulds that can produce mycotoxins grow on numerous foodstuffs such as cereals, dried fruits, nuts and spices. Mould growth can occur either before harvest or after harvest, during storage, on/in the food itself often under warm, damp and humid conditions. Most mycotoxins are chemically stable and survive food processing.

Several hundred different mycotoxins have been identified, but the most commonly observed mycotoxins that present a concern to human health and livestock include aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone and nivalenol/deoxynivalenol. Mycotoxins appear in the food chain as a result of mould infection of crops both before and after harvest. Exposure to mycotoxins can happen either directly by eating infected food or indirectly from animals that are fed contaminated feed, in particular from milk.

Mycotoxins commonly found in food and why they are of concern

The effects of some food-borne mycotoxins are acute with symptoms of severe illness appearing quickly after consumption of food products contaminated with mycotoxins. Other mycotoxins occurring in food have been linked to long-term effects on health, including the induction of cancers and immune deficiency. Of the several hundred mycotoxins identified so far, about a dozen have gained the most attention due to their severe effects on human health and their occurrences in food.

Aflatoxins are amongst the most poisonous mycotoxins and are produced by certain moulds (Aspergillus flavus and Aspergillus parasiticus) which grow in soil, decaying vegetation, hay, and grains. Crops that are frequently affected by Aspergillus spp. include cereals (corn, sorghum, wheat and rice), oilseeds (soybean, peanut, sunflower and cotton seeds), spices (chili peppers, black pepper, coriander, turmeric and ginger) and tree nuts (pistachio, almond, walnut, coconut and Brazil nut). The toxins can also be found in the milk of animals that are fed contaminated feed, in the form of aflatoxin M1. Large doses of aflatoxins can lead to acute poisoning (aflatoxicosis) and can be life threatening, usually through damage to the liver. Aflatoxins have also been shown to be genotoxic, meaning they can damage DNA and cause cancer in animal species. There is also evidence that they can cause liver cancer in humans.

Ochratoxin A is produced by several species of Aspergillus and Penicillium and is a common food-contaminating mycotoxin. Contamination of food commodities, such as cereals and cereal products, coffee beans, dry vine fruits, wine and grape juice, spices and liquorice, occurs worldwide. Ochratoxin A is formed during the storage of crops and is known to cause a number of toxic effects in animal species. The most sensitive and notable effect is kidney damage, but the toxin may also have effects on fetal development and on the immune system. Contrary to the clear evidence of kidney toxicity and kidney cancer due to ochratoxin A exposure in animals, this association in humans is unclear, however effects on kidney have been demonstrated.

Patulin is a mycotoxin produced by a variety of moulds, particularly Aspergillus, Penicillium and Byssochlamys. Often found in rotting apples and apple products, patulin can also occur in various mouldy fruits, grains and other foods. Major human dietary sources of patulin are apples and apple juice made from affected fruit. The acute symptoms in animals include liver, spleen and kidney damage and toxicity to the immune system. For humans, nausea, gastrointestinal disturbances and vomiting have been reported. Patulin is considered to be genotoxic however a carcinogenic potential has not been demonstrated yet.

Fusarium fungi are common to the soil and produce a range of different toxins, including trichothecenes such as deoxynivalenol (DON), nivalenol (NIV) and...
T-2 and HT-2 toxins, as well as zearalenone (ZEN) and fumonisins. The formation of the moulds and toxins occur on a variety of different cereal crops. Different fusarium toxins are associated with certain types of cereal. For example, both DON and ZEN are often associated with wheat, T-2 and HT-2 toxins with oats, and fumonisins with maize (corn). Trichothecenes can be acutely toxic to humans, causing rapid irritation to the skin or intestinal mucosa and lead to diarrhoea. Reported chronic effects in animals include suppression of the immune system. ZEN has been shown to have hormonal, estrogenic effects and can cause infertility at high intake levels, particularly in pigs. Fumonisins have been related to oesophageal cancer in humans, and to liver and kidney toxicity in animals.

How can I minimise the risk from mycotoxins?

It is important to note that mould that produces mycotoxins can grow on a variety of different crops and foodstuff and can penetrate deep into food and do not just grow on the surface. Mould usually does not grow in properly dried and stored foods, so efficient drying of commodities and maintenance of the dry state, or proper storage, is an effective measure against mould growth and the production of mycotoxins.

