KMJ
KUWAIT MEDICAL JOURNAL
The Official Journal of The Kuwait Medical Association

EDITORIAL

REVIEW ARTICLE

ORIGINAL ARTICLES

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KU ISSN 0023-5776

Continued inside

Vol. 45 No. 2 JUNE 2013

KUWAIT MEDICAL JOURNAL

CONTENTS

Continued from cover

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PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13013 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

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Kuwait Medical Journal (KMJ)

Published by the Kuwait Medical Association

Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

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P.O. Box: 1202, 13013-Safat, Kuwait
Telephone: (00-965) 1881181(Ext. 201) - Fax: (00-965) 25317972, 25333276
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Book chapter

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U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed June 4, 2003, at http://www.house.gov/reform/min/inves.tobacco/index_accord.htm.)

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Editorial

Fibrothorax: A Preventable Condition

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Kuwait Medical Journal 2013; 45 (2): 95 - 96

Fibrothorax represents the most severe form of pleural fibrosis. The term indicates dense fibrosis of the visceral pleura leading to fusion of both the visceral and parietal pleura. As a result, there is contracture of the involved hemithorax and decreased expansion of the lung and thoracic cage due to progressive pleural fibrosis and symphysis of the pleural surfaces[1]. This condition can result from a variety of inflammatory processes including infection (parapneumonic effusion/empyema, tuberculous pleurisy), traumatic hemothorax that has clotted, in association with a neglected malignant pleural effusion, post-coronary bypass surgery, rheumatoid pleurisy and uremic pleurisy. The development of pleural fibrosis follows severe pleural space inflammation which is associated with an exudative pleural effusion[1]. There is influx of cytokines which facilitate the fibrin matrix formation. This is an exudative process in which a proteinaceous peel is permitted to develop over the lung and this peel prevents the lung's re-expansion[1,2]. This contemporary clinical problem continues to challenge the thoracic surgeon.

Complicated parapneumonic effusions with loculated empyema are still a continuing problem and early operative intervention should be seriously entertained in those cases where standard tube drainage is ineffective. Suboptimal management of the inflammatory conditions because of inadequate antibiotic therapy or inadequate drainage or both can result in a trapped lung[3]. Pleural infection is a serious respiratory pathology caused by:

1. Community-acquired pathogens; Streptococcus species, *Staphylococcus aureus*, anaerobes and mixed species
2. Hospital-acquired pathogens; Staphylococcus species, Gram-negative aerobes and anaerobes.

All patients should receive antibiotics and this should be guided wherever possible by bacterial culture results. A prolonged antibiotic course may be necessary and can be administered as an outpatient[4].

Drainage of infected pleural collections is indicated in the following circumstances: frank-purulent effusion, turbid or cloudy effusion, presence of organisms by sampling, fluid with a pH < 7 and loculated parapneumonic effusion[4]. A small-bore pleural catheter 10 - 14 F will be adequate for draining most of the cases of parapneumonic effusions. To date, there are no randomized studies comparing the efficacy of small versus large chest tubes[5].

The use of intrapleural tissue plasminogen activator as an intrapleural fibrinolytic may represent a promising treatment option that demonstrated efficacy in complicated pleural fluid collection[6]. The benefit is due to disruption of septations associated with pleural infection, release of infected fluid more effectively and avoiding the need for surgery. The First Multi-center Intrapleural Sepsis Trial (MIST1) assessed the effect of streptokinase on pleural infection in adults. The primary end point of the study (resolution of chest radiograph) showed lack of efficacy for streptokinase[7]. The recently published MIST 2 trial is designed as a double placebo-randomized controlled trial with four treatment arms, comparing intrapleural tissue plasminogen (tPA) and DNasease, tPA and placebo, placebo and DNase and double placebo. The results of the primary outcome which is improvement in chest radiograph demonstrated a significant improvement with combination of tPA and DNase compared with placebo, with no significant effect using either agent alone[8].

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The perception for open intervention is sometimes received with distress particularly when young patients and or young physicians are involved. The increase in pulmonary function following an effective decortication has been documented for a long time. Early surgical intervention has improved the outcome and has a shorter hospital stay. Video-assisted thoracoscopic surgery (VATS) has a significant impact on surgical management of pleural infection[9]. To date 14 papers were identified and provide best evidence that VATS decreases the length of hospital stay and lowers postoperative complications. However, it provides equal resolution of disease to thoracotomy[10].

The advent of effective antituberculous drug therapy and drainage of tuberculous pleural effusion should bring the visceral pleura into opposition with the parietal pleura and prevent the development of fibrothorax. There was insufficient evidence to support the use of systemic steroids in tuberculous pleurisy[11].

The advances in thoracic trauma and early drainage of hemothorax prevent the formation of clots and peel. In addition to the use of intrapleural fibrinolytic therapy and thoracoscopy, fibrothorax occurs in less than 1% of hemothorax cases[12].

Fibrothorax resulting from a malignant pleural effusion usually suggests a much delayed diagnosis or a failure to gain early and adequate control of the pleural space. If a peel has been allowed to form over the lung, a decortication may be necessary to produce adequate re-expansion of the lung and such an operation in that setting carries significant risk for a short-term gain[1].

In conclusion, patient's drug compliance status and physician's adequate care for pleural drainage is important in the prevention of pleural fibrosis and fibrothorax. Strict adherence to the principle of complete drainage may require insertion of several chest tubes. Fibrinolytic therapy is potentially beneficial in adults. The use of VATS to deal with multiple located pleural fluid collections will usually eliminate lung entrapment, fibrothorax and the need for decortication.

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Review Article

New Perspectives in Klinefelter Syndrome

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Kuwait Medical Journal 2013; 45 (2): 97 - 107

ABSTRACT

Histopathology of the testes in Klinefelter syndrome (KS) (47, XXY- no mosaicism) is characterized by complete fibrosis and hyalinization of seminiferous tubules, resulting in azoospermia and failure of fatherhood. This occurs through a gradual process that begins in the fetus, progresses through infancy and accelerates dramatically at the time of puberty. But recently with amniocentesis and study of aborted fetuses in different stages, seminiferous tubules showed germ cells. Therefore, new salvages have been undertaken recently for gonosomes in these patients. One method involves cryopreservation of sperms in school-age boys at the age of 11 - 15 years having testicular volumes between 2 - 4 ml.
Another salvage process attempts to pick patients with low-grade mosaicism who may have normal cell line and isolated foci of spermatogenesis in their seminiferous tubules. This is done by analyzing 150 well-spread G-banded metaphases instead of the usual 20 or less metaphase spreads and increasing the number of cells analyzed either by karyotyping or by FISH in interphase nuclei. This is a good marker for intracytoplasmic sperm injection.
Another complication of KS is precocious osteoporosis which was believed to be due only to early onset of testosterone deficiency. However, reduced bone mass might be present also in KS men with normal testosterone levels and even with testosterone replacement therapy. Possible new determinants for osteoporosis in KS might be related to the androgen receptor (AR) function and insulin-like factor 3 (INSL3) levels.

KEY WORDS: germ cells, Klinefelter syndrome, osteoporosis, sperms

INTRODUCTION

Klinefelter syndrome (KS) is a genetic disorder in which there is at least one extra X chromosome to a normal human male karyotype. The non-mosaic karyotype of 47, XXY constitutes 80% of cases and is known also as the classical or pure form. It is characterized by gynecomastia, small, firm testis with hyalinization of seminiferous tubules, hypergonadotrophic hypogonadism and azoospermia[1]. As its clinical presentation may be subtle, many of those affected may be unaware or diagnosed only during evaluation for hypogonadism and / or infertility. It is the most common sex chromosomal disorder and is usually acquired through non-disjunction during maternal or paternal gametogenesis[2]. In the general population, its prevalence is 0.1 - 0.2%[2] and it affects up to 3% of infertile men and 11% of men with azoospermia[3]. It is the commonest cause of testicular failure which results in impairment in both testosterone production and spermatogenesis[4].

Clinical characteristics of Klinefelter syndrome

During childhood period a KS male presents learning disabilities, verbal cognitive deficits, speech difficulties and trouble in spelling, reading and mathematics. In this respect, KS males are at higher risk of behavioral disorders and psychiatric problems than the general population[5]. The onset of puberty in KS boys is usually spontaneous and occurs at the expected age. However, from adolescence onwards, the testes become increasingly firm and never reach the size observed in normal adults with features of eunuchoidism and gynecomastia. This situation results in sparse facial, body and genital hair[5]. In early adulthood the most frequent problems leading to diagnosis may be infertility and / or azoospermia[2]. Later in life signs of hormonal testicular failure, such as sexual dysfunction, and co-morbidities such as endocrine, metabolic and cardiovascular diseases, osteoporosis and autoimmune diseases may also lead to the diagnosis of KS[6].

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The adult KS phenotype is typically characterized by tall stature, narrow shoulders, broad hips, sparse body hair, gynecomastia, small and firm testes. Several cross-sectional studies found a strong correlation between circulating testosterone and cardiovascular risk factors due to the effect of androgens on adipose tissue, insulin sensitivity, endothelial function, vascular tone, atherosclerosis and left ventricular dysfunction. Hypogonadism in KS may lead to an elevated incidence of metabolic syndrome, diabetes mellitus and cardiovascular diseases[7]. Finally, hypoandrogenism developing later in life in undiagnosed KS could precipitate sexual dysfunction and mood disorders and deeply affect quality of life[8].

Autoimmunity and Klinefelter syndrome

Adults with KS have an increased risk of several autoimmune disorders including systemic lupus erythematosus (SLE), thyroid disease, rheumatoid arthritis, Sjogren syndrome and diabetes mellitus[9]. Although treatment of these disorders would usually be the same as that in the general population, a specific response to testosterone treatment may be found. SLE, which predominately affects women, deserves special mention. Males with KS appear to be at a risk of SLE similar to females, and 14 times higher than in normal males[10]. This increased risk may be related to a gene dose effect for the X chromosome and can be explained by the effect of CD40L. This is a T cell co-stimulatory molecule that plays an important role in B cell activation through ligation with CD-40. CD40L is over-expressed on both T cell surface and in the serum in lupus patients. Serum CD40L levels correlate with both anti-dsDNA production and disease severity in lupus patients. The gene encoding for CD40L is located on the X chromosome. Gene dose balance of CD40L expression is maintained by random X chromosome inactivation in female cells which is achieved by heavy DNA methylation. Such gene escapes inactivation in patients with lupus leading to hyper-expression of CD40L due to a gene dose effect[11].

HISTOPATHOLOGY OF KLINEFELTER TESTIS DURING DEVELOPMENT

The fetal period

From the studies of fetuses aborted at a gestational age of 18 - 22 weeks, the degenerative process has already started at this early stage. Thus, a significantly reduced number of germ cells were seen in studies of testicular biopsies from 47, XXY midterm fetuses, whereas the density and number of testicular tubules and mesenchymal structures appeared normal[12-14].

Neonatal period

The testosterone levels were significantly lower from birth to eight months in infants with KS, suggesting an already impaired Leydig cell function at this early age. By contrast, LH, FSH, inhibin B and Anti-Mullerian Hormone (AMH) levels were normal. In accordance with the normal histology of the Sertoli cells as reported in earlier studies, this finding suggests that the Sertoli cells are qualitatively and quantitatively normal in 47, XXY children in infancy[15].

The childhood and adolescence

All studies have shown preservation of seminiferous tubules with a reduced number of germ cells, whereas the Sertoli cells and Leydig cells have appeared normal and of juvenile type[16]. The biopsies of pre- and peripubertal boys showed germ cells, but the number of spermatogonia present was markedly reduced and no meiotically dividing germ cells or postmeiotic spermatids appeared in any of the biopsies[17,18].

As the KS boys entered puberty, their testis initially grew up to a volume of 6 ml. However, as serum-testosterone levels increased, the depletion of germ cells, the hyalinization of the tubules, the degeneration of the Sertoli cells and the hyperplasia of the Leydig cells accelerated[18]. This was associated with a decrease in the testis volumes to a prepubertal size of 2 - 4 ml[19]. The degeneration process was accompanied by a relative Leydig-cell insufficiency reflected by impaired serum testosterone levels and increasing LH levels.

Adult life

As described by Klinefelter in 1942, the histology of the testes is characterized by extensive fibrosis and hyalinization of the seminiferous tubules, and hyperplasia of interstitium in the adult patient[1]. Foresta and colleagues studied ten 47, XXY males aged 28 - 37 years and found Sertoli-cell-only pattern in eight of ten biopsies, whereas the remaining two showed Sertoli cells and few spermatogenic cells[20]. In 1969, Skakkebaek[21] described two types of tubules in relation to Sertoli cell morphology containing either small immature Sertoli cells (chromatin positive) or larger and more differentiated Sertoli cells (chromatin negative). Later, these immature Sertoli cells were studied further and were found to have an impaired physiological activity resulting in a compromised protein and steroid hormone synthesis[22].

Infertility and fertility potential in KS

A dissociated gonadal dysfunction with lack of sperm in semen and reduced testis volume, reflecting a severe disorder of the seminiferous tubules, with normal / low testosterone levels, indicating a mild dysfunction of the interstitial compartment, was described in the initial report by Klinefelter and colleagues[1]. Other recent reports[18,23], further indicate that the establishment of the dysfunction of the

seminiferous tubule components is also dissociated. In fact, germ cells are already affected in early postnatal life while Sertoli cells secrete normal levels of AMH and inhibin B until mid-puberty. Similarly, Leydig's cells seem to produce androgens normally until mid-puberty; thereafter, although androgen levels might be within the normal range in a proportion of patients with KS, there is an increase in LH, indicating a suboptimal Leydig cell functional capacity. Pacenza *et al*[23], showed that FSH levels are increased approximately one year before LH levels during puberty in patients with KS, which suggests that Sertoli cell function is affected not only more severely than that of Leydig's cells but also earlier.

However it is believed that some spermatogonia in Klinefelter subjects are capable of completing the spermatogenic process leading to the formation of mature spermatozoa[24]. The fact that the germ-cell degeneration accelerates dramatically at the onset of puberty makes it tempting to retrieve germ cells at an earlier age for cryopreservation and future utilization[25].

OTHER FEATURES OF THE KLINEFELTER PHENOTYPE

One gene that is of physiological importance in the testis is the androgen-receptor gene (AR, mapped to Xq11.2-12). The AR gene contains a polymorphic stretch of CAG repeats in exon 1. That the length of this stretch is inversely related to the receptor's basal and ligand-induced activity *in vitro* and may influence physiological response to androgens[26,27], demonstrated that Klinefelter males with a longer CAG repeat tend to be more severely affected than those with a shorter CAG stretch in the AR. This association was found in relation to socio-educational status, growth pattern, bone density and occurrence of gynecomastia. The effect of testosterone treatment was also correlated to the length of the CAG repeat in the AR. Males with short repeats responded to testosterone substitution with a more pronounced suppression of LH and larger increment of testosterone levels than males with longer CAG repeats in the AR. The variation in the CAG length can, at least partially, explain the variation in the Klinefelter phenotype, as this polymorphism was linked to variability in some androgen-dependent functions in normal healthy 46, XY males[26]. Many Klinefelter males present the classical hypogonadal phenotype even though they have testosterone levels in the low normal range. This might reflect some degree of androgen resistance as suggested by the high-normal LH levels as well as from the demonstrated associations between number of the CAG repeats in the AR and phenotypical characteristics in Klinefelter males.

WHAT ARE THE MECHANISMS OF GERM CELLS DEPLETION?

One of the fundamental questions is whether the abnormal karyotype affects primarily germ cells or somatic cells in the testis, in particular Sertoli cells, which are thought to be main mediators of signals from the outside to the germ-cell compartment. Leydig cells may also be affected, and it is therefore probable that the testicular phenotype is a result of impaired function and interaction of several cell types.

1. Gene dosage and X- chromosome inactivation

The vast majority of the 47, XXY patients never experience meiosis, and their germ cells disappear at the mitotic stage of spermatogonia or during earlier differentiation. Therefore, a predominant hypothesis is that the altered dosage of some genes on X chromosome may affect the development and / or degeneration of the germ cells in males with 47, XXY[28].

It is well known that in females, one of the two X chromosomes is randomly inactivated in the somatic cells to obtain a gene dosage, which is equivalent to that in males. Although many genes escape inactivation, the inactivated X chromosome is microscopically visible as the Barr body (sex chromatin) in female cells[29]. The inactivation of an extra X chromosome in human somatic cells is mediated primarily by a RNA product from the gene called X-inactive-specific transcript (XIST) located on the long arm of the inactive X chromosome[30]. Therefore, the expression of XIST is a marker of the presence of the second and any further extra X chromosomes in the somatic cell[31]. Somatic cells in the males with 47, XXY inactivate the supranumerary X chromosomes most probably in the same manner as the somatic cells in females. XIST is expressed in blood cells of Klinefelter men but not in the blood of healthy men with normal karyotype[32]. The Barr body was also found in Leydig and undifferentiated Sertoli cells in males with KS[33].

Moreover, some of the X-chromosome genes are expressed in somatic cells in the testis, and that increased expression of those that escape inactivation may affect the germ cells[34]. Among the interesting genes to look at from this perspective, are, *e.g.*, a gene encoding p120, a putative inhibin-binding protein (mapped to Xq24)[35], or the angiotensin type-II receptor gene, AT2 (Xq21.3). The AT2 receptor may be of particular interest with regard to the quickly progressing demise of germ cells in Klinefelter males, because it mediates apoptosis in some cell types and is considered to be involved in the physiological atresia of ovarian follicles[36].

2. Apoptosis

Apoptosis is a mechanism responsible for the physiological regulation of germ-cell death during

differentiation and maturation of normal human germ cells and could contribute to the excessive germ-cell demise in males with 47, XXY. Apoptosis is a prerequisite for continuous spermatogenesis[37], by selectively removing dysfunctional or damaged germ cells, and by limiting germ cell number[38]. FSH inhibits male germ-cell apoptosis in cultured rat seminiferous tubules partially *via* stem-cell factor (SCF) produced by Sertoli cells and interacts with the c-kit receptor in the germ cells[39]. The hypothetical malfunction of the FSH receptor might lower the SCF expression and thereby influence the ratio of pro- and anti-apoptotic factors early in development forcing the germ cells to undergo apoptosis.

Since estrogen receptors are present in the pituitary and spermatogenic cells, studies demonstrated using both *in vitro* and *in vivo* models that estrogen induces apoptosis in germ cells through the upregulation of Fas / FasL and that FasL-mediated signal can emanate from different generations of germ cells[40,41].

Estrogens are potential regulators of male reproduction and germ-cell death. Low concentrations of estradiol effectively inhibit male germ-cell apoptosis in the cultured human seminiferous tubules[42]. Estrogens can also cause alterations in circulating concentrations of gonadotrophins and testosterone and thus affect apoptosis in germ cells indirectly[43].

While testosterone is produced by Leydig cells, the androgen receptor has been detected in Sertoli, Leydig and peritubular cells, but not in germ cells[44]. Endocrine hormones such as testosterone and the gonadotropins (FSH and LH) have long been known to influence germ cell fate[45]. Their removal induces germ cell apoptosis in an indirect fashion, as their receptors are only located on somatic cells[46].

Testosterone deficiency has been shown to cause apoptosis induction of preleptotene and pachytene spermatocytes at stage VIII as well as sloughing of round spermatids at steps 7 - 8 due to failure of Sertoli cells to produce the adhesion molecule N-cadherin. Consistent with this idea, FSH, testosterone and SCF withdrawal lead to elevated ratios of Bax / Bcl-w and Bak / Bcl-w, which correlate with increased apoptosis of spermatogonia and spermatocytes[47].

Another supportive study has revealed that *in vitro* testosterone withdrawal increases DNA fragmentation and caspase activity in human Sertoli cells, but the effect on germ cells is minor[48].

The Bcl2 modifying factor (Bmf) is a pro-apoptotic member of the Bcl2 family of apoptosis-related proteins. It was suggested that Bmf is likely to play an important role in germ cell death in response to reduced intratesticular testosterone. It was demonstrated that when a cell's actin cytoskeleton is perturbed as a consequence of loss of adhesion of the cell from its basal lamina, Bmf is released from the actin / myosin complex and is translocated to the mitochondria and leads to the expulsion of cytochrome C from the inner mitochondrial membrane and into the cytoplasm. This, in turn, activates a caspase cascade, ultimately leading to the death of the cell[49].

Fertility and mosaicism

Advanced reproductive techniques have offered hope to many infertile couples. ART / ICSI have revolutionized the management of severe male factor infertility. Several successful pregnancies in Klinefelter patients have been reported[2].

Diagnosis of Klinefelter is often made in adults; however, it will be of great value to diagnose this condition as early as possible for example by measuring the size of testes in school going boys at the age of 11 - 15 years and by carrying out the chromosomal examination in boys with testicular volume less than two ml. The best time to start testosterone therapy is around the age of 11 - 12 years when there is marked increase in FSH levels[50]. Such screening methods could be carried out readily as a part of prophylactic examination procedures by school physicians in most countries. This may allow future fertility to be preserved for young Klinefelter patients because germ cell depletion may progress with age. Karyotyping of well spread G-banded metaphase of peripheral blood is still the gold standard for the diagnosis of chromosomal abnormalities. But several studies have reported deficits of this technique[51,52]. Counting of 15 - 20 well spread G-banded metaphase may fail to identify low-level of gonosomal mosaicism in these cases.

However, by counting 150 metaphases, low-level mosaicism could be found, which was not identified by counting few metaphase spreads as in conventional cytogenetics. Such type of mosaicism may be present in the germ cell of these cases and such germ cells with normal 46, XY cell line could be used for testicular epididymal sperm aspiration in ART / ICSI. Such cases should be followed up by pre-implantation genetic diagnosis[34].

However, Garcia-Quevedo *et al*[53] suggested that for the diagnosis of 'pure KS', it is advisable to increase the number of cells analyzed either by karyotyping or by FISH in interphase nuclei. The observation of different percentages of 46, XY cells in the analyzed tissues indicates that the degree of mosaicism is not uniform. It was demonstrated that even in cases of a low percentage of mosaicism in peripheral blood (10%), the patients present degrees of germinal mosaicism (36%) and this inferred that the analysis of lymphocytes is not a good indicator of the testicular status. The degree of mosaicism can help us to understand the reason for the variable response that some patients with KS show when faced with different

therapies (treatments with aromatase inhibitors, hCG or clomiphene citrate). It has been reported that 77% of the patients who show blood concentrations ≥ 250 ng / dl testosterone after treatment have successful sperm retrieval[54]. It could be hypothesized that the Sertoli 46, XY cells which would respond to the testosterone levels, recovering the functions of nursing, and the progression of spermatogenesis would depend on the percentage of Sertoli XY cells which colonize the seminiferous tubules[53]. The origin of mosaicism in germinal cells has been attributed to the occurrence of 'correcting mitotic errors' associated with the mitotic proliferation of the primordial germinal cells in the fetal testicle[55] and also of the spermatogonia in adult tissue[56] giving rise to isolated zones of euploid cells. These corrective processes would also have occurred in the other cell types, causing different degrees of mosaicism in each one. On the other hand, it has been described that the lack of inactivation of genes of the X supernumerary affects the germinal cells as well as somatic cells at different levels[34]. In the mouse model, Sertoli XXY cells show low levels of expression of androgen receptor (AR)[57]. In human males, a delay in disappearance of anti-Mullerian hormone expression coupled with the up-regulation of AR has been described, and it is known that both are required for the last step of Sertoli maturation during puberty[58]. This, together with an altered activation pattern of apoptosis because of the hypergonadotrophic hypogonadism[34] suggests that the degeneration of the Sertoli cells would preferentially affect the XXY cells, raising the relative proportion of the XY cells. Thus, the maintenance of the mosaicism or degeneration of the aneuploid line would be determined by the presence of two functional X chromosomes. A significant incidence of aneuploidies in postreductional cells was observed[53], giving support to the hypothesis that an altered testicular environment compromises the meiotic progression of the 46, XY cells[59].

Intracytoplasmic sperm injection (ICSI): can transgenerational transfer of pathology be an issue?