To minimize the health risk from mycotoxins, people are advised to:

- inspect whole grains (especially corn, sorghum, wheat, rice), dried figs and nuts such as peanuts, pistachio, almond, walnut, coconut, Brazil nuts and hazelnuts which are all regularly contaminated with aflatoxins for evidence of mould, and discard any that look mouldy, discoloured, or shrivelled;
- avoid damage of grains before and during drying, and in storage, as damaged grain is more prone to invasion of moulds and therefore mycotoxin contamination;
- buy grains and nuts as fresh as possible;
- make sure that foods are stored properly – kept free of insects, dry, and not too warm;
- not keep foods for extended periods of time before being used; and
- ensure a diverse diet – this not only helps to reduce mycotoxins exposure, but also improves nutrition.

WHO response

WHO, in collaboration with FAO, is responsible for assessing the risks to humans of mycotoxins – through contamination in food – and for recommending adequate protection.

Risk assessments of mycotoxins in food done by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) are used by governments and by the Codex Alimentarius Commission (the intergovernmental standards-setting body for food) to establish maximum levels in food or provide other risk management advice to control or prevent contamination. Codex standards are the international reference for national food supplies and for trade in food, so that people everywhere can be confident that the food they buy meets the agreed standards for safety and quality, no matter where it was produced.

JECFA set the tolerable intake level for many mycotoxins

JECFA or ad hoc FAO/WHO scientific expert groups consist of independent, international experts who conduct scientific reviews of all available studies and other relevant data on specific mycotoxins. The outcome of such health risk assessments can either be a maximum tolerable intake (exposure) level, or other guidance to indicate the level of health concern (such as the Margin of Exposure), including advice on risk management measures to prevent and control contamination, and on the analytical methods and monitoring and control activities.

These tolerable daily intakes are used by governments and international risk managers, such as the Codex Alimentarius Commission, to establish maximum levels for mycotoxins in food. The maximum levels for mycotoxins in food are very low due to their severe toxicity. For example, the maximum levels for aflatoxins set by the Codex in various nuts, grains, dried figs and milk are in the range of 0.5 to 15 µg/kg (a µg is one billionth of a kilogram). The Codex maximum limit for patulin in apple juice is 50 µg/L.

Exposure to mycotoxins needs to be kept as low as possible to protect the people. Mycotoxins not only pose a risk to both human and animal health, but also impact food security and nutrition by reducing people’s access to healthy food. WHO encourages national authorities to monitor and ensure that levels of mycotoxins in foodstuff on their market are as low as possible and comply with the both national and international maximum levels, conditions and legislation.

3. NIPAH VIRUS

KEY FACTS

- Nipah virus infection in humans causes a range of clinical presentations, from asymptomatic infection (subclinical) to acute respiratory infection and fatal encephalitis.
- The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management.
- Nipah virus can be transmitted to humans from
animals (such as bats or pigs), or contaminated foods and can also be transmitted directly from human-to-human.

- Fruit bats of the Pteropodidae family are the natural host of Nipah virus.
- There is no treatment or vaccine available for either people or animals. The primary treatment for humans is supportive care.
- The 2018 annual review of the WHO R&D Blueprint list of priority diseases indicates that there is an urgent need for accelerated research and development for the Nipah virus.

Nipah virus (NiV) is a zoonotic virus (it is transmitted from animals to humans) and can also be transmitted through contaminated food or directly between people. In infected people, it causes a range of illnesses from asymptomatic (subclinical) infection to acute respiratory illness and fatal encephalitis. The virus can also cause severe disease in animals such as pigs, resulting in significant economic losses for farmers.

Although Nipah virus has caused only a few known outbreaks in Asia, it infects a wide range of animals and causes severe disease and death in people, making it a public health concern.

Past Outbreaks

Nipah virus was first recognized in 1999 during an outbreak among pig farmers in, Malaysia. No new outbreaks have been reported in Malaysia since 1999.

It was also recognized in Bangladesh in 2001, and nearly annual outbreaks have occurred in that country since. The disease has also been identified periodically in eastern India.

Other regions may be at risk for infection, as evidence of the virus has been found in the known natural reservoir (Pteropus bat species) and several other bat species in a number of countries, including Cambodia, Ghana, Indonesia, Madagascar, the Philippines, and Thailand.

Transmission

During the first recognized outbreak in Malaysia, which also affected Singapore, most human infections resulted from direct contact with sick pigs or their contaminated tissues. Transmission is thought to have occurred via unprotected exposure to secretions from the pigs, or unprotected contact with the tissue of a sick animal.

In subsequent outbreaks in Bangladesh and India, consumption of fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva from infected fruit bats was the most likely source of infection.

There are currently no studies on viral persistence in bodily fluids or the environment including fruits.

Human-to-human transmission of Nipah virus has also been reported among family and care givers of infected patients.

During the later outbreaks in Bangladesh and India, Nipah virus spread directly from human-to-human through close contact with people’s secretions and excretions. In Siliguri, India in 2001, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors. From 2001 to 2008, around half of reported cases in Bangladesh were due to human-to-human transmission through providing care to infected patients.

Signs and symptoms

Human infections range from asymptomatic infection to acute respiratory infection (mild, severe), and fatal encephalitis.

Infected people initially develop symptoms including fever, headaches, myalgia (muscle pain), vomiting and sore throat. This can be followed by dizziness, drowsiness, altered consciousness, and neurological signs that indicate acute encephalitis. Some people can also experience atypical pneumonia and severe respiratory problems, including acute respiratory distress. Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours.

The incubation period (interval from infection to the onset of symptoms) is believed to range from 4 to 14 days. However, an incubation period as long as 45 days has been reported.

Most people who survive acute encephalitis make a full recovery, but long term neurologic conditions have been reported in survivors. Approximately 20% of patients are left with residual neurological consequences such as seizure disorder and personality changes. A small number of people who recover subsequently relapse or develop delayed onset encephalitis.

The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management.

Diagnosis

Initial signs and symptoms of Nipah virus infection are nonspecific, and the diagnosis is often not suspected at the time of presentation. This can hinder accurate diagnosis and creates challenges in outbreak detection, effective and timely infection control measures, and outbreak response activities.
In addition, the quality, quantity, type, timing of clinical sample collection and the time needed to transfer samples to the laboratory can affect the accuracy of laboratory results.

Nipah virus infection can be diagnosed with clinical history during the acute and convalescent phase of the disease. The main tests used are real time polymerase chain reaction (RT-PCR) from bodily fluids and antibody detection via enzyme-linked immunosorbent assay (ELISA).

Other tests used include polymerase chain reaction (PCR) assay, and virus isolation by cell culture.

**Treatment**

There are currently no drugs or vaccines specific for Nipah virus infection although WHO has identified Nipah as a priority disease for the WHO Research and Development Blueprint. Intensive supportive care is recommended to treat severe respiratory and neurologic complications.

**Natural host: fruit bats**

Fruit bats of the family *Pteropodidae* – particularly species belonging to the *Pteropus* genus – are the natural hosts for Nipah virus. There is no apparent disease in fruit bats.

It is assumed that the geographic distribution of *Henipaviruses* overlaps with that of *Pteropus* category. This hypothesis was reinforced with the evidence of *Henipavirus* infection in *Pteropus* bats from Australia, Bangladesh, Cambodia, China, India, Indonesia, Madagascar, Malaysia, Papua New Guinea, Thailand and Timor-Leste.

African fruit bats of the genus *Eidolon*, family *Pteropodidae*, were found positive for antibodies against Nipah and Hendra viruses, indicating that these viruses might be present within the geographic distribution of *Pteropodidae* bats in Africa.

**Nipah virus in domestic animals**

Outbreaks of the Nipah virus in pigs and other domestic animals such as horses, goats, sheep, cats and dogs were first reported during the initial Malaysian outbreak in 1999.

The virus is highly contagious in pigs. Pigs are infectious during the incubation period, which lasts from 4 to 14 days.

An infected pig can exhibit no symptoms, but some develop acute feverish illness, labored breathing, and neurological symptoms such as trembling, twitching and muscle spasms. Generally, mortality is low except in young piglets. These symptoms are not dramatically different from other respiratory and neurological illnesses of pigs. Nipah virus should be suspected if pigs also have an unusual barking cough or if human cases of encephalitis are present.

**Prevention**

**Controlling Nipah virus in pigs**

Currently, there are no vaccines available against Nipah virus. Based on the experience gained during the outbreak of Nipah involving pig farms in 1999, routine and thorough cleaning and disinfection of pig farms with appropriate detergents may be effective in preventing infection.

If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals – with close supervision of burial or incineration of carcasses – may be necessary to reduce the risk of transmission to people. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease.