Concerns and controversy over the safety of KS individuals using their own gametes for assisted reproduction have been raised, and several studies have focused on the analysis of the chromosome constitution of these patients' germ cells (reviewed by[60]). All reports published to date are in agreement in describing increases in sex chromosome abnormalities and hyperhaploidies in the post-reductional germ cells from 47, XXY and 46, XY/47, XXY individuals[20,61-63]. The origin of these abnormalities has been related to the possible meiotic progress of the 47, XXY germ line [21]. This hypothesis has been supported by some authors[64,65] based upon the deviation in the X / Y sperm ratio (in favour of X-bearing spermatozoa) and the presence of equivalent percentages of XX and XY sperm hyperhaploidies. However, most studies do not agree with these results but rather maintain that in KS individuals the only cells that progress through meiosis are 46, XY cells[62,24,56], thus indicating that patients with spermatogenic patches are individuals whose testicular tissue is mosaic. Therefore, the cytogenetic abnormalities observed in post-reductional germ cells must result from the abnormal meiotic progression of 46, XY spermatocytes in the compromised testicular environment, which is distinctive in patients with KS[59]. The alteration of the testicular environment has been related to abnormal hormone levels and to the dysfunction of testicular somatic cells[66]. It has been suggested that the nursing function of XXY Sertoli cells may not be as effective as those of XY cells[56]. Thus, the mosaicism level in the testicular tissue, not only concerning germ cells but also for somatic cells, could be of relevance for the final outcome of spermatogenesis in KS and could have practical implications for the clinical management of these individuals. Because the analyzed number of pregnancies from KS fathers is still low with around 200 cases, all of which are, of course, achieved by ICSI which in itself bears a slightly higher risk for chromosomal aberrations, final conclusions cannot be drawn.

Contemporary directions in management of infertility in KS patients

Since germ cell depletion starts with the onset of puberty, testicular tissue banking at early puberty may be a strategy to preserve the fertility of these patients. Cryopreservation of spermatogonial stem cells (SSCs) prior to stem cell loss is currently offered to boys undergoing gonadotoxic treatments, which may render them sterile[67]. After chemo- or radiotherapy, the frozen–thawed SSCs can be reintroduced in the patient's own testis by SSC transplantation. However, since KS testes are characterized by extensive fibrosis and hyalinization of the seminiferous tubules, the ultimate use of the frozen tissue will be different. For KS boys, *in vitro* maturation of SSCs might be considered. So far, *in vitro* spermatogenesis of human SSCs has not been possible, but this technique might become an option in the near future since the *in vitro* differentiation of mouse SSCs up to mature sperm cells has recently been reported[68,69]. Unfortunately, 10% of KS patients are diagnosed before puberty, explaining the limited experience on testicular tissue banking in KS adolescents[70].

Osteoporosis in men

Osteoporosis is defined according to measurement of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DEXA). The commonly used BMD-based operational definition of osteoporosis has

been validated for white post-menopausal women only and there is no consensus regarding a BMD-based definition of osteoporosis in men. However, it is generally accepted that a bone density T-score at or below 2.5 standard deviations (SD) below normal peak values for young adults defines osteoporosis, whereas a T-score between -1 and -2.5 SD defines osteopenia. For younger men both T-score and Z-score could be used for the diagnosis of low BMD, with a Z-score <2 SD below the gender- and- age specific population mean identifying osteoporosis[71].

Testosterone regulates male bone metabolism both indirectly by aromatization to estrogens and directly on osteoblasts through the androgen receptor (AR). The net effect of testosterone is to promote periosteal bone formation mostly during puberty[72] and to reduce bone resorption mostly during adult life[73]. The final effect of androgens on the bone is to maintain cancellous bone mass and to increase bone size by stimulation of both longitudinal and radial growth. This leads to higher bone size and bone strength compared with women. The AR pathway is particularly effective in the trabecular bone where androgens preserve or increase trabecular numbers, suppress trabecular resorption and reduce trabecular spaces thereby increasing trabecular bone volume[74]. AR knockout mice have prevalent decrease in trabecular bone[75] and patients with AR mutations show a reduced bone mass[76]. On the other hand, cortical bone is affected when both AR and estrogen receptor disruption occur[75], whereas bone loss from estrogen deficiency is mostly evident at the cortical level[77]. Testosterone is fundamental in a critical stage of bone maturation to reach the peak bone mass at the end of puberty and to keep it during adult life. A deficiency in testosterone production during puberty is an important risk factor for precocious male osteoporosis. In fact, premature male osteoporosis is usually associated with hypogonadism, as observed in KS, idiopathic hypogonadotropic hypogonadism or delayed puberty and in hyperprolactinemia[78]. A positive correlation between BMD and testosterone levels has been demonstrated in normal men, osteoporotic men and in KS[79]. It has also been reported that both serum levels of testosterone and luteinizing hormone (LH) show a significant association with osteoporosis or fractures[80]. Interestingly, LH was directly related to a positive influence on bone metabolism in men: LH receptors are present on osteoblasts and LH receptor knockout animals showed age dependent bone loss[81]. Moreover, there are connections between testosterone and the vitamin D pathway. It is well known that vitamin D is an important factor in bone metabolism and vitamin D levels less than 62.5 mmol / l are associated with an increased risk of hip fracture in men older than 65 years[82]. Testosterone acts indirectly on the parathyroid hormone-vitamin D axis, because testosterone deficiency is related to a reduction in renal 1α-hydroxylase activity with a subsequent decrease in 1, 25-hydroxy vitamin D concentration, the active form of vitamin D[83].

Osteoporosis in KS

KS subjects develop a progressive testicular failure leading to primary hypogonadism. Such a deficiency in testosterone production during puberty represents the most important risk factor for reduced bone mass and osteoporosis in KS. However, several studies showed that testosterone replacement in KS men with low testosterone levels and low BMD does not reverse the decreased bone mass[84]. This was more evident when testosterone replacement therapy was started after puberty and also after many years of therapy[85]. On the contrary, another study showed that androgen replacement therapy starting in young age (*i.e.*, before 20 years) can lead to normal BMD[86]. Of particular interest is the finding of reduced bone mass also in KS subjects with normal testosterone levels[79], suggesting that bone loss in KS might be, at least in part, independent from the presence of hypogonadism. Vitamin D levels in KS have their own impact. It has been shown that 25-hydroxy and 1,25-hydroxy vitamin D are in the low-normal range in KS subjects and that the rate of gain of BMD in the femoral neck after ibandronate therapy was closely related to 25-hydroxyvitamin D, highlighting the importance of vitamin D insufficiency or deficiency in response to therapy[87].

Treatment of osteoporosis in KS

General measures include lifestyle and dietary recommendations: exercise, a balanced diet and sun exposure should be encouraged, whereas excessive alcohol intake and smoking should be discouraged. Men with hypogonadism, including KS, should receive substitutive testosterone treatment. On the other hand, there are currently no indications for testosterone substitution in men with low BMD and normal testosterone levels. More research is needed in this field in the light of the high LH levels and clinical signs of hypogonadism that are quite invariably present in KS subjects despite testosterone levels in the low-normal range. Current recommendations in men with normal testosterone levels suggest the use of bisphosphonates as primary therapy. In subjects with low testosterone levels testosterone replacement therapy should be associated with an oral bisphosphonate that helps in achieving and maintaining the increase in BMD[88].

Although there are conflicting results on benefits of calcium and vitamin D supplementation, a calcium intake of 1000 - 1200 mg per day (1200 – 1500 mg if osteoporosis is present) and vitamin D supplementation (800 IU or calcitriol 0.50 mg per day) should be

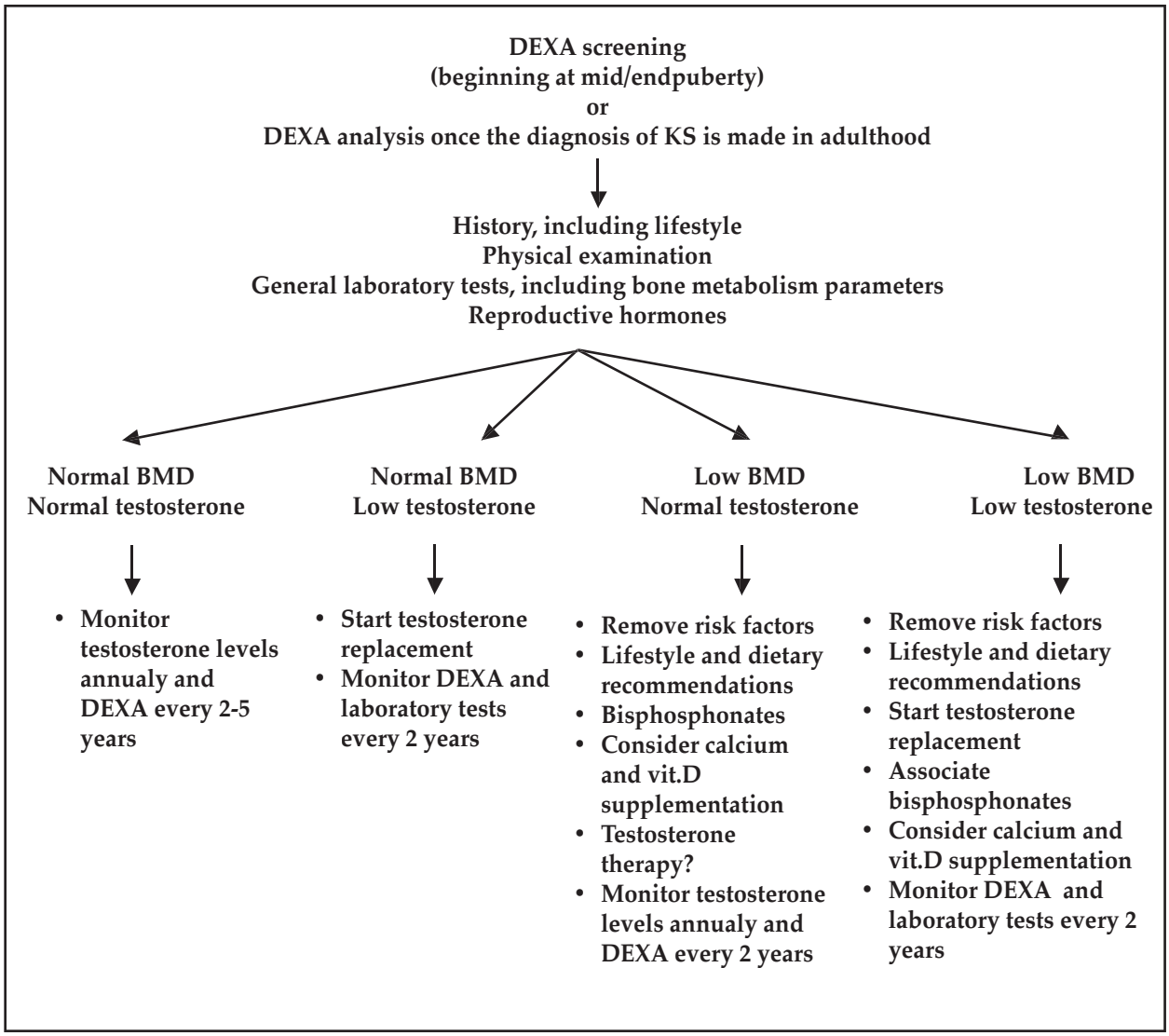

Fig. 1: Possible diagnostic and therapeutic flow chart for reduced bone mass in KS. See text for details. Evidence-based data for the treatment of osteoporosis is sparse. DEXA: dual-energy X-ray absorptiometry; BMD: bone mass density.

recommended. Finally, therapy with parathyroid hormone (*i.e.*, teriparatide) could be considered in both hypogonadal and eugonadal men to increase BMD of the spine reducing the risk of vertebral fractures, even if data about effects on non-vertebral fractures in men are lacking[89]. This treatment is recommended only for severe osteoporosis and in those who do not tolerate bisphosphonates or do not show an adequate response to them[90] (Fig.1).

INNOVATIVE DIRECTIONS

The first exon of the AR gene encodes for the transactivation domain of the AR protein. It contains the highly polymorphic CAG repeat, the length of which is inversely correlated with androgen sensitivity[91]. Although the length of CAG repeat has been associated with different disorders (male hypogonadism, cryptorchidism, prostate cancer, testicular cancer), another important aspect of AR is that the AR gene is located on the X chromosome (and therefore present in double copy in KS) and there is evidence of non-random X inactivation in men with more than one X chromosome[92]. A non-random X inactivation and lower androgen function could therefore be, at least in part, responsible for or contribute to decreased bone mass in KS, particularly evident in those patients with normal testosterone concentration. Thus, this mechanism could explain not only the high prevalence of decreased BMD in eugonadal KS patients, but also the frequent ineffectiveness of testosterone replacement therapy in improving BMD in KS. Another important aspect related to testicular failure and bone metabolism in KS is the circulating levels of insulin like factor-3 (INSL3). INSL3 is a protein hormone produced almost exclusively by pre- and post-natal Leydig cells of the testis[93]. The major known endocrine role of INSL3 is

related to the regulation of testicular descent during fetal development by acting on gubernaculum *via* its specific receptor RXFP2 (Relaxin Family Peptide 2)[94].

The dynamics of circulating levels of INSL3 is very similar to that of testosterone. After birth, INSL3 increases at about three months of age under the increased levels of LH (minipuberty)[95]. Soon after, INSL3 declines to undetectable levels and remains low during infancy[95] and then progressively increases throughout puberty[96]. Finally, INSL3 levels in adulthood decline steadily throughout life and at the age of 75 - 80 years INSL3 concentrations are reduced by about 40% with respect to levels found at 35 - 40 years[97].

Testosterone and INSL3 provide different information on the status of the Leydig cells; testosterone better reflects the steroidogenic activity that is acutely sensitive to LH, whereas INSL3 seems to be uncoupled from this rapid stimulation of steroidogenesis and better reflects the differentiation status and general wellness of the Leydig cells[98]. Reduced plasma concentrations of INSL3 are seen in situations of undifferentiated or altered Leydig cell status or reduced Leydig cell number, such as in anorchid men, men with hypogonadism, infertility or obesity[99]. Although the exact role of post-natal INSL3 is not fully understood, the general hypothesis is that reduced INSL3 activity (caused by altered testicular function, INSL3 or RXFP2 gene mutations) could cause or contribute to some symptoms and signs of hypogonadism, such as reduced BMD, Most importantly, human and mouse osteoblasts express the INSL3 receptor and that young adult men carrying the T222P mutation of the RXFP2 gene and with normal testosterone levels are at significant risk of reduced bone mass and osteoporosis[100].

Table 1: Possible mechanisms contributing to osteoporosis in KS

1.	Low testosterone levels
2.	Low vitamin D levels
3.	Low AR expression
4.	Non- random X chromosome inactivation and AR CAG length
5.	Low INSL-3 levels

Adult KS patients with reduced testosterone levels had also very low levels of INSL3[101]. These data have been confirmed in another study[99], which also showed that KS patients with the highest INSL3 levels were those who were not in need of testosterone substitution. Taken together these findings, although preliminary, would suggest that: (i) INSL3 seems more appropriate than testosterone to assess the Leydig cell function in KS; (ii) the low INSL3 levels observed from mid-puberty onward in KS could have a role in the reduced bone density and osteoporosis in these subjects; (iii) the limited efficacy of testosterone replacement therapy in KS subjects with osteoporosis could be explained by this alternative pathogenic mechanism. Table 1 summarizes the possible mechanisms involved in reduced bone mass in KS.

CONCLUSIONS

Salvage for infertility problem in KS patients now is feasible. Cryopreservation for sperms and SSCs at the age of 11-15 years and before complete fibrosis and hyalinization of seminiferous tubules is a practical solution. Retrieving low-grade mosaicism through different types and numbers of cells analyzed and150 well-spread G-banded metaphases instead of the usual 20 or less metaphase is highly recommended. However, unresolved questions are related to the choice of treatment in osteoporotic KS subjects with normal testosterone levels. Future pharmacogenomic approaches based on AR sensitivity and the possible development of drug with INSL3 properties could be of extreme interest.

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Original Article

Significance of First Thyroglobulin Level at the Time of Remnant Ablation in Predicting Clinical Course in Patients with Differentiated Thyroid Carcinoma

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Kuwait Medical Journal 2013; 45 (2): 108 - 112

ABSTRACT

Objectives: To review the significance of first thyroglobulin (Tg) values at the time of remnant ablation, in assessing the clinical course in patients with differentiated thyroid cancer (DTC)
Design: Retrospective study
Setting: Faculty of Medicine, Ege University, Turkey
Subjects: A total of 474 patients with DTC excluding those with positive thyroglobulin auto-antibodies and extra-cervical metastases
Intervention: Thyroidectomy followed by radioiodine ablation
Main outcome measures: Thyroglobulin, remission rate and clinical course
Results: The initial Tg levels at the time of ablation were classified as < 2 (Group 1), 2 - 10 (Group 2), 10 - 30 (Group 3), > 30 ng/ml (Group 4). The distribution of the patients was; Group 1: 216 (45.5%), Group 2: 126 (26.5%), Group 3: 81 (17.1%), Group 4: 51 (10.7%). Clinical outcome was categorized as: 1) complete remission, 2) Tg (+ve) and whole body iodine scan (-ve) and 3) cervical metastases. The highest remission rate (99.1 - 92.6 %) was achieved in groups 1, 2 and 3. The clinical course was found to be significantly related with the first Tg levels (Chi-Square test, χ^2, df = 6 p = 0.0001). The PPV and NPV of serum Tg > 30 ng/ml and < 30 ng/ml was found to be 47% (95% CI, 33 - 61%) and 97% (95% CI, 96 - 99%) respectively.
Conclusion: The findings suggest that first Tg-levels at the time of remnant ablation are helpful in predicting clinical course of patients with DTC. The remission rate improves with decreasing first Tg levels. The occurrence of cervical metastasis or disease progression should be evaluated when serumTg level is > 30 ng/ml.

KEY WORDS: differentiated thyroid carcinoma, I-131 scintigraphy, thyroglobulin

INTRODUCTION

Total thyroidectomy and radioiodine ablation have been used as the primary treatment modalities of differentiated thyroid cancer (DTC). Subsequent to thyroid ablation, follow-up aims at determining the risk of recurrence or residual disease as early as possible. Basal and TSH-stimulated serum Tg measurement are used as sensitive and specific markers of the disease in conjunction with 131I-whole body scintigraphy (WBS) and neck ultrasound in the follow-up of patients with DTC[1,2]. Thyroglobulin (Tg) is a glycoprotein (660,000 daltons) synthesized only by thyroid follicular cells. It specifically represents the presence of thyroid tissue as there is no evidence of Tg expression in non-thyroidal tissues. Therefore, serum Tg is accepted as the best available means for detecting the presence of normal and / or malignant thyroid tissue since there are no other sources to falsely elevate it[3]. Some authors have recently suggested the utility of high serum thyroglobulin level at the time of remnant ablation as an early indicator of metastasis[4-10]. However, the role of first serum thyroglobulin level as an early prognostic factor for predicting recurrent disease is still controversial. This is mostly related to the fact that serum Tg level largely depends on certain biologic factors such as amount of remnant thyroid tissue, tumor differentiation and stimulation of tumoral TSH receptors.

In the current study, serum Tg values at the time of remnant ablation after thyroidectomy are evaluated and possible relationship of these values to disease progression are examined.

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SUBJECTS AND METHODS

Patients

The clinical records of 1231 patients with DTC who had undergone total or near total thyroidectomy were retrospectively reviewed. Patients with positive thyroglobulin auto-antibodies, extra-cervical metastases or those with less than two years of follow-up were excluded from the study. Finally a total of 474 patients with DTC were included in the study.

Follow-up protocol

Five to six weeks after surgery, blood samples were taken and serum free T3, free T4, TSH, Tg (defined as first Tg level) and Tg antibodies were measured. Imaging studies including Tc99m pertechnetate thyroid scintigraphy, neck ultrasonography, and chest CT were performed to evaluate the presence of residual or metastatic thyroid tissue. High dose radioiodine ablation (3.7 - 5.55 GBq, 100 - 150 mCi) was performed for the remnant tissue within 6 - 8 weeks after surgery. Suppressive hormone therapy was started 72 hours after ablation therapy. Post therapy I-131 WBS was obtained 3 - 7 days later, depending on the iodine uptake. Six months after ablation therapy, diagnostic I-131 WBS was obtained six weeks after L-thyroxine therapy discontinuation with the patient on a low-iodine diet for at least two weeks before the study. Free T4, TSH, Tg (control Tg), and anti-Tg antibodies were measured off T4 therapy in all patients. Successful ablative therapy by scintigraphic criteria was defined as no uptake in the thyroid bed on the first diagnostic I-131 WBS. In the presence of persistent thyroid remnant, second radioiodine ablation therapy was administered at least three months after I-131 WBS. Afterwards, diagnostic I-131 WBS with serum Tg level and neck ultrasonography were performed at one year, three years and then every five years according to our clinical protocol. In patients with abnormal laboratory and imaging findings, further diagnostic investigations were performed.

Measurement of Tg and other thyroid tests

Radioimmunoassay (RIA) and immunoradiometric assay (IRMA) methods were used for the measurement of free T4 (FT4 LIA Kit, Immunotech, Prague, Czech Republic) and TSH (TSH, IRMA Kit, Immunotech, Prague, Czech Republic), serum Tg level (Tireoglobuina, Radim, Roma, Italy), and thyroglobulin antibodies (Anti-hTG, Immunotech, Prague, Czech Republic).

Assessment of clinical outcome

Clinical records including the laboratory and imaging data were reviewed and the outcome was categorized into three groups as complete remission, Tg (+) - I-131 WBS (-) group and cervical metastases group. Complete remission was defined as a negative diagnostic I-131 WBS, serum Tg level of ≤ 2 ng/ml while discontinuing L-thyroxine therapy and negative neck ultrasonography. State of Tg (+) - I-131 WBS was used to define the patients with serum Tg level of > 2 ng/ml without radioiodine uptake.

Statistical analysis

Positive predictive value (PPV) and negative predictive value (NPV) of serum Tg level in relation to clinical course was analyzed. PPV of Tg level above 30 ng/ml was calculated as follows: the number of patients without remission and first Tg level greater than 30 ng/ml was divided by total number of first Tg level greater than 30 ng/ml. The negative predictive value for remission was calculated as follows: the number of patients with remission and first Tg level 30 ng/ml or less was divided by total number of first Tg level 30 ng/ml or less. The 95% confidence intervals (95% CI) of PPV and NPV were calculated using binomial distribution. Associations between qualitative variables were assessed by the Chi-Square test. A p value < 0.05 was considered statistically significant.

RESULTS

The 474 cases included in the study consisted 392 female and 82 male patients with an age range of 16 to 82 years and a mean age of 47.7 years. Mean follow-up was 42 months. The histologic tumor type included papillary carcinoma in 402 (85%) patients, follicular carcinoma in 59 (13%), Hurtle-cell carcinoma in 11 (2.3 %) and mixed carcinomas in two (0.4 %) patients.

First thyroglobulin level: According to first Tg levels measured at time of radioablative therapy, the patients were divided into four groups: Group 1 (n = 216) first Tg < 2 ng/ml; Group 2 (n = 126) first Tg 2 - 10 ng/ml; Group 3 (n = 81) first Tg 10 – 30 ng/ml; Group 4 (n = 51) first Tg > 30 ng/ml.

The success of ablation: According to the criteria used in this study overall ablation success rate was 93% (439 / 474 patients) at six months. Second ablative therapy was required in a total of 35 patients (12, 4, 12 and 7 respectively in Groups 1 to 4) who had iodine uptake in the thyroid bed. Ablation success rates were 94%, 97%, 85%, 86% respectively in Groups 1 to 4. Statistical evaluation supported significant relation (Chi-Square test, χ^2, 13.68 df = 3 p = 0.003) between first Tg and ablation success rates among the patient groups.

Control thyroglobulin level: Control serum Tg levels measured at six months after ablation under TSH stimulation were examined with the corresponding first Tg levels in each case. It was noted that none of Group 1 and 2 patients had control-Tg levels above10 ng/ml. There were eight (9.9%) and 26 (51%) patients with control Tg > 10 ng/ml respectively in Groups

Table 1: Control Tg levels in patient groups (ng/ml)

Patients	< 2	%	2 - 10	%	>10	%	n
Group 1	208	96.3	8	3.7	0	0	216
Group 2	108	85.7	18	14.3	0	0	126
Group 3	64	79	9	11.1	8	9.9	81
Group 4	18	35.3	7	13.7	26	51.0	51

3 and 4 (Table 1). Group 4 patients constituted the majority of patients with >10 ng/ml control Tg levels (26 / 34, 76%). However, despite the highest first Tg levels, nearly one out three of Group 4 patients (18 / 51) showed decreasing Tg levels below 2 ng/ml six months after radioablative therapy. Statistical analysis supported the significant relation between groups according to first and control Tg levels (Chi-Square test, χ^2, 192.88, df = 6, p = 0.0001).

Clinical Outcome: Among the 474 patients, 439 (92.6%) patients had complete remission. Thirty-five (7.3%) patients developed disease progression. No patient had local recurrence during the follow-up period. The clinical course of these patients was found to be significantly related with the first Tg levels (Chi-Square test , χ^2, df = 6, p = 0.0001) (Table 2). One patient from the study population died of causes not related to DTC.

Complete Remission: According to the criteria used in this study, complete remission rates were 99.1%, 97.6%, 92.6% and 52.9% respectively in Groups 1 - 4 (Table 2). While similar remission rates were noted in Group 1 - 3, Group 4 showed the lowest remission rate.

State of Tg (+), I-131 WBS (-): Among the study population serum Tg level of > 2 ng/ml with a negative whole body radioiodine scan after thyroid hormone withdrawal was noted in 20 patients. These were 1, 5 and 14 patients in Groups 2, 3 and 4 respectively. Histology of these tumors was papillary in 17, follicular in two and hurtle cell carcinoma in one patient.

Cervical metastasis: Regional cervical lymph node metastasis was noted in 15 patients (3.2%) during the follow-up. Tumor histology was papillary carcinoma in 13 out of 15 patients. The number of patients with cervical metastasis was 2, 2, 1 and 10 respectively in Groups 1 to 4. While 10 of 15 (67%) patients, all from group 4, had higher levels of Tg, two patients with cervical metastasis had Tg levels < 2 ng/ml.

PPV and NPV of first Tg Level: Complete remission was noted in 423 of 412 patients whose first serum Tg level was < 30 ng/ml. Among the 51 patients with Tg > 30 ng/ml, disease progression was noted in 27 patients. The PPV and NPV of serum Tg > 30 ng/ml and < 30 ng/ml was found to be 47% (95% CI, 33 - 61%) and NPV 97% (95% CI, 96 - 99%) respectively.

DISCUSSION

Tg is synthesized exclusively by thyroidal follicular cells, either normal or neoplastic. When all normal thyroidal follicular cells are successfully ablated, Tg production would represent neoplastic thyroidal epithelial cells. It has been noted, that even if DTC cells lack radioiodine uptake ability, malignant cells may retain the Tg synthesizing capability. Therefore, serum Tg level is a fairly specific tumor marker after thyroidectomy and ablative I-131 therapy in patients with DTC[1-3].

The measurement of serum Tg level six to eight weeks after thyroidectomy has been a standard clinical practice in patients with DTC[1]. Several authors have shown that the first Tg level could be an early indicator of the existence of metastatic disease. In the study by Ronga *et al*, using ROC analysis the positive predictive value for presence of metastases exceeded 90% when the first Tg level is higher than 69.7 ng/ml[4]. Moreover, during the last two decades few authors focused on the use of first Tg as a prognostic marker for the assessment of disease progression[5-10]. It is well known that the first Tg level is dependent on the surgical trauma, presence of thyroglobulin antibodies, completeness of surgery and TSH receptor stimulation following thyroidectomy. Therefore, optimal timing of serum Tg level measurement was also considered as a challenging issue. The data obtained by Hocevar *et al* have shown that mean Tg half-life is 65.2 h and it decreases to below 5 – 10 ng/ml approximately only 25 days after surgery[11]. Thus, the

Table 2: Distribution of clinical course in differentiated thyroid carcinoma after ablation

Patients	Complete remission	%	Tg (+), I-131 WBS(-)	%	Cervical metastasis	%	n
Group 1	214	99.1	0	0	2	0.9	216
Group 2	123	97.6	1	0.8	2	1.6	126
Group 3	75	92.6	5	6.2	1	1.2	81
Group 4	27	52.9	14	27.5	10	19.6	51

(Chi-square test, χ^2 137.506 df = 3 p = 0.0001).

authors have recommended serum Tg sampling to be carried out at least one month after thyroidectomy. In agreement with these previous observations, we have also performed first Tg measurement 5 - 6 weeks after surgery. Traditionally, it is expected that the residual gland after thyroidectomy would ideally be less than two grams. As a practical guide to assess the relationship between thyroid mass and Tg secretion, it has been noted that 1 g normal thyroid releases 1 ng/ml Tg when TSH is normal and 0.5 ng/ml when the serum TSH is suppressed below 0.1 mU/l. But stimulation by TSH leads to increased Tg levels by about > 5-fold over baseline levels[1,12,13]. Surgical operations of our patients were performed by several different surgeons and therefore the amount of the residual thyroid tissue varied considerably. However, despite the variations of the remnant thyroid tissue, nearly half of the patients had serum Tg levels < 2 ng/ml at the time of ablative therapy. This suggests nearly homogenous surgical management approach by the different surgeons. The overall success rate of ablation was between 85 and 97% in our patients. The percentage of ablation failure was 7% out of the overall study population. It is noted that the success rate was lowest for those with high first Tg levels. This observation was found to be in agreement with Lee *et al*, who reported that the combined use of serum Tg levels measured just before ablation and the I-131 WBS pattern after ablation may be an early predictor of ablation success[14]. On the other hand, for the assessment of ablation success the authors have only used undetectable level of Tg at 6 - 12 months after ablation therapy with thyroid hormone suppression. Among other factors affecting ablation therapy, Karam *et al* have investigated the relationship between the ablation rates and age, sex, neck uptake, histology, stage or TSH levels. While serum Tg levels have not been considered in their study, radioiodine dose was the only variable found to be associated with success of therapy[15].

In this study, successful ablative therapy by scintigraphic criteria was defined as no uptake in the thyroid bed on the first diagnostic I131 WBS while complete remission was defined as negative diagnostic I131 WBS, Tg < 2 ng/ml under TSH stimulation and negative neck ultrasonography in the follow-up. Absence of I131 uptake in the thyroid bed six months after ablation therapy has not always correlated well with Tg < 2 ng/ml under TSH stimulation. While most DTCs produce Tg and take up iodine, iodine-concentrating ability and Tg synthesis are actually different functions in thyroid tissue. Therefore, neoplastic thyroid tissue may concentrate iodine though it may lack Tg secretion or produce Tg but does not show iodine avidity. It is believed that the presence of one function does not predict the presence of the other[16].

While we have noted 92.6% (439 / 474) complete remission rate in our patients, the remission rate was significantly inversely related to the increased levels of serum Tg . This observation is in agreement with other studies. Lin *et al* reported that postoperative level of Tg can be used as a prognostic factor in patients with DTC. For patients with Tg levels exceeding 10 ng/ml, Tg level was still found to be a useful marker to predict prognosis[8]. Kim *et al* has also reported high recurrence rate and positive Tg without evidence of disease in patients with Tg >10 μ/lt[10]. In our study population, while Tg level was categorized as less < 2, 2 - 10, 10 - 30, > 30 ng/ml, these studies have used Tg >10 ng as a cut off value for further evaluation or therapy. Unlike these reports, we have observed high remission rates even in patients with Tg levels 10 – 30 ng/ml. Clinical follow-up these patients also supported similar remission rates (92.6%) to those with Tg levels < 10 ng/ml.

In their comparative study, Toubeau *et al* found that first Tg levels above 30 ng/ml were significantly associated with disease progression[5]. The authors have suggested that low first Tg level and absence lymph node invasion might indicate that the risk of clinical evolution is very low. Hall *et al* have also reported that patients with Tg level greater than 20 pmol/l are at increased risk of recurrence and therefore might be monitored by more intensive follow-up or additional treatment. An undetectable or very low Tg level, therefore, has been accepted as a reliable predictive marker.

While the duration of clinical follow-up might be relatively short in our study, it has been previously noted that among patients who had remission two years after initial treatment, long-term follow-up showed a relapse in less than 1%[17]. According to the most recent European perspective, low or undetectable serum Tg levels generally indicate a favorable course of the disease. On the contrary, increasing levels are reported to have indeterminate prognostic significance[18]. In agreement with these, our data demonstrated that NPV of Tg level < 30 ng/ml in excluding progressive disease was 97%. Clinical follow-up also supported favorable course and final complete remission in majority of the cases. PPV of first Tg > 30 ng/ml indicated the importance of close monitoring of at least nearly half of the patients for the occurrence of persistent disease.

CONCLUSION

It is suggested that first Tg-levels at the time of remnant ablation is helpful in predicting clinical course in DTCs. The remission rate improves with decreasing first Tg levels. The occurrence of cervical metastasis or disease progression should be evaluated when serum Tg level is > 30 ng/ml.

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Original Article

Evaluation of Glucose Metabolism in Hepatitis Serology Negative Beta Thalassemia Major Patients

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Kuwait Medical Journal 2013; 45 (2): 113 -- 117

ABSTRACT

Objectives: To evaluate the impaired glucose metabolism and their possible risk factors in beta thalassemia major (TM) patients negative for hepatitis serology and PCR
Design: Prospective descriptive study
Setting: Department of Pediatric Hematology, Pamukkale University Faculty of Medicine, Denizli, Turkey
Subjects: Patients with history of familial diabetes mellitus (DM) and hepatitis serology and polymerase chain reaction (PCR) positive TM patients were excluded. An oral glucose tolerance test (OGTT) was done on 32 TM patients. Insulinogenic index, β-cell function index and insulin resistance index were calculated.
Main Outcome Measures: Glucose metabolism in beta TM patients negative for hepatitis serology and PCR
Results: Seven patients (1.8%) had impaired glucose metabolism (IGM). Three patients (9.3%) were diagnosed with DM, one (3.1%) patient with impaired glucose tolerance (IGT) and three (9.3%) patients with impaired fasting glucose (IFG). Cases with IGM had significantly higher, annual erythrocyte consumption rate (ml/kg/year), ferritin, alaninaminotransferase (ALT), post-splenectomy period, age at first transfusion when compared with normal glucose metabolism (NGM) patients ($p < 0.05$). Insulinogenic index decreased in IGM patients compared to NGM patients ($p < 0.005$).
Conclusions: Our results show that annual erythrocyte consumption rate, ferritin, post-splenectomy period, insulinogenic index and ALT values are predictive of IGM in TM patients negative for hepatitis serology and PCR.

Key Words: glucose metabolism, oral glucose tolerance test, thalassemia

INTRODUCTION

Beta-thalassemia is a heterogeneous hereditary hemoglobin disorder characterized by reduced synthesis of β-globin. Ineffective erythropoiesis and severe hypochromic microcytic anemia develop secondary to the defect of the β-globin chain. Clinically, uncontrolled iron absorption from the intestines in addition to iron accumulated as a result of chronic transfusion and ineffective erythropoiesis in thalassemia major (TM) patients requiring regular erythrocyte transfusion cause chronic hemosiderosis[1]. Chronic hemosiderosis results in complications associated with the heart, liver and endocrine organs. Life expectancy of TM patients has improved recently thanks to the improved treatment choices, while diagnosis and treatment of complications gained even further importance in improving the quality of life[2]. Among endocrine complications, disorders of the glucose metabolism are common. In patients with TM, disorders of the glucose metabolism and diabetes mellitus (DM) have been observed with frequencies of 2.3 - 24% and 14 - 31%, respectively[3]. Pathophysiology of impaired glucose metabolism(IGM) is not clearly known. Hemosiderosis, liver infections, genetic factors, serum ferritin levels, patient age and the amount of erythrocyte received are among factors that alter glucose metabolism. Acute viral hepatitis and chronic hepatitis C virus infection may be additional risk factors for diabetes development in TM patients. Destruction of β cells as a result of iron accumulation in the pancreas is known to reduce insulin secretion. On the other hand, there are studies which show effective insulin resistance even in the absence of insulin insufficiency[4–7].

The present study aims to investigate the frequency of IGM and influential factors in hepatitis serology and PCR negative TM patients, who receive regular erythrocyte transfusion and chelator treatment.

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Table 1: Clinical findings in patients with TM

Variables	n	Mean ± SD	Min - Max
Male/Female	17/15		
Age (years)		18 ± 4.5	11 - 29
Weight (kg)		50.7 ± 14.7	28.5 - 94
Height (cm)		155.2 ± 12	127 - 172
BMI (kg/m^2)		20.4 ± 3.8	14 - 34
Waist circumference (cm)		78 ± 10.5	63 - 102
Age at test (years)		18 ± 4.5	11 - 29
Age at diagnosis (months)		15.8 ± 22.7	1 - 84
Age at first transfusion (months)		16.4 ± 22.7	1 - 84
Transfusion years (years)		16.5 ± 4.9	9 - 24
Number of patients with splenectomy	21		
Post splenectomy period (years)		7.6 ± 6.5	2 - 18
Age at first chelation (years)		5.8 ± 2.4	2 - 10
Transfused erythrocyte volume (ml/kg/year)		132.8 ± 19	110 - 180

TM: Thalassemia major, BMI: Body mass index, SD: Standard deviation

SUBJECTS AND METHODS

The present study included 32 patients (mean age 18 ± 4.5 years) who were being monitored for TM diagnosis. Signed informed consent forms were obtained from patients and / or patient's family before the data were evaluated.

None of the patients were receiving agents that may potentially impair glucose metabolism. Patients with familial history of DM and hepatitis serology and PCR positive TM patients were excluded. Pubertal development was evaluated according to the Tanner classification system[8]. All patients were receiving regular erythrocyte transfusion (15 ml packed erythrocytes per kg body weight every 3 - 4 weeks to keep their hemoglobin level at a minimum of 9 g/dl before each transfusion). Chelation treatment included desferoxamine (25 - 50 mg/kg/day, 2 - 5 days / week) and deferiprone (75 - 90 mg/kg/day). Patients' weight, height, age at test, age at onset of diagnosis, age at first erythrocyte transfusion, age at first chelation, year of erythrocyte infusion, transfused erythrocyte volume (ml/kg/year), pretransfusion hemoglobin, splenectomy status, post-splenectomy period, ferritin, alanin aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglyceride, high density lipoprotein (HDL), and low density lipoprotein (LDL) were recorded. Waist circumference, systolic and diastolic blood pressure, body weight and height were measured. Body mass index (BMI = body weight (kg) / height (m^2)] was calculated.

Oral glucose tolerance test (OGTT) was performed with 75 g glucose 10 - 15 days after erythrocyte transfusion and following at least eight hours of fasting. Plasma glucose levels were measured at 0, 30, 60 and 120 minutes. Serum insulin levels were measured by chemiluminescence (Siemens Advia Centaur, Siemens Medical Solution Diagnostic Tarrytown NY, USA) and plasma glucose level was measured by hexokinase assay (Architect C8000 Abbott Illionis USA). Patients with fasting plasma glucose ≥ 7 mmol/l, or those with plasma glucose ≥ 11 mmol/l at any time were diagnosed with DM. Glucose tolerance was evaluated according to the criteria of American Diabetes Association[9]. Fasting plasma glucose values > 5.5 - 6.9 mmol/l were classified as impaired fasting glucose (IFG). Plasma glucose values two hours after OGTT ≥ 7.8 - 10.9 mmol/l were classified as impaired glucose tolerance (IGT) and values < 7.8 mmol/l was defined as normal glucose tolerance (NGT). Insulinogenic index, β-cell function index, insulin resistance index were calculated using the following formulas[10-12].

Insulinogenic index = Plasma insulin at minute 30 – Plasma insulin at minute 0 (μU/ml) / Blood glucose at minute 30 – Blood glucose at minute 0 (μmol/l)

β cell function index = 20 x Fasting insulin (μU/ml) / Fasting blood glucose (μmol/l)

Insulin resistance index (homeostasis model assessment - HOMA-IR) = Fasting insulin (μU/ml) x Fasting blood glucose (μmol/l) / 22.5

Statistical analysis

The data were statistically analyzed using computer software (SPSS 10.0, Chicago IL). We utilized the Mann-Whitney U test in the analysis of inter-group averages and Spearman correlation in correlation analysis of variables. A p-value of < 0.05 was considered statistically significant.

RESULTS

Data of the patients with TM included in the study are summarized in Table 1 and Table 2. IGM was defined as the total of patients with DM, IGT and IFG. Three (9.3%) patients were diagnosed with DM, one (3.1%) patient with IGT and three (9.3%) patients with IFG. In

Table 2: Laboratory findings of patients with TM

Patient Data	Result
Pre-transfusion hemoglobin (g/dl)	9.2 ± 0.5
Ferritin (ng/dl)	2493.6 ± 1116
ALT (U/l)	34.6 ± 26.6
AST (U/l)	39.2 ± 36.8
Total cholesterol (mg/dl)	108 ± 26.5
Triglyceride (mg/dl)	39 ± 77.2
HDL cholesterol (mg/dl)	30.2 ± 8.8
LDL cholesterol (mg/dl)	51.9 ± 21.6
Systolic blood pressure (mmHg)	105.3 ± 10.7
Diastolic blood pressure (mmHg)	63.2 ± 7.2
Insulinogenic index	25.2 ± 22.6
β cell function index	105.3 ± 62.3
Insulin resistance index (HOMA-IR)	1.7 ± 0.9

ALT: Alanin aminotransferase, AST: Aspartat aminotransferase, HDL: High density lipoprotein, LDL: Low density lipoprotein, TM: Thalassemia major, HOMA-IR: Homeostasis model assessment-insulin resistance

TM patients with IGM, a significant relationship was noted between insulinogenic index and age at first chelation and between insulinogenic index and systolic blood pressure (p = 0.028 and 0.005, respectively). In TM patients with Normal glucose metabolism (NGM), significant relationships were identified between insulinogenic index and age at diagnosis, β cell function index and weight, insulin resistance index and BMI, age at diagnosis, age at first erythrocyte transfusion, and TG and total lipids ($p < 0.005$). TM patients with IGM and NGM are compared in Table 3. There were statistically significant differences between these patients in terms of annual erythrocyte consumption rate (transfused erythrocyte volume (ml/kg/year), ferritin, ALT, post-splenectomy period and insulinogenic index ($p < 0.05$).

DISCUSSION

The main limitation of the study is the limited number of patients. The mechanism of glucose disturbances in TM patients is complex and multifactorial but is attributed mainly to insulin deficiency resulting from the toxic effects of iron accumulated in the pancreas and from insulin resistance. Insulin resistance may be due to iron deposition in both the liver and muscles. Persistent insulin resistance along with a progressive reduction in circulating insulin levels may lead to glucose intolerance and overt diabetes[5,13–16]. A recent report by Monge *et al*[17] demonstrated evidence of immune system activation against pancreatic beta

Table 3: Comparison of patients with impaired and normal glucose metabolism

Patient Data	NGM (n = 35)	IGM (n = 7)	p-value
Weight (kg)	49.7 ± 14.7	54.2 ± 15.3	0.34
Height (cm)	154.5 ± 11.9	157.7 ± 12.6	0.49
BMI (kg/m^2)	20.2 ± 4	21 ± 3.2	0.35
Age at diagnosis (months)	15.7 ± 23.8	16.4 ± 19.9	0.44
Age at test (years)	17.6 ± 4.9	19.2 ± 2.7	0.36
Age at first transfusion (months)	16.4 ± 23.8	16.4 ± 19.9	0.59
Transfusion years (years)	15.9 ± 5.2	18.8 ± 2.9	0.12
Annual erythrocyte consumption rate (ml/kg/year)	125.2 ± 12.2	160 ± 12.9	0.00*
Pre-transfusion hemoglobin (g/dl)	9.1 ± 0.5	9.5 ± 0.3	0.08
Ferritin (ng/dl)	1983.2 ± 615.5	4316.5 ± 669.1	0.00*
ALT (U/L)	28.8 ± 16.8	55.5 ± 43.4	0.03*
AST (U/L)	33.7 ± 30.2	59 ± 52.4	0.11
Post splenectomy period (years)	5.9 ± 6	13.8 ± 4.4	0.00*
Age at first chelation (years)	5 ± 2.1	8.5 ± 1.3	0.00*
Total cholesterol (mg/dl)	106.8 ± 29.3	112.4 ± 13.6	0.26
Triglyceride (mg/dl)	142.6 ± 85.1	126.1 ± 39.9	0.89
HDL cholesterol (mg/dl)	30.1 ± 9.6	30.4 ± 6.3	0.73
LDL cholesterol (mg/dl)	50.4 ± 22.7	57.1 ± 17.5	0.21
Systolic blood pressure (mmHg)	106 ± 10.3	102 ± 13	0.45
Diastolic blood pressure (mmHg)	63 ± 6.3	64 ± 11.4	0.94
Waist circumference (cm)	76.8 ± 9	83.4 ± 16.2	0.40
Insulinogenic index	29.4 ± 24	12.6 ± 11.3	0.03*
β cell function index	114.6 ± 65.5	75 ± 40	0.10
Insulin resistance index (HOMA-IR)	1.7 ± 1	1.8 ± 0.9	0.82

IGM: DM (n: 3) +IFG (n: 3) + IGT (n: 1)
IGM: Impaired glucose metabolism, NGM: Normal glucose metabolism
DM: Diabetes mellitus, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance
ALT: Alanin aminotransferase, AST: Aspartat aminotransferase
HDL: High density lipoprotein, LDL: Low density lipoprotein
BMI: Body mass index, * : statistically significant
*$p < 0.05$

cells in TM patients. The prevalence of IGM is variable. The prevalence of IGM and DM were found as 21.8% and 9.3%, respectively, in the present study. This rate is not higher than that reported in other studies[3]. In two large series, the prevalence of DM ranged from 6.5 to 23%[18,19]. These differences could be attributed to variable genetic factors, and differences in age, history of transfusion therapy, the degree of iron overload and chelation therapy. IGM appears during the second decade of life and its prevalence increases with age[3,16,20]. Chern *et al*[17] reported that the mean age of IGM was 17.2 ± 4.3 years in TM patients. A recent report demonstrated that the mean age at diagnosis of diabetes was 18.2 ± 3.6 years in TM patients[3]. Similarly, TM patients with IGM had a higher mean age compared to those with NGM in the present study.

Significant clinical characteristics of TM accompanied with IGM were ferritin level, volume of blood transfused per year (annual erythrocyte consumption rate) and splenectomy. Previous studies have demonstrated that higher red cell consumption and splenectomy had greater endocrine complications such as impaired glucose homeostasis, because they have a greater rate of iron loading[16,21–23]. In our study, we also found higher ferritin levels, annual erythrocyte consumption rates, and post splenectomy periods for patients with IGM. Ferritin levels, annual erythrocyte consumption rate, and post-splenectomy period also increased in TM patients with DM, IGT and IFG, although these were limited in number.

Iron chelation therapy reduces iron damage to tissues and helps protect against DM. However, many studies have demonstrated other systemic and endocrine complications related to multiple transfusions, even in patients treated with iron chelating therapy[3,16,24–26]. Poor compliance with chelation therapy and iron overload are the most important risk factors for DM development in TM patients[8]. The chelation regimen used had no significant effect on glucose metabolism[21]. Mean age at first chelator treatment was statistically significantly higher in patients with IGM compared to patients with NGM in our study. Given that patients with IGM had a higher mean age, we believe that it should be questioned whether chelation treatment had been administered at desired dosages and for optimum duration since it was difficult in the past to access chelating agents.

The IGM in our thalassemic patients resulted from insulin deficiency secondary to pancreatic β-cell damage from chronic iron overload. Insulin resistance index, insulinogenic index and β cell function index are measures of pancreatic cell damage[27]. The β-cell function index and insulinogenic index also decreased compared to those with NGM although β-cell function index was not statistically significant. A minimal increase was noted in insulin resistance index. We believe that significantly different value of insulinogenic index between TM patients with NGM and IGM may indicate pancreatic cell damage. A statistically significant difference was also noted between the insulinogenic index and systolic blood pressure and age at first chelation treatment in patients with IGM. Impairment of the insulinogenic index with older ages at first chelation treatment underlines the importance of chelation treatment in patients with TM. In addition, systolic blood pressure is considered a risk factor for IGM in patients with TM. In a study, three indices have been shown to be reduced in pediatric TM patients with IGM and it was suggested that these could not describe pancreas damage, while another study demonstrated that insulin resistance index was predictive of IGM[21, 27].

Alanine aminotransferase and AST values were higher in TM patients with IGM compared to those with NGM, with ALT being significantly higher in the present study. Acute viral hepatitis and chronic hepatitis C virus infection may be altering glucose metabolism in TM patients[5]. Previous studies, which included TM patients who were positive for hepatitis C virus antibody, reported that neither of the two parameters reflected an IGM[4,21]. The present study did not include patients' positive for hepatitis C virus antibody and acute viral hepatitis. We therefore believe statistically significant ALT increases may be of assistance as an indicator of IGM.