As Nipah virus outbreaks have involved pigs and/or fruit bats, establishing an animal health/wildlife surveillance system, using a One Health approach, to detect Nipah cases is essential in providing early warning for veterinary and human public health authorities.

**Reducing the risk of infection in people**

In the absence of a vaccine, the only way to reduce or prevent infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the Nipah virus.

Public health educational messages should focus on:

- **Reducing the risk of bat-to-human transmission:** Efforts to prevent transmission should first focus on decreasing bat access to date palm sap and other fresh food products. Keeping bats away from sap collection sites with protective coverings (such as bamboo sap skirts) may be helpful. Freshly collected date palm juice should be boiled, and fruits should be thoroughly washed and peeled before consumption. Fruits with sign of bat bites should be discarded.

- **Reducing the risk of animal-to-human transmission:** Gloves and other protective clothing should be worn while handling sick animals or their tissues, and during slaughtering and culling procedures. As much as possible, people should avoid being in contact with infected pigs. In endemic areas, when establishing new pig farms, considerations should be given to presence of fruit bats in the area and in general, pig feed and pig shed should be protected against bats when feasible.
Reducing the risk of human-to-human transmission: Close unprotected physical contact with Nipah virus-infected people should be avoided. Regular hand washing should be carried out after caring for or visiting sick people.

Controlling infection in health-care settings
Health-care workers caring for patients with suspected or confirmed infection, or handling specimens from them, should implement standard infection control precautions at all times.

As human-to-human transmission has been reported, in particular in health-care settings, contact and droplet precautions should be used in addition to standard precautions. Airborne precautions may be required in certain circumstances.

Samples taken from people and animals with suspected Nipah virus infection should be handled by trained staff working in suitably equipped laboratories.

WHO response
WHO is supporting affected and at risk countries with technical guidance on how to manage outbreaks of Nipah virus and on how to prevent their occurrence.

The risk of international transmission via fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva from infected fruit bats can be prevented by washing them thoroughly and peeling them before consumption. Fruit with signs of bat bites should be discarded.

4. PHYSICAL ACTIVITY

KEY FACTS
- Insufficient physical activity is one of the leading risk factors for death worldwide.
- Insufficient physical activity is a key risk factor for noncommunicable diseases (NCDs) such as cardiovascular diseases, cancer and diabetes.
- Physical activity has significant health benefits and contributes to prevent NCDs.
- Globally, 1 in 4 adults is not active enough.
- More than 80% of the world’s adolescent population is insufficiently physically active.
- Policies to address insufficient physical activity are operational in 56% of WHO Member States.
- WHO Member States have agreed to reduce insufficient physical activity by 10% by 2025.

What is physical activity?
WHO defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits.

The term “physical activity” should not be confused with “exercise”, which is a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness. Beyond exercise, any other physical activity that is done during leisure time, for transport to get to and from places, or as part of a person’s work, has a health benefit. Further, both moderate- and vigorous-intensity physical activity improve health.

How much of physical activity is recommended?
WHO recommends:

Children and adolescents aged 5-17 years
- Should do at least 60 minutes of moderate to vigorous-intensity physical activity daily.
- Physical activity of amounts greater than 60 minutes daily will provide additional health benefits.
- Should include activities that strengthen muscle and bone, at least 3 times per week.

Adults aged 18–64 years
- Should do at least 150 minutes of moderate-intensity physical activity throughout the week, or do at least 75 minutes of vigorous-intensity physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity.
- For additional health benefits, adults should increase their moderate-intensity physical activity to 300 minutes per week, or equivalent.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.

Adults aged 65 years and above
- Should do at least 150 minutes of moderate-intensity physical activity throughout the week, or at least 75 minutes of vigorous-intensity physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity.
- For additional health benefits, they should increase moderate-intensity physical activity to 300 minutes per week, or equivalent.
- Those with poor mobility should perform physical activity to enhance balance and prevent falls, 3 or more days per week.
- Muscle-strengthening activities should be done involving major muscle groups, 2 or more days a week.

The intensity of different forms of physical activity varies between people. In order to be beneficial for cardiorespiratory health, all activity should be performed in bouts of at least 10 minutes duration.
Benefits of physical activity and risk of insufficient physical activity

Regular physical activity of moderate intensity – such as walking, cycling, or doing sports – has significant benefits for health. At all ages, the benefits of being physically active outweigh potential harm, for example through accidents. Some physical activity is better than doing none. By becoming more active throughout the day in relatively simple ways, people can quite easily achieve the recommended activity levels.