CONCLUSIONS

In conclusion, complications associated with IGM have an increasing prevalence among patients with TM, whose life expectancy further improves every day. There is a significant body of theoretical knowledge on this subject. In light of this preliminary study, we believe that annual erythrocyte consumption rate, ferritin, post-splenectomy period, insulinogenic index and ALT values are predictive of IGM in patients negative for hepatitis serology. The frequency of IGM increases with increasing age. Glucose metabolism should be closely monitored in patients older than ten years. Chelation treatment at the right time and right doses may prevent the development of IGM. Further studies are required on this issue.

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Original Article

Nutritional Knowledge, Attitude and Practice of High School Girls Living in Kuwait: A Pilot Study

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Kuwait Medical Journal 2013; 45 (2): 118 - 122

ABSTRACT

Objective: Nutritional inadequacy in high school girls is detrimental as they are the future mothers who will need to cope with nutritional, physical and emotional demands of pregnancy, childbirth and lactation. This study was undertaken to study nutritional knowledge, attitude and practice of adolescent school girls in Kuwait.

Design: Prospective study

Setting: A governmental high school in Kuwait

Subjects and Methods: Seventy-two school girls aged 15 to 17 years and 12 school teachers were enrolled. A dietary questionnaire on nutritional knowledge, food habits, eating behavior with food frequency sheet was used along with anthropometric measurements.

Main Outcome Measures: Nutrition knowledge and its source as well as attitudes and practices of subjects.

Results: Family was the primary source of knowledge for 45.83% compared to 18.06% school girls who chose the internet. The studied girls showed significantly lower knowledge about different nutrients and nutrients` function compared to their teachers. This deficient knowledge affected the girls' food frequency sheets and limited their choices. Their lifestyle was less than satisfactory in the majority where they preferred sedentary activities. Fortunately, only 15.27% of the studied girls were overweight, 4.17% obese and 2.78% morbidly obese.

Conclusion: Although there is an insignificant effect of deficient nutritional knowledge and dietary behavior of the studied high school girls on their physical growth, this deficient nutritional knowledge is likely to have a negative impact on their nutritional status as future mothers. We thus recommend that nutritional education programs should be incorporated within the curriculum intended for school girls in Kuwait.

KEY WORDS: knowledge, nutrition, obesity, schoolgirls

INTRODUCTION

Dietary inadequacy is more common among adolescent girls than in any other segment of the population. The significance of this statistic is increased by the fact that adolescence is a time when inadequate nutrition can lead to health problems that persist throughout life. Special concern is focused on nutritional inadequacy in female adolescents because they may become pregnant and need to cope with the additional nutritional, physical and emotional demands of pregnancy, child birth and lactation[1].

Dietary knowledge and access to resources are critical to improve health and nutrition in a sustainable way. Adolescence is the time to learn and adopt healthy habits to avoid many health and nutritional problems later in life[2]. Particularly, health and nutrition knowledge and healthy habits of female adolescents will have critical roles to play in maintaining future family health and nutrition[3].

The data that describes the nutritional knowledge of adolescent girls as potential mothers is scarce in Kuwait. Such data is needed in order to assess the current situation and advise appropriate educational program for such girls. This study was thus designed to assess the nutritional knowledge of Kuwaiti high school girls and study their food habits and their free-time activities so as to develop a strategy for improving their health and nutritional status. The anthropometric measurements

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of the enrolled girls were assessed as well to study the interaction between their knowledge and their attitude towards these nutritional facts. A secondary aim was highlighting the nutritional knowledge and nutritional status of their teachers being the raw models for these high school girls.

SUBJECTS AND METHODS

Subjects

The present pilot study was performed on 72 girls aged 15 to 17 years, enrolled from the selected government high school in Kuwait. All the high school girls in the science section of the selected high school were invited to attend a meeting where they listened to a scientific lecture followed by introduction of the questionnaire and later taking their anthropometric measurements. The meeting was announced one week earlier to the event. The science section classes are six and each contains 25 students. From these girls only 116 girls attended. Ninety-one girls stayed to fill the questionnaire out of which only 72 were statistically valid. The sample size was determined by Epi Info statistical package considering that the prevalence of incorrect nutritional knowledge of the adolescent girls in this age group in the literature is 25%[4] and the worst acceptable prevalence is ± 5%. Power analysis was 80% for detection of the sample size to identify the β-error.

Twelve teachers among those teaching the high school girls also participated in the study. They represented all school teachers who taught the science section who were seven teachers in addition to another five who taught both the science and literature sections.

Methods

Questionnaire

A reliable dietary questionnaire on food habits, eating behavior and nutritional knowledge of adolescents was constructed in simple Arabic language based on Parmenter and Wardle[5] nutrition knowledge questionnaire and Turconi and associates[6]. Permission from the school director and class teachers was obtained before administration of the questionnaire.

Before conducting the main study, a pilot study was done with the assistance of the children's teacher involving the application of the questionnaire to ten children chosen at random. This was done to assess whether the students could comprehend it easily.

Based on the experience obtained from the pilot study, the questionnaire was modified and then administered to the students.

The questionnaire was in simple Arabic language. All questions could be answered by 'Yes' or 'No' or as multiple choice questions. The questionnaire comprised of 30 questions about nutrition and socio-demographic characteristics. The questionnaire included questions concerning knowledge of nutrients and their function as well as the attitude towards meal timings, meal skipping and need for snacks; variation and balance of nutrients in a meal; proper food, hygiene and human health. Additionally, nutritional practice was judged by questions addressing food habits and choices as well as hygienic measures followed and the physical activity and lifestyle.

Food frequency sheet

Anthropometric measurements according to Lee and Nieman[7]:

- A spring balance was used for recording weight (approximated to the nearest 0.5 kg).
- Height was measured (approximated to the nearest 0.5 cm).
- Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. BMI percentiles were calculated as percentage from median for age and sex.

Statistical analysis

The collected data was coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences). Descriptive statistics were done for categorical data by number and percentage. The prevalence rate for a certain item was calculated as the number of cases per 100 students. Kolmogorov Smirnov test was used to differentiate parametric from non-parametric data. A comparison of different variables in various groups was done using the student t' test. Chi-square (χ^2) test was used to compare frequency of qualitative variables among the different groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The studied high school girls lacked knowledge of the food group items, healthy foods and determinants of caloric requirements of adolescent girls (total prevalence of knowledge is < 50% for each of them). Less than a quarter knew the definition of balanced diet and the energy content of fats and carbohydrates. Overall, the knowledge about nutrients and their functions was significantly lower in high school girls compared to the school teachers (Table 1).

Table 1 also shows significantly lower food choices in high school girls compared to the teachers with high frequency of intake of fast food and usage of computer and mobile phones (> 80%) and low frequency of sports performance (> 90%) among the studied girls. Additionally, school teachers had non-significantly lower lifestyle compared to the girls with more use of computer and internet and weak performance in

Table 1: Knowledge, attitude and practice of the studied high school girls and their teachers

Variables	High school girls Mean ± SD	School teachers Mean ± SD	p-value
Knowledge of nutrients	53.70 ± 14.1	63.89 ± 8.74	< 0.01
Knowledge of nutrients` function	45.39 ± 19.6	77.08 ± 13.82	< 0.001
Attitude	64.34 ± 25.18	68.75 ± 18.72	> 0.05
Food choices	53.19 ± 12.08	60.43 ± 7.54	< 0.01
Lifestyle	28.38 ± 16.68	23.06 ± 10.00	> 0.05

$p < 0.01$: highly significant, $p < 0.001$: very highly significant, $p > 0.05$: not significant

sports. Regarding the attitude of school girls towards certain nutritional issues it was non-significantly lower than the school teachers.

The current study reveals that the commonest source for nutritional knowledge of high school girls was the family (45.83%) followed by books and journals and the internet (18.06% each), the school (11.11%) and finally the friends compared to books and journals in 33.33% among teachers followed by family (25.00%), then school and friends (16.67% each) with high statistical significance between them (Table 2).

Table 2: Sources of nutritional knowledge among studied girls and their teachers

Source of knowledge	High school girls Number (frequency)	School teachers Number (frequency)	p-value
School	8 (11.11)	2 (16.67)	< 0.001
Books and journals	13 (18.06)	4 (33.33)	
Internet	13 (18.06)	1 (8.33)	
Friends	5 (6.94)	2 (16.67)	
Family	33 (45.83)	3 (25.00)	

$p < 0.001$: very highly significant

The BMI percentiles of the school girls revealed that 5.66% of them were underweight, 72.22% were of normal weight, 15.27% were overweight, 4.17% were obese and 2.78% were morbidly obese (Table 3). As regards the school teachers, 50.00% were within normal weight range, 33.33% were overweight and only 16.67% were obese with high statistical significance when compared to the high school girls (Table 3). Overweight and obese high school girls had lower nutrition knowledge scores as well as food choices and more sedentary lifestyle compared to girls with normal weight but these comparisons did not reach statistical significance ($p > 0.05$).

Table 3: Body mass index categories among studied girls and their teachers

Body mass index	High school girls Number (frequency)	School teachers Number (frequency)	p-value
Underweight	4 (5.56)	0 (0.00)	< 0.001
Normal weight	52 (72.22)	6 (50.00)	
Overweight	11 (15.27)	4 (33.33)	
Obese	3 (4.17)	2 (16.67)	
Morbidly obese	2 (2.78)	0 (0.00)	

$p < 0.001$: very highly significant

DISCUSSION

The knowledge about nutrients and their function showed a mean of 53.70 ± 14.10 and 45.39 ± 19.60 in high school Kuwaiti girls respectively compared to 63.89 ± 8.74 and 77.08 ± 13.82 in the school teachers. In addition, food choices were proper in only 53.19 ± 12.08 of high school girls compared to 60.43 ± 7.54 of teachers with high frequency of intake of fast food and usage of computer and mobile phones and low frequency of sports performance. Similarly, students at Tswaing High School in South Africa did not have adequate knowledge on nutrition, diet and exercise[8]. The authors of the latter study recommended programs or seminars that could assist in informing students on the importance of diet and exercise.

As regards the prevalence of knowledge of carbohydrates (CHO), the current study showed that less than a quarter of the studied Kuwaiti schools girls had knowledge as regards the CHO sources and their energy content. In a similar study done in South Africa, it was found that the students had average knowledge about CHO sources and function[9].

The present study revealed that the commonest source for nutritional knowledge is the family followed by the books, journals and internet in the studied school girls compared to mainly books and journals among teachers. This result enforces the family influence on teenagers in Kuwait in this domain. Since the nutritional knowledge is less than satisfactory among high school Kuwaiti girl, parents must be encouraged to participate in nutritional educational programs as previously advised in a study by Slusser *et al*[10]. Additionally, a need for more updated and reliable nutritional sources for the high school girls emerges. For instance, Rankins *et al*[11] previously stated that MedlinePlus has good potential for efficiently communicating trustworthy diet-related disease-prevention behavior to adolescents in an existing classroom curriculum. Moreover, Fahlman *et al*[12] conducted a pilot study in the USA and concluded that nutrition curriculum delivered by trained professionals resulted in significant positive changes in both nutrition knowledge and behaviors in middle school children.

On studying the percentile BMI of the school girls in the present study, 15.27% of them were overweight, 4.17% were obese and 2.78% were morbidly obese. These figures are close to those of Hana *et al*[13] who reported that 19.3% of the girls aged 9 - 14 years in Giza governorate, Egypt, were overweight yet the same study reported that 12.8% of the girls were obese. On the other extreme, Guthrie and Picciano[1] reported that between 30-35% of American teenagers are overweight and between 3% and 20 % are obese. Worth noting here is that a previous study in Kuwait done by Abdelalim *et al*[14] reported that 18.4% and 16.7% of their 5th grade students from al-Ahmadi governorate were overweight and obese respectively. It is clear that the percentage of overweight is close to the results of the current study which is not true for obesity. This can be attributed to the fact that while the latter study included younger boys our series comprised adolescent girls who are well known to care about their body image.

The high prevalence of eating junk food, more usage of computer and video games and less sport performance among our series of high school girls contribute markedly to the high percentage of obesity and its rising tide. Similarly in the study carried on 4852 American children and adolescents aged 8 - 18 years it was clear that low nutrient density food contributed more than 30% of daily energy[15].

Fortunately, the low prevalence of knowledge of the different food items and the less than satisfactory food choices and life style of the high school Kuwaiti girls did not make their BMI reach the alarming western levels. Nevertheless, it is alarming that the current study found overweight and obese school girls to have distinctly less nutritional knowledge and worse food choices and lifestyle compared to ones with normal weight, though this didn`t reach statistical significance (probably because of the small sample size). Worth noting here is that despite the intuitive appeal of education as a mean of improving diet, many studies in this area have failed to find significant associations between nutritional knowledge and dietary behavior[16].

CONCLUSION

In conclusion, Kuwaiti schoolgirls have deficient knowledge about healthy food and the importance of sound nutrition. Obesity and overweight are emerging problems among adolescent schoolgirls who reported excessive intake of junk food and beverages with high prevalence of computer and video games and minimal sport performance.

Although there is an insignificant association between the nutritional knowledge and dietary behavior of the studied adolescent school girls on one side and their BMI on the other, this deficient nutritional knowledge is likely to have a negative impact on their nutritional status as future mothers as well as the nutritional status of their children to come. We thus recommend that nutritional education programs are incorporated in the schedules for high school girls to prepare them for this critical growth period. Additionally, teaching the importance of sports, health hazards of junk food and the proper and limited usage of computer, and video games is essential.

ACKNOWLEDGEMENTS

The authors acknowledge the help provided by Dr Niran El-Naqeeb, head of the Pediatric Department, Al-Adan Hospital, MoH, Kuwait and thank her for the continuous support throughout this study. Mrs. Nouf Al-Ajmi, head of the Food and Nutrition department at Al-Adan Hospital, MoH, Kuwait was an asset for this study. She spared no effort to facilitate and organize the dietician participation in the field work of this study.

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Original Article

Knowledge and Perception of Breast Cancer and Practice of Breast Self-Examination among Female Patients Attending Primary Health Care Centers in Al Khobar City, Saudi Arabia

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Kuwait Medical Journal 2013; 45 (2): 123 - 129

ABSTRACT

Objective(s): To assess the knowledge of risk factors and screening methods for breast cancer, perception of the disease, and practice of breast self-examination (BSE) among female patients attending Primary Health Care Centers (PHCCs) in Al-Khobar city, Saudi Arabia
Design: Descriptive cross-sectional study using interview-based questionnaires
Setting: Primary Health Care Centers
Subjects: Six hundred Saudi and non-Saudi Arabic speaking females aged 25 years or more
Main Outcome Measures: Level of knowledge and perception of breast cancer; proportion of women practicing BSE
Results: Forty-eight percent women had poor knowledge about breast cancer. Around 85% women recognized postmenopausal hormone therapy, period of breast feeding and smoking to be risk factors for breast cancer. Only 25% women knew that mammogram is the best screening method. Almost half (49.2%) of participants were seriously concerned about getting breast cancer. In the multiple regression analysis, age, education and occupation of women were significant positive predictors of level of knowledge ($p < 0.05$). Television was the most important source of knowledge (44.1%). BSE was practiced by 44.6% women. Logistic regression analysis showed that practice of BSE in women was more likely with increasing age, educational level and knowledge scores as well as in homemakers and health-care workers ($p < 0.05$).
Conclusion: The study showed that a substantially high proportion (48%) of female PHCC attendees had knowledge deficits regarding breast cancer. BSE was not being practiced by 55.4% women. There is a need to target women for educational programs on breast cancer particularly through PHCCs.

KEY WORDS: awareness level, mammary carcinoma, screening for mammary tumors

INTRODUCTION

Breast cancer continues to be a major cause of morbidity and mortality across the world with one million cases diagnosed every year. It is the commonest cancer in women, comprising 18% of all female cancers[1]. In Saudi Arabia, while it was once presumed that the incidence of breast cancer was low, more recent data has indicated that it is as significant disease in this community, as elsewhere in the world[2]. The pattern of breast cancer in the country is also very disturbing. Ezzat *et al* observed that breast cancer affects younger premenopausal patients and a higher proportion present with metastatic or locally advanced disease[3]. The Saudi National Cancer Registry Report in 2007 revealed that breast cancer ranked first among females accounting for 26% of all newly diagnosed female cancers in the year 2007. Cancer incidence is predicted to continue rising in response to the changes in lifestyle witnessed during the last three decades among the Saudi population[4].

A study in Buraidah (Qassim) showed insufficient knowledge among female teachers about the risk factors of breast cancer, mammography screening and BSE[5]. Female high school and college students of Jeddah also showed limited knowledge of the disease with increased likelihood of hampering the screening programs[6]. A recent study in Al-Hassa (2009) found that women irrespective of their educational status, had knowledge deficits regarding breast cancer risk factors and there was underutilization of the recommended breast cancer screening modalities[7].

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Breast cancer is influenced by multiple risk factors with family history / genetic background accounting for approximately 15% of all cases[8]. The most well-known risk factors for breast cancer can be linked to the hazardous effects of hormonal exposures such as early age at menarche, late age of menopause, less number of children, nulliparity and first child after the age of 30 years. Furthermore, little or no breast feeding, long-term use of hormone replacement therapy and weight gain are related to increased breast cancer risk with different effects for premenopausal and postmenopausal women[9].

Breast self-examination (BSE) and mammography can help in early detection of breast cancer when it is most treatable. Boyle and Levin declared in 2008 that the current information at hand could prevent up to one-third of new cancers and increase survival for another one-third of cancers if detected at an early stage. Awareness of cancer signs and symptoms and attitude towards detection methods are an important part of this strategy[10]. Approximately 70% of all breast masses are self-detected, yet many women fail to carry out BSE as a monthly practice[11]. Many factors have been associated with BSE performance including knowledge and beliefs about breast cancer among women[2,5]. In Saudi Arabia, very few studies have been carried out to assess awareness of breast cancer risk factors and screening procedures, attitude towards the disease and practice of BSE. This study was therefore conducted with the following objectives: 1) To assess the knowledge of risk factors and screening methods of breast cancer, perception of the disease and the practice of BSE among ≥ 25 to 70-year-old female patients attending PHCCs in Al-Khobar city and 2) to correlate women's knowledge and perceived susceptibility and seriousness towards breast cancer with socio-demographic variables and practice of BSE.

SUBJECTS AND METHODS

Design and Setting: A descriptive, cross-sectional study conducted in selected PHCCs of Al-Khobar city during a one -week period in November, 2011.

Study subjects and sampling: Sample size was determined using the Epi-Info, version 6 and was based on an estimated 274,004 women registered at the PHCCs in Al-Khobar. It was assumed that 50% of women attending PHCCs lacked knowledge about breast cancer with an absolute precision of 4%. The sample size was estimated to be 599 at 95% confidence interval. Five out of ten PHCCs in Al-Khobar city with the largest population in the catchment area were chosen for the study. The study population included Saudi and non-Saudi women speaking the Arabic language and in the age group 25 to 70-year-old. Consecutive women arriving in the center and fulfilling the eligibility criteria were chosen. The number of study subjects selected from each center was proportionate to the number of annual attendees in a center.

Data Collection: The data collection tool was a piloted, interview-based questionnaire constructed in arabic. It included questions related to socio-demographic information (age, marital status, educational level and occupation), knowledge questions on the risk factors of breast cancer as described in literature[10,12], signs and symptoms of breast cancer, the best screening method and the correct timing of BSE. The total number of knowledge questions was 19. Each correct answer of the knowledge questions was given a score of one and the total score for each woman was calculated. Analysis of the data showed that knowledge scores of the women were normally distributed with the median (50^{th} percentile) and 75^{th} percentile values corresponding to 10 and 12 respectively. Hence level of knowledge was categorized into good if the score was ≥ 13, fair if it was 10 - 12 and poor if it was < 10. Questions were asked regarding perceived susceptibility and seriousness of breast cancer among the women, such as, her perceived risk and concern of getting breast cancer, whether she considered breast cancer was a hopeless disease without cure and whether getting breast cancer would endanger her life and marriage. Women were finally asked whether they practiced BSE.

Participants were asked to define their sources of knowledge about breast cancer.

Data was collected by trained fourth-year female medical students, supervised by faculty members of Family and Community Medicine, College of Medicine, University of Dammam, Saudi Arabia.

Statistical analysis

Statistical analysis was conducted using SPSS version 18. Descriptive statistics with cross-tabulation were performed. The Chi square–test was used to observe a) the influence of age on knowledge level of breast cancer and b) the practice of BSE in relation to perceived seriousness of the disease; t-test was done to observe any statistically significant difference between the mean knowledge scores of those practicing BSE from those not involved in the practice and one-way analysis of variance (ANOVA) tested the effect of education and occupation on the knowledge scores of women. Multiple regression analysis was done with knowledge score as the dependent variable. Independent variables included age (code 1: < 30years, code 2: 30 - 46 years, code 3: > 46 years) education level (code 1: illiterate / just literate, code 2: primary / middle school, code 3: high school, code 4: college / university) and occupational status (code 1: homemaker, code 2:

workers in non-health care fields, code 3: students, code 4: health care workers). Binary logistic regression analysis was performed to determine the predictors of BSE practice (code 0: No BSE; code 1: BSE done). Independent variables included knowledge score, age, educational level and occupational status. A p-value value less than 0.05 was considered significant.

Ethical considerations: Permission to conduct the study was obtained from the Ministry of Health. Ethical considerations were followed throughout the study. The purpose of the study was explained to the participants. Subjects were assured of anonymity and confidentiality.

RESULTS

1. Socio-demographic Data

A total of 600 women participated in the study. Table 1 presents the socio-demographic data of the studied women. The mean age of women was 35.98 (SD 9.05) years. More than half of the women were in the age category of 30 - 46 years, most of them were married (85.3%), while only few (5.5%) were widowed or divorced. Regarding the educational level, 40.3% of the women were college graduates / postgraduates, followed by 26.2% who had a high school degree. More than two-thirds of the women were home makers.

Table 1: Distribution of women according to the socio-demographic characteristics (N = 600)

Socio-demographic variables	Frequency	Percentage
Age		
< 30	184	30.7
30 - 46	328	54.7
> 46	87	14.5
Marital Status		
Single	55	9.2
Married	511	85.3
Widowed or divorced	33	5.5
Educational Level		
Illiterate or read and write	68	11.3
Elementary or middle school	133	22.2
High school	157	26.2
University or postgraduate	242	40.3
Occupation		
Homemakers	409	68.2
Non-health care workers	97	16.2
Students	21	3.5
Health care workers	73	12.2

2. Knowledge of Breast Cancer

The mean score of women for the knowledge questions was 9.76 (SD 2.89). Fig. 1 shows that 48% of the women had poor knowledge about breast cancer. The univariate analysis between age and awareness level showed that the extent of good, fair and poor knowledge were not significantly different in the three age groups (p = 0.882).

Table 2 shows the mean knowledge scores by educational level and occupational status; the lowest score was obtained by women who were illiterate or

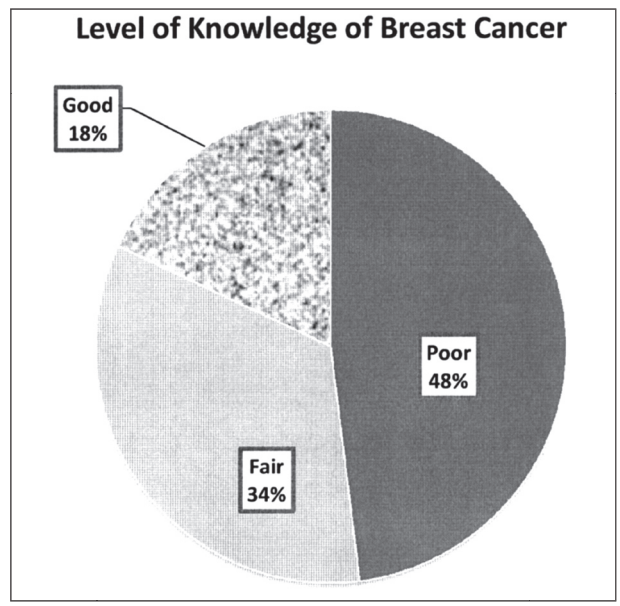

Fig. 1: Level of knowledge about breast cancer among female attendees of primary health care centers, Al-Khobar, Saudi Arabia (N = 600)

Table 2: Mean knowledge score of breast cancer by level of education and occupational status of women (N = 600)

Socio-demographic variables	Number	Mean Score	± SD	Significance*
Educational level				
Illiterate / read and write	68	8.28	2.83	F = 19.32
Primary / Intermediate	133	9.11	2.85	p < 0.001
High school	157	9.46	2.53	
College / University	242	10.72	2.85	
Total	600	9.76	2.89	
Occupational Status				
Homemaker	409	9.33	2.85	
Non-health care workers	97	9.93	2.62	F = 15.89
Student	21	10.48	2.93	p < 0.001
Health care workers	73	11.73	2.61	
Total	600	9.76	2.89	

*One-way ANOVA

Table 3: Multiple regression analysis model of the socio-demographic correlates of breast cancer knowledge

	B	SE	95% Confidence Interval		p-value
			Lower	Upper	
Constant	6.13	0.55	5.06	7.2	< 0.001*
Age	0.43	0.18	0.79	7.8	< 0.02*
Education	0.69	0.12	0.45	0.93	< 0.001*
Occupation	0.50	0.12	0.27	0.74	< 0.001*

* Statistically significant. Model: F = 27.01; p-value < 0.001; R^2 = 0.12

had no formal school education whereas the highest score was taken by the college / university graduates, the difference being statistically significant ($p < 0.05$). Knowledge score by occupational status showed that women working in the health-care field had the highest score compared to the other groups ($p < 0.05$).

Multiple regression analysis showed that age ($p < 0.05$), educational level ($p < 0.05$) and occupational status ($p < 0.05$) were significant positive predictors of the knowledge score. However these three independent variables explained only 12% ($R^2 = 0.12$) of the variation in knowledge level (Table 3).

Table 4 shows that a majority of the women (> 80%) knew that postmenopausal hormone therapy, short period of breast feeding, smoking and first pregnancy over 30 years of age were risk factors for breast cancer. On the other hand, X-ray exposure, early menarche and late menopause were known to one-third or lesser proportion of women. Signs and symptoms of breast cancer were correctly known to more than two-thirds of the respondents. Only one-fourth (24.4%) of the respondents were aware that mammogram was the best screening method for diagnosis of breast cancer.

The most important source of breast cancer information among the women was the television (44.1%) followed by information from print media (38.5%), family and friends (27%), PHCCs / schools (14.7%) and the internet (14.4%).

3. Perception of Breast Cancer

An enquiry into the perceived susceptibility and seriousness of breast cancer showed that, half of the participants (50%) did not believe themselves to be more susceptible than other women, as opposed to 49% who were concerned about getting breast cancer. Two-thirds (63.5%) of the women believed that having breast cancer would endanger their lives and about 45% thought that it would affect their marriage adversely. Lastly, more than a quarter of women (26.4%) were not aware that breast cancer could be curable (Table 5). There was no significant relationship between perceived susceptibility and seriousness for breast cancer and socio-demographic variables.

Table 4: Distribution of women according to knowledge of breast cancer (N = 600)

Knowledge of Breast Cancer	Response	
	Correct n (%)	Incorrect n (%)
Risk Factors		
Family history	310 (51.9)	290 (48.1)
Oral contraceptive pills	350 (58.5)	250 (41.5)
Postmenopausal hormonal therapy	515 (87)	85 (13)
Breast feeding less than one year	504 (84.3)	96 (15.7)
Cigarette smoking	499 (83.2)	101 (16.8)
Obesity	298 (49.7)	302 (50.3)
First pregnancy over 30 years age	405 (67.5)	195 (32.5)
Nulliparous	242 (40.3)	358 (59.7)
Age 50 - 70 years old	222 (37.2)	378 (62.8)
Puberty <12 years age	163 (27.5)	437 (72.5)
Menopause > 55 years age	196 (32.8)	404 (67.2)
History of Breast biopsy	129 (21.6)	491 (78.4)
Exposure to X-ray	208 (34.7)	392 (65.3)
Screening		
Best method -- Mammogram	146 (24.4)	454 (75.6)
Early detection, better prognosis	521 (87)	79 (13)
Signs and symptoms		
Breast masses	521 (87)	79 (13)
Nipple secretions	411 (68.5)	189 (31.5)
Nipple cracks	387 (64.5)	213 (35.5)
Best Timing for BSE		
Immediately after menstrual period	311 (51.8)	289 (48.2)

4. Practice of Breast Self-Examination

BSE was not being practiced by more than half of the women (55.4%). The overall mean knowledge score for those doing BSE was higher (10.57, SD 2.9) than those not involved in the practice (9.1, SD 2.7), the difference being statistically significant ($p < 0.05$). The logistic regression analysis showed that increasing knowledge score was a significant positive predictor

Table 5: Perceived susceptibility and seriousness among women for breast cancer. (N = 599)*

Perceived susceptibility and seriousness	Agree n (%)	Uncertain n (%)	Disagree n (%)
I think I'm more susceptible to have the disease than other women	107 (17.8)	192 (32)	300 (50)
I believe having breast cancer will endanger my life	381 (63.5)	62 (10.3)	156 (26)
I believe having breast cancer will affect my marriage	267 (44.5)	79 (13.2)	254 (42.3)
I think there is no cure for breast cancer	100 (16.7)	58 (9.7)	442 (73.7)
I am concerned a lot about getting breast cancer	294 (49.2)	69 (11.5)	235 (39.2)

*one woman did not respond

Table 6: Logistic regression analysis model of the knowledge score and socio-demographic correlates of breast self-examination

Correlates	B Coefficient	SE	Odds Ratio	Confidence interval		p-value
				Lower	Upper	
Knowledge score	0.154	0.03	1.17	1.1	1.2	< 0.001*
Age Group						
< 30 years			Reference			
30 - 46 years	0.506	0.21	1.66	1.1	2.5	< 0.02*
> 46 years	0.85	0.30	2.3	1.3	4.2	< 0.01*
Educational Level						
Illiterate			Reference			
Primary / middle	0.82	0.35	2.27	1.15	4.46	< 0.02*
High School	0.83	0.35	2.3	1.16	4.55	< 0.02*
College / University	1.46	0.36	4.3	2.12	8.75	< 0.01*
Occupational Status						
Student			Reference			
Homemaker	1.27	0.56	3.55	1.19	10.58	< 0.02*
Non-health care worker	0.64	0.59	1.89	0.6	5.96	0.28
Health care worker	1.271	0.59	3.56	1.11	11.39	< 0.03*
Constant	- 4.26	0.72	0.014			< 0.001*

*Statistically significant,Model: Chi-square 69.04, p-value < 0.001

of BSE practice ($p < 0.05$). Older women (> 46 years of age) were twice as likely to perform BSE as those less than 30 years of age ($p < 0.05$). College / university educated women were four times more likely to be involved in BSE practice than the illiterate group ($p < 0.05$) and workers in the health-care field as well as homemakers were almost 3.5 times more likely to practice BSE than students ($p < 0.05$) (Table 6).

Practice of BSE was less common among women whose perceived seriousness for breast cancer was high in terms of the disease endangering their life (61.7% Vs 65%; $p < 0.05$) and marriage (41.9% Vs 46.7%; $p < 0.05$) and who had no hope for cure of breast cancer(12.7% Vs 19.9%; $p < 0.05$).

DISCUSSION

This study aimed to find out the level of breast cancer knowledge, the perceived susceptibility and seriousness of the disease and practice of BSE among females attending PHCCs in Al-Khobar city, Saudi Arabia. The study findings showed that almost half of the interviewed women (48%) had poor knowledge about risk factors of breast cancer. These findings are similar to other Saudi studies conducted in Buraida and Al-Hassa where 52.1% and 59.5% women respectively, had deficits regarding knowledge of risk factors for the disease[5,7]. A study conducted in Qatar showed women to have better awareness of breast cancer risks related to positive family history (67.7%) and exposure to radiation (63.8%) but poorer knowledge for other risk factors compared to the present study[12]. School teachers from Buraida also showed less awareness of risk factors than women from our study. The most common disease-risks reported by teachers were lack of breast feeding (52.7%), female sex hormones (38.6%), positive family history (22.1%) and radiation exposure (17.8%)[5]. In a study conducted in the UK, British women considered family history (90%), past history of breast cancer (70%) and smoking (60%) to be significant risk factors[13]. Smoking as a health risk for cancer was also reported by many PHCC attendees from Qatar (72.3%)[12] and Riyadh (94.3%)[14] as well as our study population (83.2%). The strong link between smoking and cancer in general, is well known and logically leads to the most commonly identified risk factor for breast cancer in most studies. Better awareness of breast cancer risk factors should guide women to take care of their health and avoid the modifiable risk factors. Moreover women with non-modifiable risk factors should be guided to seek early advice by regular involvement in screening procedures. It was encouraging to note that most women in our study (87%) knew about the good prognosis of breast cancer if diagnosed early. Similar findings were reported among women from Qatar (94.6%) and Saudi men and women from Riyadh (80.7%)[12,14]. With this belief, it would be possible to motivate women better for screening programs in future.

Knowledge of signs and symptoms of breast cancer are important in motivating women to seek advice for early diagnosis and treatment. Around two-thirds of women in this study (≥ 65%) knew about the signs and symptoms of breast cancer with painless breast lump (87%) being the most identified feature. Women from Qatar (67.7%), Iran (44%) and the UK (70%) also reported painless breast mass to be the most common symptom of the disease[12,13,15]. In general, women are usually aware of this clinical feature of breast cancer through mass media, family and friends.

Our study showed that increasing level of education was independently and positively related to the knowledge score in the multiple regression analysis, a finding which was expected. Other Saudi studies too have observed knowledge of breast cancer to be better in women with higher educational standing[2,5,7]. Moreover, data on the National American survey on cancer risk revealed poor knowledge among the least educated women[16]. Occupational status was also a positive significant predictor of the knowledge score with workers in the health-related fields having better knowledge than homemakers and workers of other sectors, pointing to the need to especially target the latter groups for health education.

Increasing age has been associated with better knowledge in several studies[5,7,14]. Our study also showed this relationship in the multiple regression analysis ($p < 0.05$).

The most common sources of knowledge about breast cancer among women were television (44.1%) programs followed by print media (30.5%). Other Saudi studies have mentioned the same sources to be common[5,14]. Unfortunately, the health education sessions at the PHCCs were not identified as a popular source (14.7%) considering the important role of primary health care workers to disseminate health knowledge. This needs the attention of primary health care services for more intensive health education activities on breast cancer.

While half of the study population (50%) did not believe in their increased risk of getting breast cancer compared to other women, another half (49.2%) expressed high concern about getting the disease in future. Corresponding figures for women in Qatar were similar, 56.9% and 56.2% respectively[12] and were also similar to studies conducted in South Africa and Hong Kong[17,18]. However fewer British women (28%) were reported to worry about getting breast cancer[13]. A majority of our study subjects believed that breast cancer was curable (73.7%) similar to women from Qatar, many of whom did not think it was a hopeless disease (67%)[12]. On the other hand, more than half (58.2%) of the female teachers from Buraidah held pessimistic views about the curability of breast cancer mainly because of popular misconceptions[5].

More than half of the participants did not perform BSE (55.4%), which is unlike findings from western countries where close to 80% women were found to be involved in the practice[19]. Other studies from Saudi Arabia also observed BSE practice to be uncommon among women such as those from Buraidah (32.4%) and Riyadh (41.2%)[2,5]. Lower figures for practice of BSE than ours have been reported among women from Qatar (35%), Turkey (40.9%) and Iran (17%)[12,15,20]. In general, there is need to promote this screening tool in the region.

Logistic regression analysis showed that increasing age and knowledge scores of the participants were significant independent predictors of BSE practice in our study ($p < 0.05$). Women in Riyadh, Buraidah and Qatar also demonstrated this link between level of knowledge and practice of BSE[2,5,12]. Moreover, participants who had undergone some level of formal education were two to four times more likely to practice BSE than the illiterate women ($p < 0.05$). This finding suggests that there is a need to target women with no formal education for adoption of BSE practice.

Contrary to our expectations, women whose perceived seriousness of breast cancer was high were less likely to perform BSE. Similar findings have been reported for women in another study[12]. Perhaps these women have a high element of fear should they discover any abnormalities which prevents them from performing the procedure. This needs the attention of health care workers.

In Saudi Arabia, the national drive for breast cancer screening was initiated a few years ago and it is hoped that more women will adopt BSE among other screening procedures. Though screening by BSE has not contributed to a decline in breast cancer mortality in western countries[21] it is believed that in countries where breast cancer is diagnosed at an advanced stage, teaching and practice of BSE is important and will probably be effective in reducing breast cancer mortality[22]. This situation justifies the importance of BSE in Saudi Arabia

CONCLUSION

The findings of this study showed that a substantially high proportion (48%) of female PHCC attendees had poor knowledge of breast cancer and screening methods. Lack of knowledge for risk factors was particularly seen for questions on early menarche (72.5%), late menopause (67.2%), history of breast biopsy (78.4%), exposure to X-rays (65.3%), nulliparity (59.7%) and age-group likely to get breast cancer (62.8%). About three-quarters (75.6%) of the women were unaware of mammogram as the best screening method for breast cancer. Level of knowledge was positively and independently correlated with age ($p < 0.05$), educational level ($p < 0.05$) and occupational status ($p < 0.05$) of women. Practice of BSE was not being advocated by more than half (55.4%) of the studied population. Women with higher knowledge scores on breast cancer, increasing age and educational level as well as health care workers and homemakers were significantly more likely to practice BSE ($p < 0.05$). There is a need to especially target local women with no formal schooling, non-health care workers and women with high perceived seriousness of the disease for educational programs on breast cancer. The focus in educational sessions should be in areas of knowledge

deficiencies observed in the study. Moreover the practice of BSE which is the best option for interval screening among women of all ages, needs to be encouraged together with breast clinical examination to facilitate early diagnosis of mammary carcinoma .

Despite several campaigns in the Eastern Province on breast cancer such as the Al Shaqyah Wardyah campaign, the message about the disease has not reached the local population adequately. PHCCs should cooperate with these campaigns to reach out to all adult females and high school girls of the local region. Better awareness of breast cancer is likely to motivate women for screening procedures from early ages and contribute to a decline in breast cancer mortality in this region.

ACKNOWLEDGMENT

Thanks are due to the fourth year medical students (Academic year 2011 - 2012) for collection of the data. Special thanks are extended to Dr. Maryam Khalid Al Soweilem for her hard work and contribution in this research publication. Many thanks to the PHCC attendees who participated in the study.

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Original Article

Hypernatremia among In-Patients in Intensive Care Unit and Medical Wards of a General Hospital in Kuwait

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Kuwait Medical Journal 2013; 45 (2): 130 - 133

ABSTRACT

Objectives: To determine the incidence and etiology of hypernatremia in adult patients admitted to a general hospital in Kuwait
Design: A hospital based retrospective study carried out between July 2009 and December 2009
Setting: Intensive Care Unit (ICU) and Medical inpatient wards, Department of Medicine, Al-Jahra Hospital, Kuwait
Subjects: Ninety-two hypernatremia patients (41 male and 51 female) out of a total of 1825 patients were analyzed and their etiology studied
Intervention: All blood samples were analyzed in biochemistry department on LX20 machine. Information regarding age, gender, highest serum sodium levels, clinical diagnoses and further clinical information suggesting causes of hypernatremia was gathered.
Main Outcome Measures: Frequency, etiology, outcome and management of hypernatremia in adult inpatients
Results: Out of a total of 1825 patients analyzed, 5.04% were diagnosed with hypernatremia with mean serum sodium of 150.9 mmol/l. Among major causes of hypernatremia were hyperglycemia (21.7%), IV fluids (21.7%) and dehydration (17.4%).
Conclusion: The overall incidence of hypernatremia in this hospital was 5.04%. Hyperglycemia and IV fluid administration were the commonest causes (21.7% each). All patients were treated based on the treatment recommendations mentioned in the discussion. There were no cases with cerebral edema due to the treatment. However two patients with severe hypernatremia and sodium level of ≥ 165 mmol/l, who had central diabetes insipidus (CDI) secondary to traumatic head injury, died in spite of the appropriate management of hypernatremia.

KEYWORDS: diabetes insipidus, dehydration, hypernatremia, sodium levels

INTRODUCTION

Hypernatremia is defined as serum sodium levels greater than 145 mmol/l. It is a common electrolyte disorder. Because sodium is a functionally impermeable solute, it contributes to tonicity and induces the movement of water across cell-membranes[1]. Therefore, hypernatremia invariably denotes hypertonic hyperosmolality and always causes cellular dehydration, at least transiently[1]. It can be classified, based on urine osmolality and urine sodium, as renal or non-renal. Hypernatremia may progress to seizures, coma and death.

The resultant morbidity may be inconsequential, serious or life threatening. Hypernatremia frequently develops in hospitalized patients as an iatrogenic condition and some of its most serious complications result not from the disorder itself but from inappropriate treatment[1,2]. Hence, we wanted to increase awareness regarding the causes and the recommended prompt treatment in order to prevent complications.

Hypernatremia has rarely been studied in hospital in-patients. We therefore, undertook this study in one of the major general hospitals in Kuwait.

SUBJECTS AND METHODS

A retrospective study of adult patients, admitted to medical wards and intensive care unit over a period of six months, from July to December 2009, for incidence of hypernatremia was carried out. Hypernatremia was defined as a serum sodium level more than 145 mmol/l. All blood samples were analyzed in the biochemistry department on LX20 machine. Information regarding age, gender,

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Table 1: Demographic characteristics and level of serum sodium in hypernatremia patients in Al-Jahra hospital

Age and Gender	Total patients		Sodium level (mmol/l)	
	n	%	Mean	Median (Range)
Age group (yrs)	11	12	157	149.1 (146.3 - 201.1)
13 - 24	20	21.7	150.2	147.5 (146.2 - 162.3)
25 - 44	23	25	149	148.2 (146.1 - 157.4)
45 - 64	38	41.3	150.6	148.9 (146.1 - 163.7)
≥ 65				p = 0.243
Gender				
Male	41	44.6	152	147.8 (146.1 - 201.1)
Female	51	55.4	149.4	148.7 (146.1 - 163.7)
				p = 0.706
All patients	92	100	150.9	148.4 (146.1 - 201.1)

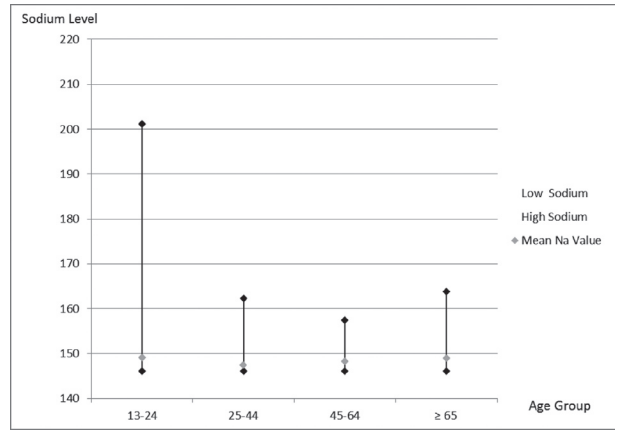

Fig 1: Demographic characteristics and level of sodium in hypernatremia patients in Al-Jahra hospital

the highest serum sodium (whenever several results were available in the same patient), clinical diagnosis and further clinical information suggesting causes of hypernatremia were recorded. The sodium levels were categorized into three types: mild (146 - 155), moderate (156 - 165) and severe (more than 165 mmol/l).

Statistical analysis: The statistical software, statistical package for social sciences (SPSS version 16.0) was used for data analysis and presentation. The descriptive statistics has been presented as mean, median and range. Sodium levels between male and female patients were compared using non-parametric Mann-Whitney U test, and among different diagnosis with Kruskal-Wallis test. A p-value < 0.05 was considered significant.

RESULTS

A total of 1825 patients were studied during a period of six months (July to December 2009). Ninety-two patients (5.04%) were found to have hypernatremia. Forty-one (44.6%) were male and 51 (55.4%) were female (Table 1) (Fig. 1).

The overall mean age was 54.8 years (range: 13 and 95 years). The most affected were those, 65 years and above (41.3%), although an increasing trend with age was observed. The mean age among females (60 years) was found to be significantly higher ($p < 0.013$) as compared to 48.4 years in males. The median sodium level was 148.4 mmol/ l (range: 146.1 - 201.1 mmol/l).

Genderwise, no significant difference ($p = 0.706$) was found in sodium levels (147.8 in males Vs 148.7 in females). No significant differences in sodium levels were observed in the four age-groups ($p = 0.427$), though they were higher (149.1 mmol/l) in the younger age-group (13 - 24 years).

Most of the patients (77, 83.7%) had mild hypernatremia (146 - 155 mmol/l), while 13 (14.1%) had moderate hypernatremia (156 - 165 mmol/l). Two patients had severe hypernatremia (> 165 mmol/l, Table 2).

The most common causes of hypernatremia were IV fluids and hyperglycemia. The mean sodium concentration in the IV fluid and hyperglycemia subset of patients was 150 mmol/l (Table 2).

Table 2 : Diagnosis and sodium levels in hypernatremia patients

Diagnosis	Total patients (%)	Male	Female	Mild	Moderate	Severe	Mean	Median (Range)*
NDI	16 (17.4)	8	8	13	2	1	153.9	150.1 (146.2 - 201.1)
Vomiting	6 (6.5)	3	3	5	1	0	149.2	146.9 (146.2 - 156.8)
Dehydration	16 (17.4)	7	9	12	3	1	151.6	147.5 (146.3 - 168.1)
Diuretic use	12 (13)	7	5	11	1	0	149.5	148.9 (146.4 - 156.2)
IV Fluids	20 (21.7)	7	13	16	4	0	150	147.9 (146.1 - 162.3)
Hyperglycemia	20 (21.7)	7	13	18	2	0	150	147.9 (146.1- 163.7)
Polyuria	1 (1.1)	1	0	1	0	0	147.2	
Ethanol ingestion	1 (1.1)	1	0	1	0	0	154.9	
All patients	92 (100)	41	51	77	13	2	150.9	148.4 (146.1 - 201.1)

* No significant differences (Diagnosis Vs Sodium level, p = 0.678)

DISCUSSION

The incidence of hypernatremia in our study (5.04%) correlates well with most of the other studies. A female preponderance was noticed. A majority of our patients (81.52%) had moderate hypernatremia (156 - 165 mmol/l). Most of the studies on hypernatremia are in the pediatric age group and only two studies were in adult hospitalized patients.

The commonest cause of hypernatremia in our study was dehydration and the commonest etiological factors of dehydration were vomiting, diarrhea, insensible and sweat losses as with fever or diuretics; and caused a mild to moderate hypernatremia.

Dehydration is frequently confused with hypovolemia, occasionally leading to inaccuracies in diagnosis and therapy. Hypernatremia reflects a relative deficit of water in relation to sodium. Water loss, leading to an elevation in plasma sodium concentration and an intracellular water deficit due to osmotic movement of water from cells into extracellular fluid is called dehydration[1-4].

Patients with dehydration are always hypernatremic as only water is lost. Those patients, with salt and water loss typically have plasma sodium that is normal or even reduced. So the clinical distinction between pure water loss and salt with water loss is made by measurement of serum sodium level[5].

However, hypernatremia can occur with salt and water loss, if water is lost in excess of salt, and water is not replaced. Such patients may be considered to have both dehydration and hypovolemia and have impairment in both plasma tonicity and volume[1,5].

Unlike hypernatremia in outpatients, hospital acquired hypernatremia affects patients of all ages[1].

Proper treatment requires a two-pronged approach, addressing the underlying cause and correcting the prevailing hypertonicity. In patients with hypernatremia that developed over a period of hours, rapid correction improves prognosis without increasing the risk of cerebral edema. In such patients, reducing the sodium concentration by 1 mmol/l/hr is appropriate[6-8].

The pace of correction should be slower in patients who develop hypernatremia over longer duration or unknown duration and should be at a rate of 0.5 mmol/l/hr. So generally the recommendation is for a correction of 10 mmol/l/day except for those in whom the disorder has developed over a period of hours. The goal of treatment is to reduce the serum sodium concentration to 145 mmol/l[5,6]. The preferred route of administering fluids is the oral route or by feeding tube[9,10]. If neither is feasible, fluid should be given intravenously.

Except in cases of frank circulatory compromise, 0.9% sodium chloride is unsuitable for managing hypernatremia. The following is a simple formula that helps in correcting the hypernatremia[5,8,10-12].

Formula:

1. Change in serum Na^+ = $\frac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{Total body water} + 1}$

(To estimate the effect of one liter of any infusate on S. Na^+)

2. Change in Serum Na = $\frac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{S. } Na^+}{\text{Total body water} + 1}$

(To estimate the effect of one liter of any infusate containing Na^+ and K^+ on S. Na^+)

After selecting the appropriate infusate, the rate of infusion must be determined. This can be calculated using the above formula. The required volume of infusate, and hence the infusion rate is determined by dividing the change in the serum sodium concentration targeted for given treatment period by the value obtained from formula no. 1.