Regular and adequate levels of physical activity:
- improve muscular and cardiorespiratory fitness;
- improve bone and functional health;
- reduce the risk of hypertension, coronary heart disease, stroke, diabetes, various types of cancer (including breast cancer and colon cancer), and depression;
- reduce the risk of falls as well as hip or vertebral fractures; and
- are fundamental to energy balance and weight control.

Insufficient physical activity is one of the leading risk factors for global mortality and is on the rise in many countries, adding to the burden of NCDs and affecting general health worldwide. People who are insufficiently active have a 20% to 30% increased risk of death compared to people who are sufficiently active.

Levels of insufficient physical activity

Globally, around 23% of adults aged 18 and over were not active enough in 2010 (men 20% and women 27%). In high-income countries, 26% of men and 35% of women were insufficiently physically active, as compared to 12% of men and 24% of women in low-income countries. Low or decreasing physical activity levels often correspond with a high or rising gross national product. The drop in physical activity is partly due to inaction during leisure time and sedentary behaviour on the job and at home. Likewise, an increase in the use of “passive” modes of transportation also contributes to insufficient physical activity.

Globally, 81% of adolescents aged 11-17 years were insufficiently physically active in 2010. Adolescent girls were less active than adolescent boys, with 84% vs. 78% not meeting WHO recommendations.

Several environmental factors which are linked to urbanization can discourage people from becoming more active, such as:
- fear of violence and crime in outdoor areas
- high-density traffic
- low air quality, pollution
- lack of parks, sidewalks and sports/recreation facilities.

How to increase physical activity?

Countries and communities must take action to provide individuals with more opportunities to be active, in order to increase physical activity.

Policies to increase physical activity aim to ensure that:
- in cooperation with relevant sectors physical activity is promoted through activities of daily living;
- walking, cycling and other forms of active transportation are accessible and safe for all;
- labour and workplace policies encourage physical activity;
- schools have safe spaces and facilities for students to spend their free time actively;
- quality physical education supports children to develop behaviour patterns that will keep them physically active throughout their lives; and
- sports and recreation facilities provide opportunities for everyone to do sports.

Policies and plans to address physical inactivity have been developed in about 80% of WHO Member States, though these were operational in only 56% of the countries in 2013. National and local authorities are also adopting policies in a range of sectors to promote and facilitate physical activity.

WHO response

The “Global Strategy on Diet, Physical Activity and Health”, adopted by the World Health Assembly in 2004, describes the actions needed to increase physical activity worldwide. The Strategy urges stakeholders to take action at global, regional and local levels to increase physical activity.

The “Global Recommendations on Physical Activity for Health”, published by WHO in 2010, focus on primary prevention of NCDs through physical activity. It proposes different policy options to reach the recommended levels of physical activity globally, such as:
- the development and implementation of national guidelines for health-enhancing physical activity;
- the integration of physical activity within other related policy sectors, in order to secure that policies and action plans are coherent and complementary;
- the use of mass media to raise awareness of the benefits of being physically active;
- the surveillance and monitoring of actions to promote physical activity.

To measure physical activity in adults, WHO has developed the Global Physical Activity Questionnaire (GPAQ). This questionnaire helps countries monitor insufficient physical activity as one of the main NCD risk factors. The GPAQ has been integrated into the
WHO STEPwise approach, which is a surveillance system for the main NCD risk factors.

A module to assess insufficient physical activity among schoolchildren has been integrated into the Global school-based student health survey (GSHS). The GSHS is a WHO/US CDC surveillance project designed to help countries measure and assess the behavioural risk factors and protective factors in 10 key areas among young people aged 13 to 17 years.

In 2013, the World Health Assembly agreed on a set of global voluntary targets which include a 25% reduction of premature mortality from NCDs and a 10% decrease in insufficient physical activity by 2025. The “Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020” guides Member States, WHO and other UN Agencies on how to effectively achieve these targets. A sector specific toolkit is under development by WHO to assist Member States implement actions and achieve the targets.