Our patients were clinically classified based on the causes into hypovolemic, euvolemic and hypervolemic hypernatremia. The underlying causes like vomiting, inappropriate IV fluid use and hyperglycemia were managed first and using the above mentioned formula the hypernatremia in these patients was successfully treated without any treatment associated morbidity or mortality. Two patients died secondary to post-traumatic brain injury that had developed central diabetes insipidus (CDI) leading to severe hypernatremia.

CONCLUSION

The overall incidence of hypernatremia in Al-Jahra hospital was 5.04%. Hyperglycemia and IV fluid administration were the commonest causes followed closely by dehydration. Mild hypernatremia is the commonest and severe hypernatremia is usually associated with death. No significant differences in sodium levels exist in different ages and sexes.

Prompt treatment of hypernatremia is necessary but care should be taken to avoid excessively rapid correction or overcorrection, which increases the risk of iatrogenic cerebral edema. Most importantly, the fluid prescription should be reassessed regularly along with laboratory values and the patients' clinical status.

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Original Article

Prognostic Value of Initial Arterial Lactate Levels in Childhood Acute Carbon Monoxide Poisoning

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Kuwait Medical Journal 2013; 45 (2): 134 - 137

ABSTRACT

Objective: To compare the prognostic values of lactate and carboxyhemoglobin (COHb) levels on clinical neurological and cardiac involvement in children with carbon monoxide poisoning
Design: Clinical Trial (Prospective Study), over a two year period
Setting: Pediatrics Emergency Department, Eskisehir Osmangazi University School of Medicine, Turkey
Subjects and Methods: A total of 77 children aged one month to 17 years who were referred to the pediatric emergency department (PED) between 1st April 2009 and 30th April 2011 and diagnosed with carbon monoxide intoxication were assessed for age, gender, symptoms, clinical findings, blood lactate levels, COHb levels, morbidity and mortality.
Intervention: Patients with more than 5% COHb, lactate, CK-MB (creatine kinase-myocardial band) and troponin levels were studied.
Main Outcome Measures: Symptoms, laboratory results and neurological and cardiac complications were studied to determine whether there is a correlation among patients with neurologic and cardiac signs and COHb and lactate levels the latter being a marker for tissue hypoxemia. Increased CK-MB and troponin levels were evaluated as markers of cardiac involvement.
Results: There was a significant positive correlation between initial lactate levels in blood gas analysis, early neurologic findings and delayed neurological sequelae (DNS) and cardiac involvement as compared to COHb levels.
Conclusion: The initial lactate levels have higher prognostic value for cardiac involvement and DNS as compared to COHb and it may be helpful for treatment.

KEY WORDS: carboxyhemoglobin, CK-MB, DNS, lactate, troponin

INTRODUCTION

Carbon monoxide gas (CO) is a colourless, odourless, tasteless and non-irritating but highly toxic gas which is not differentiated by the five senses. It is seen in smoke produced due to lack of adequate oxygen in surrounding air or insufficient burning of fuels such as gas oil, benzene, bottled gas, coal and firewood. It constitutes 3.6 - 9.4% of pediatric intoxications. It is one of the most important causes of deaths due to intoxications (58.2 - 75%). About 3800 - 5000 persons die each year due to CO intoxication by accident or suicide in USA and approximately one third of these are pediatric patients[1].

There is no specific diagnostic finding in CO intoxication. The patient's medical history and more than one person involved in the same environment are important factors in the CO intoxication. Definitive diagnosis is made by carboxyhemoglobin (COHb) levels in blood gas analysis. COHb levels may be low in delayed measurements and the levels may not correlate with clinical signs and prognosis[2]. Therefore, increased blood lactate level which indicates tissue hypoxia may be a guide for general perfusion and organ function. Serum lactate levels increase from excessive lactate production in ongoing anerobic metabolism or reduced lactate metabolism due to hypoperfusion of the liver or kidney[3]. The measurement of blood gas and lactate is important to determine the severity of hypoperfusion and acidosis. The risk of toxicity in CO poisoning is higher in tissues which are sensitive to hypoxia, especially, the brain and heart[4,5].

There is no adequate information about the value of serum lactate and COHb levels in determining cardiac and neurologic involvement in CO poisoning, particularly during childhood. There are a limited number of studies on this subject. In the present study, we aimed to compare the value of lactate and COHb levels for clinical diagnosis as well as clinical follow-

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up. We evaluated the symptoms, laboratory results and neurologic and cardiac status of children diagnosed with CO poisoning in the pediatric emergency department (PED) of Eskisehir Osmangazi University School of Medicine, Turkey and aimed to determine whether there is a correlation among the neurologic and cardiac status and COHb and lactate levels.

SUBJECTS AND METHODS

A total of 77 cases diagnosed as CO intoxication in our PED between 1st April 2009 and 30th April 2011 were included in the study. CO intoxication was diagnosed by medical history and blood COHb level above 5%. Patients with previously known chronic liver disease, heart disease or rhythm disorder or who previously received oxygen were excluded. In this prospectively designed study, personal data, symptoms, cardiac and neurologic signs and delayed neurologic sequelae (DNS) were recorded. A blood sample was also obtained for arterial blood gas analysis in all cases using syringes containing heparin on admission and immediately after 100% oxygen treatment by non-rebreathing mask was started. The levels of lactate, COHb, pH, pCO_2, pO_2 and HCO_3 were measured using 'Roche Omnis-S' blood gas device. The relationship between COHb and lactate levels was statistically analyzed using Pearson Correlation Analysis Test.

For cardiovascular evaluation, 12-lead electrocardiography (ECG) records were obtained in all cases. The levels of creatine kinase-myocardial band (CK-MB) and troponin-I among the myocardial enzymes were measured during the emergency department admission. CK-MB band was measured by commercial ready kit (Olympus) using 'Olympus AU 640' device, and troponin-I was also measured by ready kit (Axsym Troponin-I ADV) using 'Abbott Axsym' device. CK-MB levels below 3 U/l and troponin-I levels below 0.2 ng/ml were considered as normal. Patients with increased myocardial enzymes were assessed by pediatric cardiologist and echocardiographic investigations were performed. Patients were discharged when COHb level decreased below 2% and clinical signs and findings improved. They were divided into groups according to presence of neurologic signs *i.e.*, history of syncope before admission and / or altered level of consciousness, seizure, vertigo, syncope and abnormal CNS examination at presentation. Groups with or without neurological signs were compared for COHb and lactate levels. DNS is described as neurologic abnormality from 3 - 245 days after patient fully improved. The mean COHb and lactate levels of patients with and without DNS were compared separately. In our study, extremely increased CK-MB and troponin-I levels were considered as cardiac involvement. Also, patients were divided into groups according to presence of cardiac involvement. The correlation among the levels of COHb, CK-MB and troponin-I was evaluated and the differences between the mean CK-MB and troponin levels of patients with increased or normal lactate levels were analyzed.

Ethics Committee approval was obtained for this study (TN: PR 12-06-25-68).

Statistical Analysis: Data were analyzed using Statistics Program SPSS 17. Kolmogorov-Smirnov Distribution Test was used for normal distributed variables as well as definitive statistical methods (frequency, percentile, mean, standard deviation). For the quantitative data of two groups, parameters were compared using Independent Samples t-Test. One Way Anova and Tukey Tests were used for the comparisons of quantitative data of more than two groups. Two quantitative data were compared using Pearson Correlation Analysis. Results were evaluated with 95% confidence interval. A p-value of < 0.05 was considered significant and a p-value < 0.001 was considered highly significant.

RESULTS

Table 1: Correlation analysis for the relation between lactate and COHb levels

		Number	Ratio	p-value
COHb level	Lactate level	77	0.330	0.004*

*$p < 0.05$
There is a significant correlation between lactate and COHb levels. (p values of < 0.05 were considered significant, $p < 0.001$ was considered highly significant).

Forty-three patients (55.8%) were girls and 34 (44.2%) were boys .The mean age was 9.19 ± 4.75 years. There was a positive significant correlation of 33.0% between COHb and lactate levels ($r = 0.330$; $p = 0.004$) (Table 1).

Lactate levels were significantly higher in patients with Glasgow Coma Scale (GCS) score of < 14 (4.060 ± 1.526) compared to patients with GCS score of 15 (2.241 ± 1.315) ($p < 0.001$). Lactate levels (4.980 ± 2.372) were significantly higher in patients with DNS than those without DNS (2.681 ± 1.301) ($p = 0.000$**). Patients with loss of consciousness had higher lactate levels compared to patients without loss of consciousness (3.561 ± 0.64 Vs 2.356 ± 0.884) ($p = 0.000$**). Lactate levels were significantly higher in those with syncope (3.666 ± 0.635) compared to cases without syncope (2.556 ± 0.964) ($p = 0.000$**). Lactate levels were significantly higher in patients with seizures (3.755 ± 0.790) compared to those without (2.905 ± 0.937) ($p = 0.000$**) (Table 2).

There was no significant difference in COHb levels in patients with GCS score of < 14 or 15 (4.060 ± 1.526 Vs 2.241 ± 1.315) ($p = 0.306$). COHb levels were

Table 2: Distribution of lactate levels according to neurologic findings

Neurologic findings		n	Mean ± SD	p-value
Glasgow Coma Scale (GCS)	<14	31	4,060 ± 1,526	0.000**
	15	46	2,241 ± 1,315	
Abnormal neurologic sign	Yes	4	4,080 ± 0,183	0.000**
	No	73	2,027 ± 1,687	
Delayed neurologic sequelae	Yes	10	4,980 ± 2,372	0.014*
(DNS)	No	67	2,681 ± 1,301	
Vertigo	Yes	6	2,495 ± 1,100	0.457
	No	71	3,025 ± 1,698	
Consciousness change	Yes	29	3,561 ± 0,604	0.000**
	No	48	2,356 ± 0,884	
Syncope	Yes	27	3,666 ± 0,635	0.000**
	No	50	2,556 ± 0,964	
Seizures	Yes	18	4,237 ± 1,887	0.000**
	No	59	2,715 ± 0,968	
Cognitive disorder	Yes	4	3,755 ± 0,790	0.084
	No	73	2,905 ± 0,937	

*:p < 0.05 **:p < 0.01
p values of < 0.05 were considered significant, p < 0.001 was considered highly significant

similar in patients with or without vertigo, altered consciousness and seizures (p > 0.05). No significant difference was determined in COHb levels between patients with DNS (29.450 ± 8.091) and without DNS (19.227 ± 9.754) (p = 0.778). COHb levels in patients were significantly higher with positive neurological signs (4.060 ± 1.526) than in patients with GCS score of 15 (2.241 ± 1.315) (p = 0.002**). Also, COHb levels were significantly higher in patients with cognitive disorder (31.575 ± 9.419) compared to those without cognitive disorder (20.202 ± 9.659) (p = 0.027) (Table 3).

A significant positive relation of 70.3% was found between CK-MB and lactate levels (r = 0.703; p =0.000). There was also a significant positive correlation between troponin-I and lactate levels

Table 3: Distribution of COHb levels according to neurologic findings

Neurologic findings		n	Mean ± SD	p-value
Glasgow Coma Scale (GCS)	<14	31	22,000 ± 11,062	0,306
	15	46	19,580 ± 9,426	
Abnormal neurologic sign	Yes	4	29,450 ± 8,091	.002**
	No	73	19,227 ± 9,754	
Delayed neurologic sequelae	Yes	10	19,227 ± 9,754	0.778
(DNS)	No	67	16,017 ± 11,465	
Vertigo	Yes	6	16,017 ± 11,465	0.255
	No	71	20,938 ± 9,990	
Consciousness change	Yes	29	20,093 ± 11,171	0.487
	No	29	21,917 ± 8,502	
Syncope	Yes	27	20,848 ± 10,653	0.973
	No	33	20,936 ± 9,531	
Seizures	Yes	18	23,400 ± 10,699	0.345
	No	40	20,670 ± 9,837	
Cognitive disorder	Yes	4	31,575 ± 9,419	0.027*
	No	51	20,202 ± 9,659	

*p < 0.05, **p < 0.01
p values of < 0.05 were considered significant, p < 0.001 was considered highly significant

Table 4: The relation among lactate, COHb and cardiac involvement (with CK-MB and troponin-I)

Cardiac Markers		COHb level	Lactate level
CK-MB#	Ratio	0.703	0.284
	p-value	0.000**	0.012*
Troponin- I	Ratio	0.489	0.225
	p-value	0.000**	0.049*

*p < 0,05, **p < 0,01
p-values of < 0.05 were considered significant, p < 0.001 was considered more significant
#creatine kinase-myocardial band

(r = 0.489; p = 0.000). CK-MB and COHb levels showed a significant positive correlation (r =0.284; p = 0.012) (Table 4).

There was a significant positive correlation (r = 0.225; p = 0.049) between troponin-I and COHb according to correlation analysis performed to determine this relation. Similarly, COHb increased increasing troponin-I (Table 4).

DISCUSSION

CO is an odourless, colourless and tasteless gas that can easily be absorbed from the lungs. Most of the inhaled CO gas is excreted unchanged from the lungs, 10 - 15% binds to myoglobin and cytochrome-C proteins and less than 1% is dissolved in the plasma. CO binds rapidly to hemoglobin because its affinity for hemoglobin is 200 - 250 times that of oxygen and leads to the formation of COHb. It causes tissue hypoxia due to decreased oxygen carrying capacity of blood and oxygen supply to tissues is reduced, and O_2 dissociation curve is shifted to the left. It was considered that direct toxic effect of plasma CO plays an important role in tissue brain damage resulting from released free O_2 radicals due to ischemia. Also, lipid peroxidation is important for cellular damage[1,2]. Increased blood lactate level is expected in states of inadequate tissue perfusion and it should be a marker for organ dysfunction[3]. The prognosis of CO poisoning varies from patient to patient. Numerous factors including exposed CO amount, oxygen concentration in surrounding air, duration of exposure, age, gender, metabolism, co-morbidities and drugs used by patient may affect the prognosis. There are some studies providing the effects of oxygen application before the measurement and elapsed time after exposure on COHb levels and its half-life[4]. In a study by Benaissa *et al*, lactate levels were found significantly higher in CO intoxication cases with neurologic signs. However, the clinical importance of lactate level was controversial because of only slightly increased levels in the study[5].

Hampson *et al*, reported no correlation between clinical findings on admission and COHb level in CO poisoning[6]. On the other hand, several studies

have found a relation between the severity of clinical signs, particularly neurological signs and COHb level[7] . In another study by Moon *et al*, the prognostic value of initial lactate level in CO poisoning was emphasized[8].

Similarly, lactate level had been reported as a useful parameter to determine the risk of DNS[9]. In our study, initial lactate levels were found higher in cases with DNS compared to those without DNS ($p = 0.014$). Cortical blindness in two, epilepsy in five, balance disorder in three patients were seen during follow-up and magnetic resonance imaging (MRI) evidence was positive in these cases. Conversely, no significant COHb difference was found in cases with or without DNS ($p = 0.778$). This result indicates that lactate level is a more important marker than COHb level for prognosis, therapy choice and morbidity in CO poisoning.

In a previous case report, the prognostic value of initial lactate level was emphasized[10]. Also, Sokal *et al*, reported that initial lactate level markedly increases in severe CO poisoning compared to mild CO poisoning[11].

In line with these reports, mean lactate and COHb levels were found higher in cases with abnormal positive neurologic signs than those without in the present study ($p = 0.000$).

Approximately 37.2% of our patients had a history of syncope. In patients with CNS symptoms including altered levels of conciousness, initial lactate levels were significantly higher than the others.

Cardiac involvement varying from rhythm disorder to ischemia is observed due to high affinity of CO to cardiac myoglobin in CO intoxications. There are only few studies reporting cardiac involvement in pediatric population and most of these are case reports. Another study reported mild to moderate reversible myocardial function impairment within 24 hours after CO poisoning[12].

Gandini *et al*, reported transient myocardium and mitral valve function disorder in a 12-year-old patient without significant clinical signs and excessive COHb levels[13]. Similarly, another study highlighted the importance of enhanced cardiac enzymes as markers for cardiac involvement in CO intoxication[14].

Therefore, a higher initial lactate level may be a superior marker than a high COHb level for cardiac damage.

CONCLUSION

Although initial lactate levels of patients with DNS were found higher than those without DNS ($p = 0.014$), initial COHb levels of patients with DNS were not higher than those without DNS ($p = 0.778$). Likewise, we found higher lactate levels in cases where cardiac enzymes were elevated. Hence, we conclude that increased arterial lactate which is a marker for tissue hypoxia should be considered along with initial COHb for predicting the clinical course and prognosis of CO poisoning cases, especially in children. However, further studies are needed to provide more conclusive proof.

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Case Report

Alkaptonuria in 17-Month-Old Female Child: A Case Report

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Kuwait Medical Journal 2013; 45 (2): 138 - 140

ABSTRACT

Alkaptonuria is a rare inborn metabolic disorder with Mendelian recessive inheritance characterized by triad of homogentisic aciduria, arthritis and ochronosis. The incidence is one per 0.25 - 1 million persons. A 17-month- old female child of non-consanguineous parents presented with darkening of clothes / diapers moistened with urine when left unwashed for hours. There was no other medical problem in the family. Physical examination including joints revealed a healthy child with normal growth parameters. There was no pigmentation of the sclera, conjunctiva and cornea and ear cartilage. Her urine appeared normal colored on voiding. However, it turned black on standing at room temperature. Regular laboratory investigations were within normal range and skeletal survey showed no degenerative changes. Urine for alkalization and reducing substances was positive. Urine organic acidogram-chromatogram study showed (1137.87%) 2845-fold increase in homogentisic acid and confirmed the diagnosis of alkaptonuria. She was started on Vitamin C (0.5 gm twice a day). She is now asymptomatic over a 13-month follow-up period.

KEYWORDS: alkaptonuria, homogentisic acid, ochronosis

INTRODUCTION

Alkaptonuria is a rare inborn metabolic disorder with Mendelian recessive inheritance characterized by a triad of homogentisic aciduria, arthritis and ochronosis, It was identified in 1500 BC in ancient Egyptian mummies[1,2]. It manifests in the form of urine turning dark on standing and alkalinization due to excretion of excessive amounts of homogentisic acid (HGA), large joint arthritis and black onchronotic pigmentation of cartilage and collagenous tissue. The incidence of this disorder is one per 0.25 - 1 million persons[3].

CASE REPORT

A17-month-old female child of non-consanguineous parents presented to us with darkening of clothes / diapers moistened with urine when left unwashed for hours. This was noted since the age of five months. There was no other complaint. There was no medical problem in the family. Her mother had history of medical termination of pregnancy at five months amenorrhoea since the fetus was found to have a solitary kidney. Physical examination including joints revealed a healthy, active and playful child and normal growth parameters with height of 72 cm, weight at 10.5 kg and head circumference at 47.5 cm. Systemic examination was unremarkable with normal respiratory, cardiovascular, gastrointestinal and central nervous systems. There was no pigmentation of sclera, conjunctiva and cornea and ear cartilage. Her urine appeared normal colored on voiding. However, it turned black on standing at room temperature. Regular laboratory investigations were within normal range: hemoglobin - 12.5 gm/dl, total leucocyte count - 11.3 x 10^3/microliter, differential count of polymorphs 21%, lymphocytes 73%, eosinophils 3% and monocytes 3%, random blood sugar 88 mg/dl, serum calcium 9.3 mg/dl, serum phosphorus 4.5 mg/dl, serum creatinine 0.3 mg/dl, serum bilirubin 0.5 mg/dl and alkaline phosphatase 146 iu/l. Examination of fresh voided urine revealed normal pale-yellow colored specimen with specific gravity of 1.015, pH, 6.0, and absence of albumin / sugar / bile salts / bile pigments. Microscopic examination was normal. Porphobilinogen was also absent. Ultrasonography of the abdomen revealed normal liver, spleen and kidneys. Skeletal

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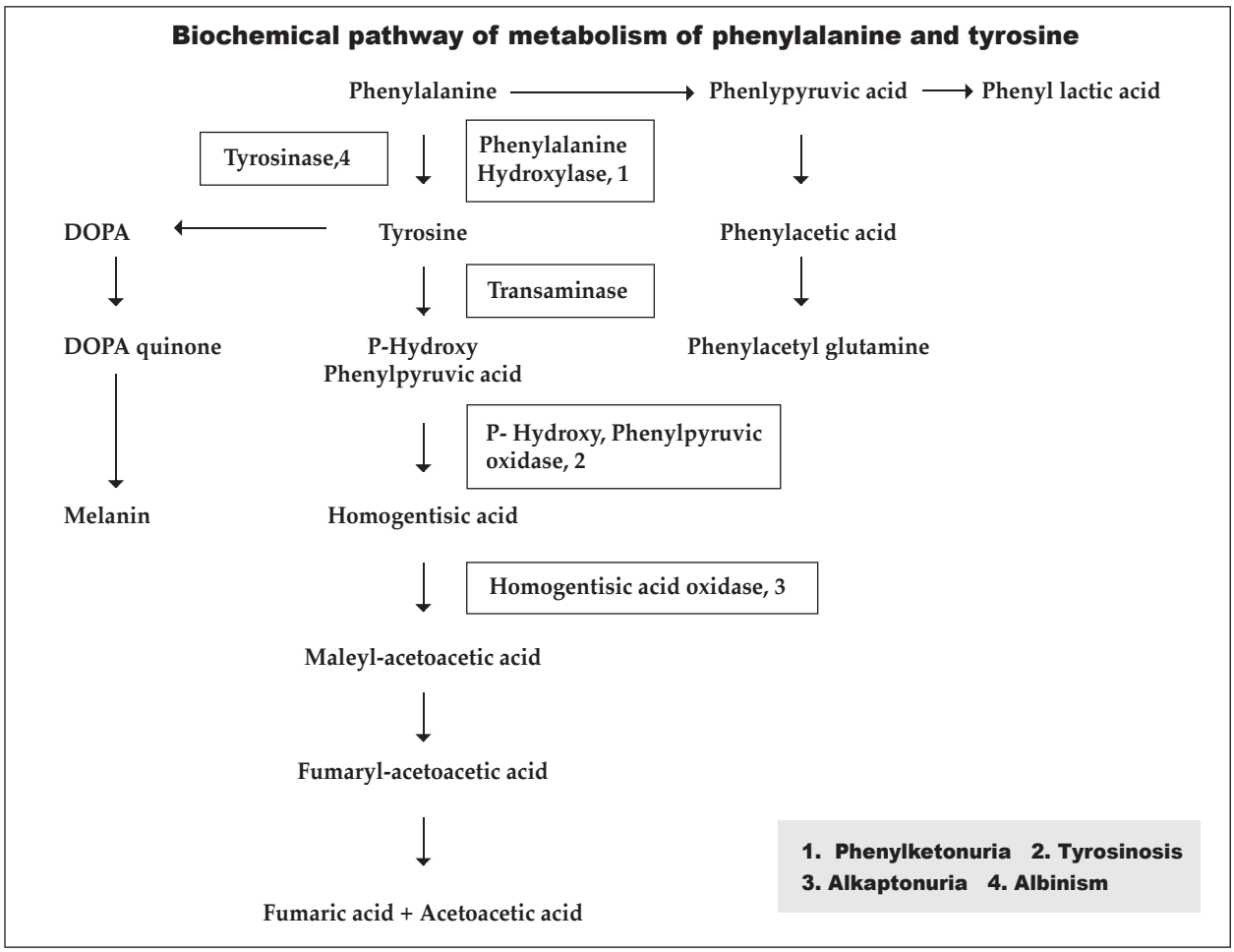

Fig. 1: Pathogenesis of alkaptonuria[9]

survey showed no degenerative changes. Urine for alkalization and reducing substances was positive. Urine chromatogram study for organic acids showed 1137.87% homogentisic acid (reference range: 0 - 0.40%) as tested by GC / MS method along with mild rise in glycerol - 3 to 3.79% (reference range: 0 - 0.8%) and palmitic acid to 34.18% (reference range: 0%). The rise in homogentisic acid was reported as 2845-fold. The child was then diagnosed as a case of alkaptonuria. She was started on Vitamin C (0.5 gm twice a day). She is now asymptomatic over a 13-month follow-up period.

DISCUSSION

Alkaptonuria is a rare inborn metabolic disorder with Mendelian recessive inheritance characterized by the triad of homogentisic aciduria, arthritis and ochronosis due to deficiency of homogentisic acid oxidase (HGAO) enzyme which catalyzes the conversion of HGA to maleyl acetoacetate, fumaric acid and acetoacetic acid[3]. In the absence of the enzyme HGAO, HGA and benzoquinone acetic acid (BQA) builds up in the body[3-5] (Fig.1). A small amount is eliminated in urine and the remaining gets deposited in connective tissues where it becomes toxic and harmful to the bones and the cartilages[4,5]. HGA is itself colorless but is readily oxidized to brown-black pigment on exposure to air especially in the presence of alkali. This may be one of the reasons why darkening of urine may not be noted in an affected child and diagnosis is delayed until patient reaches the third or fourth decade of life when arthritis or ochronosis appear[4,6,7]. Widespread deposition of pigment in alkaptonuric patient called ochronosis (darkening of tissues due to slow accumulation of the black polymer of HGA in cartilage and other mesenchymal tissues) occurs only on long exposure to HGA. Pigmentation of the skin, appendages, sclera and earlobe starts appearing with advancing age[6]. Multiple large joint involvement due to ochronosis often necessitates joint replacement[4,5]. The degenerative changes in the lumbar spine lead to complete ankylosis[5]. Ochronotic granules cause cardiac valvular calcification, atherosclerotic plaques in vessels and calculi in

kidneys / prostate[8]. Eventually multi-systemic involvement proves fatal. Genetically, homozygosity mapping located the alkaptonuric gene to 3q2 in a 16-cM region. Sucrase-isomaltase deficiency and neonatal hyperparathyroidism could be co-inherited with alkaptonuria. Diagnostic tests are: (1) Positive test of urine for alkalization and reducing substances and (2) HGA measurement in urine by paper / thin layer chromatography or spectrophotometry. No definite treatment is established so far. Low protein diet, especially low in phenylalanine and tyrosine is advocated in combination with ascorbic acid. Dietary restrictions on tyrosine and phenylalanine are known to substantially reduce HGA excretion. Ascorbic acid does not change the level of excretion of HGA; however its derivative BQA disappears from urine. High doses of ascorbic acid may prevent deposition of polymerized ochronotic pigment and may therefore, prevent or delay subsequent symptoms. A new drug nitisinone that inhibits the enzyme-producing HGA is on trial for the evaluation of long-term therapy[4].

CONCLUSION

We report this rare case of non-inherited alkaptonuria diagnosed in a 17-month-old female child of non-consanguineous parents.

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

ACKNOWLEDGMENT

Competing Interests: The authors declare that they have no competing interests

Disclosure: Financial support: None.

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Case Report

Congenital *Plasmodium Falciparum* in a Neonate in Kuwait

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Kuwait Medical Journal 2013; 45 (2): 141 - 142

ABSTRACT

We report the case of a newborn infant who was diagnosed with congenital malaria. This baby was admitted for evaluation of fever which began four days prior to admission. The newborn was pale and had spleenomegaly and normal neonatal reflexes.
Laboratory tests, including a peripheral blood smear, revealed *Plasmodium falciparum* in the red cells. His mother had suffered from malaria eight months back in India for which she took quinine for seven days.
The newborn was successfully treated with quinine. He was discharged from the hospital in a good condition with negative blood smears.

KEY WORDS: congenital malaria, *Plasmodium falciparum*, spleenomegaly

INTRODUCTION

Congenital malaria is a rare disease. The fetus associated with pregnancy malaria may result in premature delivery, mental retardation, perinatal mortality, anemia, abortion, low birth weight and death of the mother.

Congenital malaria infection refers to the diagnosis of malaria parasites in the newborn within the first seven days after birth. There is no possibility of postpartum infection by either mosquito bite or blood transfusion[1]. Clinically apparent congenital malaria is rare in areas in which malaria is endemic and levels of maternal antibodies are high. Normally, symptoms occur 10 to 30 days postpartum[2]. The most common clinical features in 80% of cases are fever, anemia and spleenomegaly[2]. Other signs and symptoms include hepatomegaly, jaundice, regurgitation, loose stools, and poor feeding. Occasionally, drowsiness, restlessness, and cyanosis may be seen[2,3]. Respiratory distress may also be present[4,5]. The diagnosis is frequently missed. Those with asymptomatic parasitemia at birth may either suppress spontaneously, or present with clinical symptoms in the late neonatal period.

CASE REPORT

A 38-day-old male infant was admitted to our pediatric ward for evaluation of fever. The onset of the fever was four days prior to hospitalization. There was no history of diarrhea, vomiting, or cough. The child was on exclusive breast feeding since birth.

His mother was a 25-year-old Indian woman who came from India four months ago. She had a history of malaria eight months back in India for which she took quinine for seven days. She was a primigravida who had normal vaginal delivery. On physical examination, he had a body temperature of 38 °C, a pulse rate of 200 / min and a respiratory rate of 42 / min. The patient appeared pale. His sclera was normal. Heart and lung examinations were normal. His abdomen was soft and without any distension. His spleen was palpable 2 cm below the left costal margin. The liver span was normal. Laboratory data including blood sugar, serum creatinine, serum sodium, and potassium, were all within normal range. Other laboratory findings included an ESR 128 mm / hr, CBC: Hb 7 g /dl, WBC 7.4 x 10^9/l, Neutrophils 11%, Lymphocytes 82%, Monocytes 1%, Hct 30%, platelet count 89 x 10^9/l, and reticulocyte count 2.64%. Urine and its culture as well as chest X-ray were normal. Other causes of hemolytic anemia were ruled out. G6PD level was 322.6 (normal).

On peripheral blood smear examination, *Plasmodium falciparum* and *Plasmodium vivax* parasites were detected, although blood cultures were negative.

Blood transfusion was given and the infant was treated successfully with quinine and clindamycin. He

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was discharged after seven days. At time of discharge his hemoglobin was 9 g/dl.

DISCUSSION

Congenital malaria can be acquired by transmission of parasites from mother to child during pregnancy or perinataly during labour. The incubation period for malaria varies from eight days to months or even longer[3].Transplacental infection of the neonate, or congenital malaria, is rare. In most cases, the mother has been infected with the parasite during pregnancy[3]. Malaria infection is more frequent and serious during the first pregnancy, as is the occurrence of congenital malaria[3,6]. There have been some reports of mothers with malaria who have lived in endemic areas for years without any symptoms and became symptomatic after living in a malaria-free area. This indicates that the onset of infection might be prior to living in malaria-free areas.

The major diagnostic criteria are to find *P.falciparum* in the blood smears – in both the thick and thin films. The thick film of peripheral blood may be more helpful to detect the parasite[3,7]. At birth, 29% of newborns who suffer from congenital malaria have parasitemia. Between 1% and 4% of pregnant women with overt malaria attacks have babies with congenital malaria. Congenital malaria can cause serious outcomes both to the pregnant women and the fetus. It may result in miscarriage, fetal growth restriction / small for gestational age (SGA) infant, preterm birth (< 37 weeks of gestation), low birth weight (LBW) (< 2500 g at birth), perinatal death, congenital infection, maternal anemia, and possible maternal death.

Pregnant women with malaria must be treated promptly with an effective antimalarial agent to clear parasites rapidly. Treatment involves antimalarial drugs and supportive measures. The choice of drug for treatment of malaria infection depends on the clinical severity, epidemiologic resistance patterns, and available data about the safety of the drug in pregnancy. In chloroquine-sensitive areas, chloroquine is recommended for first-line therapy. For chloroquine-resistant malaria, we suggest quinine combined with clindamycin. As for the fetus same treatment applies, as in our case where the baby was treated with quinine and clindamycin.

In a case report by Lane, a 21-year-old woman, who immigrated to the Unites States, from an endemic area, gave birth to a female infant. At four weeks of age she developed anemia and was diagnosed to have *Plasmodium vivax* by blood smear. The baby was successfully treated with chloroquine and blood transfusion[4].

Another case was reported from Iran of a 21-day-old male neonate admitted for the evaluation of fever and poor feeding. He was diagnosed to have malaria and was treated successfully with quinine[2].

CONCLUSION

This case shows the importance of diagnosing malaria even in infants. Congenital malaria should be considered in any newborn with a history of fever, and a recent travel of the pregnant mother to any endemic areas.

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Case Report

A 25-Year-Old Woman with Petechial Rash and Acute Hepatitis Following a Febrile Illness

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Kuwait Medical Journal 2013; 45 (2): 143 - 145

ABSTRACT

As the spread of dengue and dengue hemorrhagic fever are increasing, atypical manifestations of dengue, such as dengue encephalitis, dengue myocarditis, and dengue hepatitis and dengue cholecystitis are also on the rise. These manifestations are under-reported because of lack of awareness. Dengue is endemic in India and the last epidemic occurred in Delhi in 2003. We report a case of a 25-year-old female Indian patient who presented to our hospital with complaints of fever and rash. In addition, she developed ascites during her stay in the hospital. She was diagnosed as having dengue hemorrhagic fever (DHF) with acute hepatitis. She made a complete recovery with supportive management.

KEY WORD: dengue fever, hepatitis, rash

INTRODUCTION

Dengue virus belongs to the family of *Flaviviridae* (genus *Flavivirus*) and it has emerged as the most common arboviral disease in the world. The disease is endemic to tropical and subtropical areas of the world with about 2.5 billion people (40% of the world's population) at risk of acquiring the infection[1]. Dengue virus (DENV) is transmitted to humans through the bite of infected female Aedes mosquitoes (particularly *A aegypti* and *A albopictus*). Mosquitoes generally acquire the virus while feeding on the blood of an infected person. After an incubation period of 8 - 10 days, an infected mosquito is capable of transmitting the virus to susceptible individuals for the rest of its life during probing and blood feeding. Four distinct viruses (termed dengue virus types 1 - 4 [DENV 1 - 4]) cause dengue fever (DF). Humans are the main amplifying host of the virus[2]. Infection with one of the four serotypes of DENV causes a wide spectrum of clinical diseases including: asymptomatic infection, undifferentiated fever, DF, and dengue hemorrhagic fever (DHF). DHF occurs in a minority of patients and is characterized by bleeding and plasma leakage, which may lead to shock[3].

Some people infected with DENV are asymptomatic. Young children often have a fever with a rash, but other symptoms are minor. Older children and adults may also have mild symptoms; however, they are more likely to experience classic DF. Symptoms of DF include a high fever (up to 40.5 ºC), severe headache, retro-orbital pain, severe muscle and joint pain, swollen lymph nodes, general malaise, nausea, and vomiting. A macular erythematous rash with petechiae may also be observed[4]. The differential diagnosis for DF and DHF is broad including: meningococcal meningitis, septicemia and disseminated intravascular coagulation (DIC). Other differential diagnosis are hemorrhagic fevers (Crimean Congo hemorrhagic fever, Ebola, *etc.*), thrombotic thrombocytopenic purpura (TTP), falciparum malaria, leptospirosis, aplastic anemia, acute leukemia, and yellow fever.

Direct person-to-person transmission of DENV has not been documented. A few case reports have been published of transmission of DENV through exposure to dengue-infected blood, organs, or other tissues from blood transfusions; solid organ or bone marrow transplants; needle stick injuries; and mucous membrane contact with dengue-infected blood[5].

The treatment of DF and DHF is essentially supportive by antipyretics and fluid resuscitation. Monitoring of laboratory parameters and replenishment with blood products as necessary are indicated in severe cases of DHF[6,7].

CASE HISTORY

A 25-year-old Indian woman presented to the emergency department of Infectious Disease Hospital (IDH) in Kuwait with petechial hemorrhagic rash on both forearms for the last three days. In the last 10 days, she had been experiencing a high fever associated with

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Table 1: Hematologic and serum biochemical laboratory data

Variables	Reference range, adults	On admission	5th day	10th day	On discharge
Hemoglobin (g/dl)	12 – 16 in women	15.2	9.5	10.2	13
White blood cells (per mm^3)	4500 - 11000	4000	5400	5000	4800
Differential count (%)					
* Neutrophil	40 – 70	64	54.6	53.4	46.3
* Lymphocytes	22 – 44	29	36.2	37.4	42.6
* Monocytes	4 – 11	2	8.7	8.2	10.6
* Eosinophils	0 – 8	2.4	0.1	0.5	0.1
* Basophils	0 – 3	0.0	0.4	0.1	0.4
Platelet count (per mm^3)	150,000 – 400,000	51,000	110,000	227,000	552,000
Mean corpuscular volume (μm^3)	80 - 100	86.4	83.4	85	84.7
Partial thromboplastin time (sec)	22 - 34	89.2	65.3	52.7	40.3
Prothrombin time (sec)	10.3 - 13.2	13.4	15	15.2	14.4
International normalized ratio	-	0.9	1.1	1.2	1.1
Sodium (mmol/l)	135 - 145	130	126	124.8	128.4
Potassium(mmol/l)	3.4 - 4.8	4.5	3.6	3.5	4.47
Glucose (mg/dl)	70 - 110	104	97	113	105
Albumin (g/l)	35 - 50	30	28	26.4	28.5
Alkaline phosphatase (u/l)	45 - 115	323	338	296	300
Aspartate aminotransferase (u/l)	10 - 42	1523	978	256	129
Alanine aminotranseferase (u/l)	14 - 54	624	343	130	97
Billrubin (mg/dl)					
Total	3.4 - 20	19.1	18.5	17.1	16.5
Direct	0.0 - 5	7.6	7	6	6.5

rigors. In addition, she complained of a rash all over the body, but she was unable to further characterize it. She noted severe pain in both legs during the febrile portion of her illness. There was no history of hematuria, melena, cough, or hemoptysis. She was not taking any routine prescription medications or using over-the-counter products or supplements. She had no known drug allergies. She was married with one child and unemployed. She had no history of smoking, drinking alcohol and drug abuse. She had returned from India just one week ago.

On physical examination, she was apparently alert, well-developed and well-nourished. The patient had a regular pulse rate of 90 b/min and a respiratory rate of 14 breaths/min. Her temperature was 38 ºC and blood pressure was 110/70 mmHg. The cardiac examination revealed a normal S1 and S2 with no murmur. Auscultation of the lungs was normal. No palpable organomegaly or tenderness was found on abdominal examination. No signs of meningeal irritation were detected. Examination of the extremities revealed a petechial rash across both forearms and maculopapular rash all over the body. Conjunctival hemorrhages were noticed bilaterally. Petechiae were also apparent on her soft palate with congested throat and enlarged left deep cervical lymph node. After five days of admission, she developed lower limb edema, ascites and right pleural effusion.

Table 1 shows the results of laboratory investigations on admission, day 5, day 10 and at discharge. Her serum blood urea nitrogen and creatinine were normal. Blood cultures did not show any growth. The result of urine analysis and urine culture result were negative. On admission, posteroanterior, lateral chest radiographs as well as abdominal ultrasonography were unrevealing. However, later on, ascites and right pleural effusion were revealed. Monospot test was negative and ESR was normal. Serology for measles, rubella, EBV, CMV, yellow fever and rickettsia were negative but serology of dengue virus IgM was positive. The diagnosis was eventually confirmed by paired immunoglobulin M samples demonstrating an acute rise in antibodies. Hepatitis screening for viruses (A, B, C, D, E) were negative and VDRL was non-reactive.

The patient was admitted to an inpatient medical ward for 14 days and managed mainly with supportive therapy in the form of adequate and cautious fluids replacement, as well as prophylactic antibiotic coverage to prevent secondary bacterial sepsis, regular monitoring of biochemical markers and neurological status. She was discharged when her platelet count, aminotransferase level, albumin level, and alkaline phosphtase level returned to normal. Two weeks later, she came back for follow up showing improvement in her rash and other symptoms.

DISCUSSION

Clinically, the diagnosis of DF is suggested by the presence of fever, severe headache, macula-papular skin rash, and myalgia. In addition, it is also associated with either the isolation or identification of DENV from plasma and tissue specimens, or by demonstration

of a four-fold increase of DENV antibodies in paired serum samples. The diagnosis of DHF was established according to the adapted World Health Organization (WHO) criteria: thrombocytopenia < 100,000/mm^3, hemoconcentration and hemorrhagic manifestations such as spontaneous petechiae or a positive tourniquet test. Hemoconcentration was defined as hematocrit > 45% in men, > 40% in women and > 38% in children under 12 years of age.

Atypical manifestations of dengue infection such as hepatitis, myocarditis and encephalitis have been observed during epidemics that occurred in Ceara in 1994 and in Campos in 2005[8,9]. The extent to which the liver is affected by DENV ranges from mild lesions to fulminant hepatitis[10]. Liver involvement may be characterized by manifestations such as pain in the right hypochondrium, hepatomegaly, varying degrees of jaundice[11], and an increase in liver markers, principally ALT and AST, similar to those found in acute hepatitis caused by the A, B, C, D and E viruses. Kuo *et al*[12] reported that approximately 90% of the patients had abnormal AST levels. On the other hand, 80%, 7%, 16% and 83% respectively of patients with classic dengue had abnormal levels of ALT, bilirubin, alkaline phosphatase and gammaglutamyl transferase (GGT). Liver involvement occurred through an inflammatory process in the parenchyma provoked directly or indirectly by the virus. This leads to reduction in the diameter of the lumen of the biliary canaliculi which ultimately causes obstruction or even jaundice. Some viral strains also seem to have a prominent liver tropism especially DENV-1 and DENV-3.

In this case, the aminotransferase levels of the patient were more than ten times the reference values and she had negative results for hepatitis A, B, C, D and E.

It is important to emphasize that our patient had no previous active liver disease but the abnormal aminotransferase levels can be attributed to the dengue infection. She returned to normal values within 2 - 3 weeks following the onset of symptoms.

The increase in aminotransferases mainly AST has been associated with the severity of the disease. It may serve as an early indicator of dengue infection. Indeed, liver injury is a good positive predictive factor for the development of DHF[13]. This increase usually happens within the first nine days of symptoms and normalizes in about two weeks. Increased levels of alkaline phosphatase and serum bilirubin are noted in a smaller proportion of cases[14].

In this case report, the dengue infection as well as the oral intake of acetaminophen may have favored liver injury. The progressive decrease in hematocrit levels, as well as thrombocytopenia, hypoalbuminemia, ascites, pleural effusion, spontaneous petechiae and positive serological tests confirmed the diagnosis of DHF. The hypoalbuminemia found in this case was probably a result of both capillary leakage induced by dengue infection and liver failure.

Finally, this patient was diagnosed with DHF which is a complication of DF and associated with acute hepatitis.

CONCLUSION

It is important to take dengue fever into consideration when making a differential diagnosis on a case presenting with fever and acute hepatitis and coming from endemic area such as India.

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Case Report

Rare Clinical Presentation of Intestinal Fixation Anomaly with Traumatic Cecal Perforation

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Kuwait Medical Journal 2013; 45 (2): 146 -148

ABSTRACT

Intestinal fixation anomalies are a part of intestinal malrotation. It is a rare occurrence for an unexpected malrotation of the gut to be revealed on laparotomy for other reasons in adults. There are no reports of intestinal fixation anomalies with traumatic perforation in the world literature. We hereby present a case of a 15-year-old girl with traumatic cecal perforation, who on laparotomy showed an intestinal fixation anomaly. We describe the challenges faced in the management of this patient.

KEY WORDS: intestinal malrotation, Ladd's procedure

INTRODUCTION

Intestinal fixation anomalies are a part of intestinal malrotation[1]. Here the mesentry is not fixed to the retroperitoneum and can cause internal hernia. We report a case of a young girl with traumatic cecal perforation who on laparotomy was found to have an intestinal fixation anomaly and discuss the complications and challenges of managing the patient. It is a rare occurrence for an unexpected malrotation of the gut to be revealed on laparotomy for other reasons in adults.

CASE REPORT

A 15-year-old girl presented to us with abdominal distension, pain, and constipation for five days following trivial abdominal trauma. She had no past history of abdominal symptoms. On examination she had guarding and rigidity all over the abdomen with features of sepsis *i.e.*, tachycardia and fever of 39.5° C. An erect X-ray abdomen showed massive pneumoperitoneum (Fig.1). A laparotomy revealed anterior cecal perforation with large amounts of fecal peritonitis (Fig. 2). The cecum was free floating and subhepatic. The small intestine mesentery was short and not fixed to the retroperitoneum. The coils of the small intestine were twirled around the mesentery and any attempt to fix the mesentery would mean that the intestine would be caught with it (Fig.3). Any injury to the mesentery would mean that the distal bowel would lose its blood supply. There was no scope for performing a Ladd's procedure due to the existing fecal peritonitis and absence of peritoneal bands.

Closure of cecal perforation with defunctioning loop ileostomy was done. Postoperatively, the patient had persistent gastric paresis and developed high nasogastric tube output. Obstruction of 3rd part of duodenum was revealed with the aid of gastrograffin follow through. Endoscopy confirmed that the obstruction was due to superior mesenteric artery syndrome (SMA syndrome). A feeding nasojejunal tube (NJ tube) was placed. The NJ tube was removed six weeks later after the patient gained weight and tolerated oral feeds.

Barium studies were done six months later to rule out any proximal intestinal obstruction following which reversal of ileostomy was done. No attempt was made to fix the mesentry as adhesions had already developed. Patient is doing well for the past one year postoperatively.

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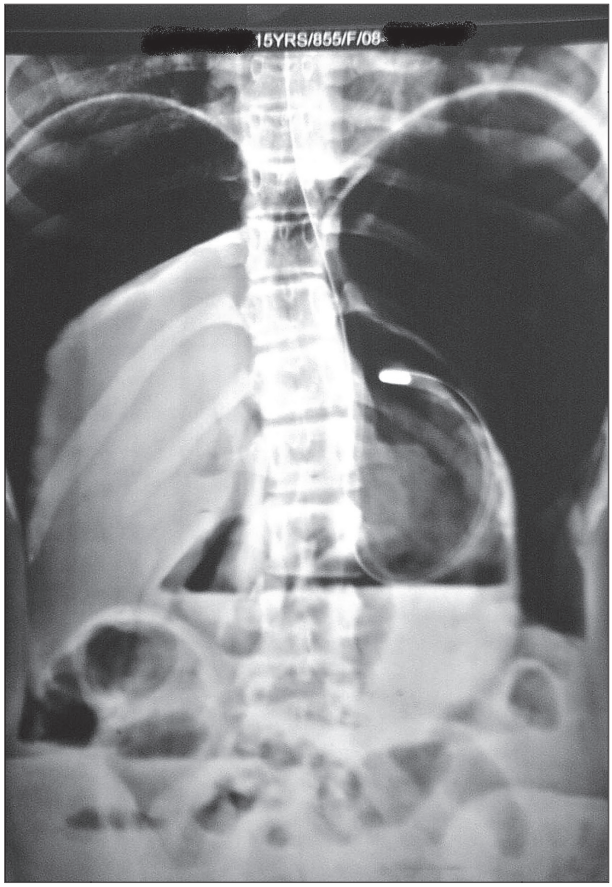

Fig.1: Erect X-ray abdomen showing massive pneumoperitoneum and air fluid levels

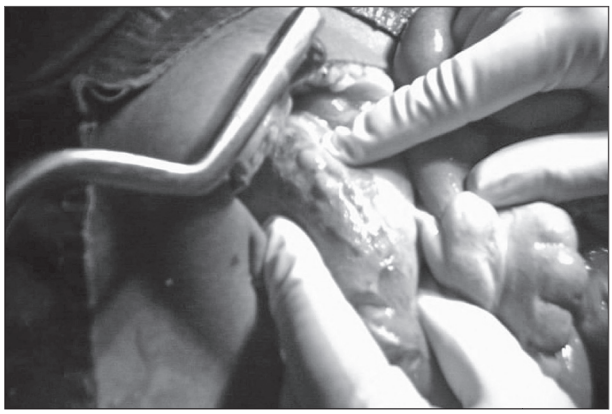

Fig. 2: Anterior cecal perforation with large amounts of fecal peritonitis

DISCUSSION

Intestinal malrotation is a developmental anomaly of intestinal fixation and rotation caused by a disruption in the normal embryologic development of the bowel. Normal rotation takes place around the superior mesenteric artery. Incomplete rotation and midgut volvulus is the commonest type of anomaly.

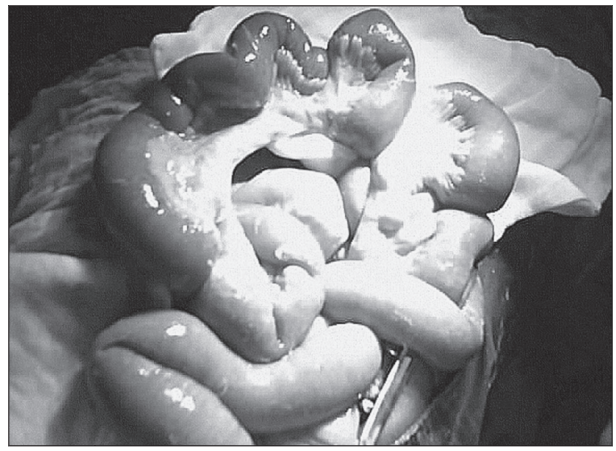

Fig. 3: Massive defect in the mesentry with twirling of the intestine into the defect

Intestinal obstruction is the commonest presentation in symptomatic cases [1]. There are no reports of intestinal fixation anomalies with accidental perforation in world literature.