WHO has established several partnerships to help support Member States in their efforts to promote physical activity — these include the United Nations Educational, Scientific and Cultural Organization (UNESCO) and United Nations Sport for Development and Peace (UNOSPD). The 2030 Agenda for Sustainable Development and the commitment made by world leaders to develop ambitious national SDG responses provides an opportunity to refocus and renew efforts at promoting physical activity. WHO is working on a new global action plan, which will leverage the contributions of all relevant sectors, in particular, environment, education, health, sports and technology to accelerate progress in achieving the global voluntary NCD targets set by the World Health Assembly for 2025 and the SDG targets set for 2030.

The plan will provide policy options for Member States, international partners and WHO, and developed in close collaboration with all relevant stakeholders, taking into account current scientific knowledge, available evidence, a review of international experience, innovations, and data.

5. TAENIASIS / CYSTICERCOSIS

**KEY FACTS**

- Taeniasis is an intestinal infection caused by adult tapeworms.
- Three tapeworm species cause taeniasis in humans, *Taenia solium*, *Taenia saginata* and *Taenia asiatica*. Only *T. solium* causes major health problems.
- *T. solium* taeniasis is acquired by humans through the ingestion of tapeworm larval cysts (cysticerci) in undercooked and infected pork.
- Human tapeworm carriers excrete tapeworm eggs in their faeces and contaminate the environment when they defecate in open areas.
- Humans can also become infected with *T. solium* eggs by ingesting contaminated food or water or as a result of poor hygiene.
- Ingested *T. solium* eggs develop to larvae (called cysticerci) in various organs of the human body. When they enter the central nervous system they can cause neurological symptoms (neurocysticercosis), including epileptic seizures.
- *T. solium* is the cause of 30% of epilepsy cases in many endemic areas where people and roaming pigs live in close proximity.
- More than 80% of the world’s 50 million people who are affected by epilepsy live in low and lower-middle income countries.

**Transmission and burden**

Taeniasis is an intestinal infection caused by 3 species of tapeworm: *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm) and *Taenia asiatica*. Humans can become infected with *T. saginata* or *T. asiatica* when they consume infected beef meat or pig liver tissue, respectively, which has not been adequately cooked, but taeniasis due to *T. saginata* or *T. asiatica* has no major impact on human health. Therefore, this factsheets refers to the transmission and health impacts of *T. solium* only.

Infection with the *T. solium* tapeworm occurs when humans eat raw or undercooked, infected pork. Tapeworm eggs pass with the faeces and are infective for pigs. Infection in humans with the *T. solium* tapeworm causes few clinical symptoms. However as well as being infective for pigs, *T. solium* eggs may also infect humans if they are ingested, causing infection with the larval parasite in the tissues (human cysticercosis). This infection can result in devastating effects on human health. The larvae (cysticerci) may develop in the muscles, skin, eyes and the central nervous system. When cysts develop in the brain, the condition is referred to as neurocysticercosis. Symptoms include severe headache, blindness, convulsions, and epileptic seizures, and can be fatal. Neurocysticercosis is the most frequent preventable cause of epilepsy worldwide, and is estimated to cause 30% of all epilepsy cases in in countries where the parasite is endemic.

Cysticercosis mainly affects the health and livelihoods of subsistence farming communities in developing countries of Africa, Asia and Latin America. It also reduces the market value of pigs and cattle, and makes pork unsafe to eat. In 2015, the WHO Foodborne Disease Burden Epidemiology Reference
Group identified *T. solium* as a leading cause of deaths from food-borne diseases, resulting in a considerable total of 2.8 million disability-adjusted life-years (DALYs). The total number of people suffering from neurocysticercosis, including symptomatic and asymptomatic cases, is estimated to be between 2.56–8.30 million, based on the range of epilepsy prevalence data available.

*T. solium* cysticercosis was added by WHO to the list of major Neglected Tropical Diseases (NTDs) in 2010 with NTD roadmap goals of making available a validated strategy for control and elimination of *T. solium* taeniasis/cysticercosis and those interventions to be scaled up in selected countries by 2020.

**Symptoms**

Taeniasis due to *T. solium, T. saginata* or *T. asiatica* is usually characterized by mild and non-specific symptoms. Abdominal pain, nausea, diarrhoea or constipation may arise when the tapeworms become fully developed in the intestine, approximately 8 weeks after ingestion of meat containing cysticerci.

These symptoms may continue until the tapeworm dies following treatment, otherwise it may live for a number of years. It is considered that untreated infections with *T. solium* tapeworms generally persist for 2–3 years.

In the case of cysticercosis due to *T. solium*, the incubation period prior to the appearance of clinical symptoms is variable, and infected people may remain asymptomatic for many years.

In some endemic regions (particularly in Asia), infected people may develop visible or palpable nodules (a small solid bump or node that can be detected by touch) beneath the skin (subcutaneous). Neurocysticercosis is associated with a variety of signs and symptoms depending on the number, size, stage, and location of the pathological changes as well as the host’s immune response, but can also be clinically asymptomatic. Symptoms may include chronic headaches, blindness, seizures (epilepsy if they are recurrent), hydrocephalus, meningitis, dementia, and symptoms caused by lesions occupying spaces of the central nervous system.

**Treatment**

Taeniasis can be treated with praziquantel (5–10 mg/kg, single-administration) or niclosamide (adults and children over 6 years: 2 g, single-administration after a light meal followed after 2 hours by a laxative; children aged 2–6 years: 1 g; children under 2 years: 500 mg).

In neurocysticercosis, since the destruction of cysts may lead to an inflammatory response, treatment of active disease may include long courses with praziquantel and/or albendazole, as well as supporting therapy with corticosteroids and/or anti-epileptic drugs, and possibly surgery. The dosage and the duration of treatment can vary greatly and depend mainly on the number, size, location and developmental stage of the cysts, their surrounding inflammatory edema, acuteness and severity of clinical symptoms or signs.

**Prevention and control**

To prevent, control and possibly eliminate *T. solium*, proper public health interventions with an approach spanning veterinary, human health and environmental sectors are required. Eight interventions for the control of *T. solium* can be used in different combinations designed on the basis of the context in the countries:

- mass drug administration for taeniasis;
- identification and treatment of taeniasis cases;
- health education, including hygiene and food safety;
- improved sanitation;
- improved pig husbandry;
- anthelmintic treatment of pigs (Oxfendazole at doses of 30 mg/kg – commercially produced and registered for the treatment of cysticercosis in pigs);
- vaccination of pigs (TSOL18 vaccine – commercially available); and
- improved meat inspection and processing of meat products.

Reliable epidemiological data on geographical distribution of *T. solium* taeniasis/cysticercosis in people and pigs is still scarce. Appropriate surveillance mechanisms should enable new cases of human or porcine cysticercosis to be recorded in order to help identify communities at high risk and focus prevention and control measures in these areas.

**WHO’s role**

Working with veterinary and food safety authorities as well as with other sectors is essential to attaining the long-term outcomes of reducing the burden of disease and safeguarding the food value chain. The WHO Neglected Tropical Diseases (NTDs) team is working closely with other WHO departments in the areas of mental health, research and development, food safety, water, and sanitation, as well as partner agencies such as the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) to meet the needs for interdisciplinary collaboration to control *T. solium*, with the final goal to prevent human suffering due to neurocysticercosis.

To meet the need for clear guidance on a step-wise approach for the development of control programmes, WHO with countries and key partners has taken the
first steps towards identifying the “best-fit” strategy to interrupt transmission of *T. solium* and improve case detection and management of neurocysticercosis using the tools currently available.

Improved, simple, cost-effective and rapid diagnostic tools are still needed for use in field conditions to detect *T. solium* carriers as well as human and porcine cysticercosis cases, and to direct programme planning and monitoring. In December 2015, a stakeholder meeting on *T. solium* taeniasis/cysticercosis diagnostic tools was held at WHO headquarters to address the lack of a suitable diagnostic toolbox for taeniasis, cysticercosis and neurocysticercosis.

WHO programmes for the control of neglected tropical diseases and of mental health are also steering the development of evidence based standard guidelines for diagnosis and treatment of *T. solium* neurocysticercosis to support clinical management and inform national policies and programmes.

Several countries are mounting pilot programmes with the available tools while conducting operational research to measure impact and refine strategies. More countries are interested in joining the WHO network for the control of taeniasis/cysticercosis. Robust surveillance data is fundamental to assess disease burden and to evaluate progress. As for other neglected diseases which occur in underserved populations and remote areas, data is especially scarce. WHO counters this situation by collecting and mapping data on *T. solium*, and risk factors associated with the occurrence of the parasite, like information on pig keeping, food safety and sanitation.

Sustainable funding and anthelmintic drug donations are urgently needed to progress towards the control goals of *T. solium*. 