The result of a non-rotated gut is location of the colon on the left side and a narrow-based mesentery in the upper mid-abdomen that is fixed to the right abdominal wall by adhesions known as Ladd bands. Anomalies commonly associated with intestinal malrotation include duodenal atresia (50%) and jejunal atresia (33%). Disorders of intestinal rotation and mesenteric fixation to the posterior abdominal cavity are also common in infants and children who have congenital diaphragmatic hernia, gastroschisis and omphalocele.

Intestinal malrotation is believed to occur in one per 200 to one per 500 live births, with symptomatic malrotation occurring in one per 6,000 live births. Symptomatic malrotation is evident clinically in the first postnatal month in 64% of patients, and 82% are diagnosed in the first postnatal year; 18% to 25% of symptomatic patients are diagnosed at one year of age and older. Because malrotation is discovered incidentally in some patients, the true incidence of malrotation is underestimated[2].

Incomplete fixation means potential hernial pouches form when the mesentery of the right and left colon and the duodenum do not become fixed retroperitoneally. If the descending mesocolon between the inferior mesenteric vein and the posterior parietal attachment remains unfixed, the small intestine may push out through the unsupported area as it migrates to the left upper quadrant. This creates a left mesocolic hernia with possible entrapment and strangulation of the bowel. If the cecum remains unfixed, volvulus of the cecum may occur along with terminal ileum and proximal ascending colon[3].

Ladd's procedure is the treatment of choice. However this option could not be exercised here as there were no peritoneal bands and with cecal perforation, it would be unwise to go ahead with appendicectomy. These were some of the challenges faced. The patient landed with SMA syndrome; however, this reverted once the patient gained weight due to the enteral feeding with NJ tube. The defunctioning ileostomy was reversed six months later and there were adhesions formed which would prevent a volvulus.

CONCLUSION

Management of intestinal malrotation discovered incidentally during laparotomy may prove very challenging especially in the setting of peritonitis. Ladd's procedure may not be feasible in such conditions.

ACKNOWLEDGMENT

Competing interests: The authors declare that they have no competing interests.

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Case Report

Calciphylaxis in a Renal Allograft Recipient –An Uncommon Entity, Need for Vigilance: A Case Report

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Kuwait Medical Journal 2013; 45 (2): 149 - 151

ABSTRACT

Calcific uremic arteriolopathy (CUA) is characterized by small vessel medial calcification, panniculitis and dermal necrosis producing exquisitely painful and difficult to heal wounds. It is seen primarily in patients with end-stage renal disease (ESRD). It is infrequently reported in post-transplant patients. In this report, we describe a case of CUA in a 46-year-old gentleman suffering from ESRD due to diabetes. He had undergone renal transplantation two years back and had subsequently developed chronic allograft nephropathy. The patient was on conservative management. He presented with a painful, non-healing skin ulcer on right lower limb. His biochemical markers were suggestive of altered calcium-phosphorous status and secondary hyperparathyroidism. A skin biopsy from the ulcer was consistent with calciphylaxis. He was treated with intensified hemodialysis, antimicrobials, meticulous wound care with subsequent skin grafting which however, proved unsuccessful. A high index of suspicion needs to be exercised while dealing with non-healing ulcers in chronic renal failure including post-renal transplant patients.

KEYWORDS: calciphylaxis, renal transplantation, ulcer

INTRODUCTION

Calcific uremic arteriolopathy (CUA) is an uncommon entity described primarily in patients with end-stage renal disease (ESRD). It is characterized by small vessel medial calcification, panniculitis and dermal necrosis producing exquisitely painful and difficult to treat ulcers. The incidence of calciphylaxis in hemodialysis population is between 1 - 4 %[1] with a mortality of about 60%[2]. The various risk factors that have been identified include obesity, malnutrition, hypoalbuminemia, hypercalcemia, hyperphosphatemia and secondary hyperparathyroidism[3]. Sepsis secondary to super infection of the ulcerated region is the main cause of death in these patients[3]. The diagnosis of CUA needs a high index of suspicion under an appropriate clinical context. Definitive diagnosis is facilitated often by pathognomonic histologic findings. Calciphylaxis occurring after kidney transplantation has rarely been reported. We describe here a case of distal lower limb calciphylaxis that occurred in a renal transplant recipient.

CASE REPORT

A 46-year-old gentleman had undergone live renal transplantation with spouse as donor two years back for diabetic ESRD. His maintenance immunosuppresion comprised of tacrolimus, mycophenolate, mofetil and prednisolone. Subsequently, he had progressed to chronic allograft nephropathy and was on conservative management maintaining a baseline creatinine between 3 - 3.5 mg / dl with good urine output. He presented to us with a painful, skin ulcer on the right lower limb following a trivial trauma, which progressed rapidly over a week (Fig. 1). On clinical examination, he was afebrile and hemodynamically stable; all the

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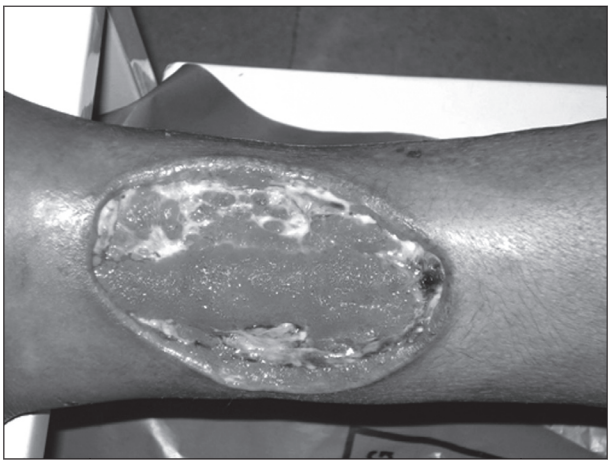

Fig. 1: Chronic non-healing ulcer on right lower limb

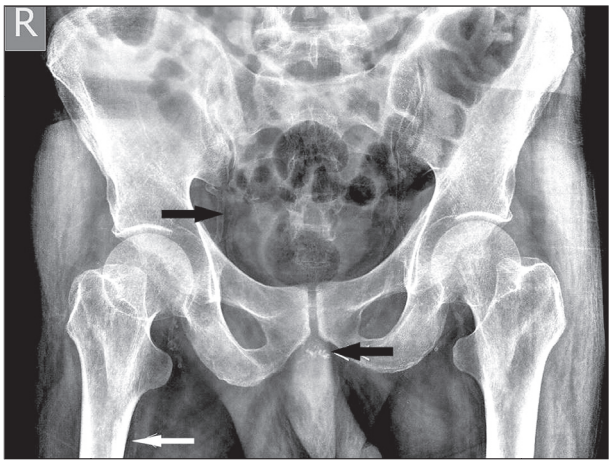

Fig. 2: Calcified vessels (arrow), soft tissue calcification (arrow heads)

peripheral pulses were felt. There were however signs of peripheral neuropathy. Laboratory results included the following: hemoglobin 9.2 gm/dl, leukocytes 8,600 / cmml, platelets 190,000 / cmm, glucose 186 mg / dl, urea 68 mg / dl, serum creatinine 3.8 mg / dl, sodium 138 mmol / l, potassium 4.3 mmol / l, serum calcium 8.6 mg / dl, phosphate 6.5 mg / dl, calcium phosphorus product 55.9, intact parathyroid hormone (IPTH) 456 pg / ml, albumin 2.8 gm / dl, hs C-reactive protein (CRP) 6.80 μg / ml (normal 3 - 100 μg / ml). Swab culture from ulcer yielded *Stapylococus aureus* sensitive to amoxycillin and clavulinic acid and linezolid. A plain X-ray of the pelvis showed extensive vascular calcification of medium sized vessels along with other soft tissue calcifications (Fig. 2). A skin biopsy showed necrotic fibro-collagenous tissue with focal areas of calcification (Fig. 3) along with small vessel medial calcification suggestive of calciphylaxis (Fig. 4). Due to superadded infection his immunosuppression was tapered down and he was managed in consultation with the department of plastic surgery with debridement, daily dressings of ulcer, tight control of blood sugar along with appropriate antibiotics and opiates for pain control. In view of significant metabolic acidosis and altered calcium, phosphorus, IPTH homeostasis he was initiated on thrice weekly hemodialysis. The patient was treated with cinacalcet 30 mg once a day for 15 days; however, the same was discontinued later owing to hypocalcemia. He underwent skin grafting after resolution of secondary infection. However, this procedure too was unsuccessful.

DISCUSSION

In nephrology practice, one often has to deal with patients having non-healing ulcers owing to various co-morbidities arising both from uremic state and from other associated primary systemic diseases. Calcipylaxis is a well-documented cause of non-healing ulcers

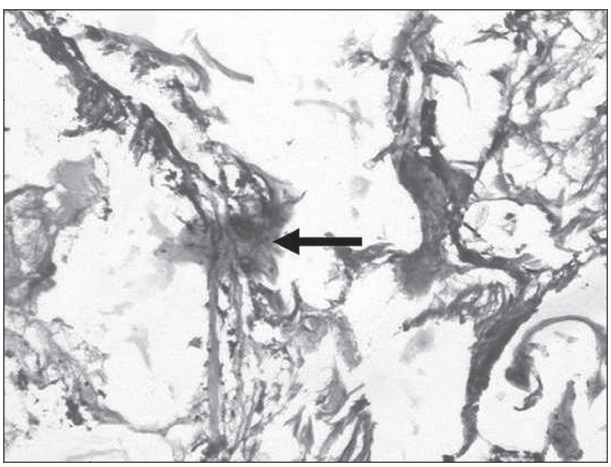

Fig. 3: Skin biopsy showing necrotic fibrocollagenous tissue with focal areas of calcification (arrow)

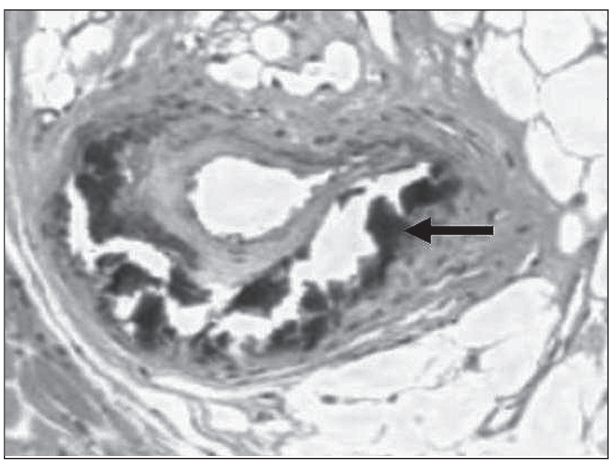

Fig. 4: Calcification of vessel media (arrow)

especially in patients with ESRD on dialysis therapy. It has been often reported in the context of deranged calcium, phosphorous and IPTH homeostasis. CUA has also been described in non-uremic conditions such as primary hyperparathyroidism, malignancy, alcoholic liver disease, connective tissue disease, diabetes mellitus, Crohn's disease and corticosteroid use[4]. However, it has been infrequently described in the post-transplant scenario[5]. It is usually associated with painful ulcerations and necrosis in the fat-rich areas such as the abdomen, thighs as well as in the lower extremities. These ulcers respond poorly to conventional modalities of management and are prone to secondary infection leading to sepsis with high mortality. Early identification and initiation of medical management with intensified hemodialysis along with aggressive wound care, appropriate antibiotics and surgical intervention has been recommended. Several therapeutic options such as sodium thiosulfate infusion, tissue plasminogen activator, bisphosphonates, parathyroidectomy and hyperbaric oxygen therapy have been evaluated. However, none have shown consistent benefit[6].

CONCLUSION

It is suggested that one needs to exercise a high index of suspicion towards this entity in the context of chronic non-healing ulcers even in post-transplant patients. Though early redressal of the same with aggressive measures has been reported to be associated with favorable outcome results could still be inconsistent as was the case in our patient. Early initiation of preventive measures is recommended.

ACKNOWLEDGMENTS

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Disclosure: Financial support: None

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Case Report

A Rare Case of Streptococcal Toxic Shock Syndrome in Kuwait

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Kuwait Medical Journal 2013; 45 (2): 152 - 154

ABSTRACT

Invasive Streptococcal A infection is a community acquired disease of high mortality that can be seen in healthy people with no underlying disease. Clinical presentation is variable which might lead initially to incorrect diagnosis. The development of toxic shock syndrome is the major predictor of mortality. The fulminant onset of the disease emphasizes the importance of early penicillin introduction in suspected cases. We describe the first reported case of group A streptococcal toxic shock syndrome in Kuwait and review the relevant literature.

KEY WORDS: group A streptococcus, Kuwait, toxic shock syndrome

INTRODUCTION

Group A streptococcus (GAS) is an aerobic gram positive cocci that commonly causes pharyngitis and a spectrum of skin and soft tissue infections[1]. Toxic shock syndrome (TSS) is a rare complication of group A streptococcus infection defined as any group A streptococcal infection associated with the acute onset of shock and organ failure. Many cases of GAS-TSS are healthy non-immunocompromised people in all age groups. Other differential diagnoses of shock in previously healthy people include staphylococcus TSS[2], gram negative sepsis, leptospirosis and heat stroke. The diagnosis of GAS-TSS requires the isolation of GAS from a normally sterile site and hypotension plus evidence of failure of two or more organ systems. Once TSS is suspected, early and proper antibiotics should be given, if mortality is to be prevented.

CASE REPORT

A previously healthy 33-year-old Indian gentleman was admitted with complaints of right-sided abdominal pain for the previous two days. The pain was associated with fever and progressive shortness of breath. There was no history of rash, sore throat or cough. He was not on any medication. Physical examination revealed a temperature of 37.9° C, a pulse rate of 137 per minute, and a blood pressure of 90 / 63 mmHg. There was no jaundice or rash. The abdomen was soft with right upper quadrant tenderness. Bowel sounds were present. Throat examination was normal. The rest of the examination was unremarkable; he had no joint pain.

Initial investigations revealed a leukocyte count of 5.6×10^9 / l (normal 4 -10 x 10^9 / l), and a platelet count of 98 x 10^9 / l (normal 150 – 410 x10^9 / l). The blood film showed a white blood cells shift to the left. Serum urea was 8.2 mmol / l (normal 2.5 - 7.1 mmol / l), creatinine was 147 mmol / l (normal 62 - 115 mmol / l). Liver function tests were abnormal: total bilirubin 29 umol / l (3 – 25 umol / l), alanin transferase 237 IU / l (Normal 10 - 60 U / l); albumin 23 g / l (normal 35 - 48 g / l), AST 434 IU / l (normal 10 - 42 IU / l), corrected calcium 2.31 mmol / l (2.10 - 2.60 mmol / l). Electrocardiogram and chest X-ray findings were within normal range. An ultrasound scan of the abdomen revealed a rim of fluid in the hepato-renal space. Blood was taken for culture. After 26 hours of admission the patient started to complain of shortness of breath. Examination of the chest revealed wheezes. Arterial blood gases revealed metabolic acidosis (pH 7.28, pCO_2 5.64 kPa, pO_2 8.10

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kPa, HCO_3 19.4 mmol / l). At this stage, the patient was on bronchodilators and intravenous steroids along with pipracillin-tazobactam (Tazocin). Gram stain results of blood cultures revealed Gram-positive cocci in chains. Culture on blood agar yielded β-hemolytic streptococci. The isolate was sensitive to a 0.04 IU bacitracin disk and possessed only the group A Lancefield antigen (Streptex test; Biomerieux). Biochemical identification with the API Strep system yielded a profile of 0161410, indicating very good identification with *S. pyogenes*. The isolate was sensitive to penicillin according to Clinical and Laboratory Standards Institute (CLSI) criteria (disk testing). The M protein typing was not done; therefore, intravenous benzylpenicillin and clindamycin were infused and Tazocin was stopped. Over the next 48 hours, the patient responded dramatically to antibiotics and was afebrile and liver transaminases improved.

DISCUSSION

Streptococcal toxic shock syndrome (STSS) is an aggressive syndrome. It is defined as any group A streptococcal infection associated with early onset of shock and organ failure. The criteria for the diagnosis of this syndrome are as follows[3]:

1. Isolation of GAS and
2. Clinical signs of severity as manifested by
   a. Hypotension, and
   b. At least two of the following: renal impairment, coagulopathy, liver involvement, adult respiratory distress syndrome, generalized erythematous macular rash and soft tissue necrosis.

Our case fulfils these criteria. GAS was isolated from the blood culture. Furthermore, the clinical severity of this illness is demonstrated by the presence of hypotension, renal and liver impairment. Our case represents the first reported case from Kuwait. GAS is a major bacterial pathogen. The greatest burden of GAS is the invasiveness of the disease and the post-infection sequelae. Invasive infections have been reported with increasing frequency, predominantly from North America and Europe[4]. There are an estimated 3.5 cases per 100,000 persons with a case-fatality rate of 36 percent for STSS[5]. Any person in any age group can be affected; but those < 1 year of age and those ≥ 60 years of age have the highest incidence[6]. Most do not have predisposing underlying diseases[7]. The following risk factors have been associated with the development of severe GAS infections[4] : minor trauma, injuries resulting in hematoma, bruising, or muscle strain, surgical procedures, viral infections, and use of non-steroidal anti-inflammatory drugs.

The most common initial symptom of STSS is pain, which is abrupt in onset and severe, and usually precedes tenderness or other physical findings. The pain may mimic peritonitis, pelvic inflammatory disease, pneumonia, acute myocardial infarction, or pericarditis[4]. Twenty percent of patients have an influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting and diarrhea[8]. Fever is the earliest sign. Confusion is present in 55% of patients[8]. Eighty percent of patients have signs of soft tissue infection, such as localized swelling and erythema, which in 70% of patients progress to necrotizing fasciitis or myositis and require surgical debridement, fasciotomy or amputation[8]. About 50% of patients may have normal blood pressure on admission but develop hypotension within the subsequent four hours[8].

On admission, renal involvement is indicated by the presence of hemoglobinuria and by serum creatinine values. Renal impairment precedes hypotension in 40 to 50% of patients[8]. Hypoalbuminemia is associated with hypocalcemia on admission and throughout the hospital course. The serum creatinine kinase level is a useful indicator of deeper soft-tissue infections; when the level is rising, there is a good correlation with necrotizing fasciitis or myositis. Blood cultures are positive in 60% of cases[8].

In all patients, shock is apparent at the time of presentation or within 4 - 8 hours. In only 10% of patients does systolic blood pressure become normal, 4 - 8 hours after administration of antibiotics; in all other patients, shock persists. Renal dysfunction progresses or persists in all patients for 48 - 72 hours in spite of treatment, and many patients require dialysis[8]. In patients who survive, serum creatinine level returns to normal within 4 - 6 weeks as in our patient. Acute respiratory distress syndrome occurs in 55% of patients and generally develops after the onset of hypotension[8]. Ninety percent of them require supplemental oxygen, intubation and mechanical ventilation. Mortality rates vary from 30 - 70%[8-10].

The most common isolates from patients with TSS are M types 1, 3, 12 and 28[8]. Pyrogenic exotoxin A and /or B was found in most cases of severe infection. In the United States, pyrogenic exotoxin A is most frequently associated with these infections[8], while in Sweden and the United Kingdom, exotoxin B has been most common[9]. Streptococcal pyogenic exotoxins A and B induce human mononuclear cells to synthesize not only tumor necrosis factor - α (TNFα)[11] but also interlukin-1β (IL-1β)[12] and interleukin-6 (IL-6)[12], suggesting that TNF could mediate the fever, shock, and tissue injury observed in patients with STSS[8].

Penicillin, erythromycin, and clindamycin are the drugs of choice for the treatment of *S. pyogenes*. Yet, for patients with severe infections (such as necrotizing fasciitis or myositis) in whom large numbers of streptococci are found, the effect of pencillin is diminished. Eagle's study[13] suggests

that the failure of penicillin in this setting is due to the slower growth rate of *streptococci* at large inoculum sizes. In this situation, surgical drainage, debridement, fasciotomy, or amputation may be necessary. Clindamycin is highly effective in the treatment of *S.pyogenes* for many reasons: It is a potent suppressor of bacterial toxin synthesis[14], facilitates phagocytosis of *S.pyogenes* by inhibiting M-protein synthesis[14] and suppresses synthesis of penicillin-binding proteins, which are enzymes involved in cell wall synthesis and degradation. Clindamycin has a longer postantibiotic effect than β-lactams such as penicillin, and lastly, clindamycin causes suppression of LPS-induced monocyte synthesis of TNF[15]. Administration of intravenous immunoglobulin (IVIG) can block *in vitro* T cell activation by streptococcus superantigens[16]. Many case reports have been published in which IVIG administration in the setting of streptococcal TSS appeared to correlate with clinical improvement[17].

The overall mortality rate in GAS-TSS varies in different series from 30 - 70 percent[4] with more mortality rates in adults than children.

CONCLUSION

The unusual mode of presentation, and the acute progression of the case highlights the need to be aware of this differential diagnosis in future presentations of GAS, in order to prevent serious morbidity and mortality from this common pathogen.

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Case Report

Quadricuspid Aortic Valve - A Case Report

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Kuwait Medical Journal 2013; 45 (2): 155 - 157

ABSTRACT

Quadricuspid aortic valve is a rare congenital heart defect. Several different anatomical variations of a quadricuspid aortic valve have been described and aortic regurgitation is the predominant valvular dysfunction associated with it. A 57-year-old hypertensive gentleman presented with a four months history of worsening dyspnea on exertion. The patient had a previous transthoracic echocardiography done one month ago that demonstrated mild to moderate aortic regurgitation. Transoesophageal echocardiography displayed a rare case of quadricuspid aortic valve with four cusps of equal size. The malformation was associated with moderate aortic regurgitation. The use of transoesophageal echocardiography is often warranted to diagnose quadricuspid aortic valve if optimal display of the valvular morphology is desired.

KEY WORDS: aortic valve, cardiac anomaly, echocardiography, quadricuspid

INTRODUCTION

Quadricuspid aortic valve (QAV) is a very rare congenital anomaly with an incidence of 0.008% at autopsy and 1% in patients presenting for AV surgery[1]. The most common variant has four equal cusps and most common presentation is aortic insufficiency[2]. In addition, quadricuspid AV can be associated with other congenital cardiac deformities. Hence, early recognition and follow-up is critical in these patients[3]. We report a case where transesophageal echocardiography was used for the diagnosis and identification of the quadricuspid AV.

CASE REPORT

A 57-year-old gentleman presented with a four months history of increasing dyspnea on exertion (New York Heart Association (NYHA) II) that worsened in the last seven days with orthopnea and paroxysmal nocturnal dyspnea. He had a past medical history of hypertension but he was not known to have any cardiac abnormality in the past. His family history was unremarkable.

His physical examination revealed bisferiens and a water hammer pulse with upper arm blood pressure of 180 / 90 mmHg (wide pulse pressure) and popliteal systolic blood pressure 45 mmHg higher than brachial artery pressure (Hill's sign) with a heart rate of 74 b/min. Cardiac auscultation revealed a high-pitched decrescendo early diastolic murmur in the second right intercostal space-grade III / VI. No ejection systolic murmur was heard. The apex was hyperdynamic and displaced laterally and down to the sixth intercostal space.

A 12-lead electrocardiogram demonstrated normal sinus rhythm at 70 b/min and left ventricular hypertrophy (LVH), a positive Sokolow-Lyon index and ST strain pattern in V4 - V6 leads. Chest X-ray revealed interstitial pulmonary edema.

Transthoracic echocardiography (TTE) demonstrated mild to moderate aortic insufficiency (AI) with a dilated left ventricle (LV), eccentric LVH and a global EF of 50% by Simpson's volumetric method. Moreover, a suspected but non-confirmed quadricuspid AV was seen. No other pathology was noted.

The transesophageal echocardiogram demonstrated a clear quadricuspid AV consisting of four cusps of equal size. The QAV was identified by its characteristic "X" configuration during systole (different from the "Y" of the normal tricuspid aortic valve) (Fig.1). The moderate AI with central malcoaptation of the four aortic leaflets was noted (Fig. 2). Vena contracata width was 0.3 cm by color Doppler, aortic regurgitation jet

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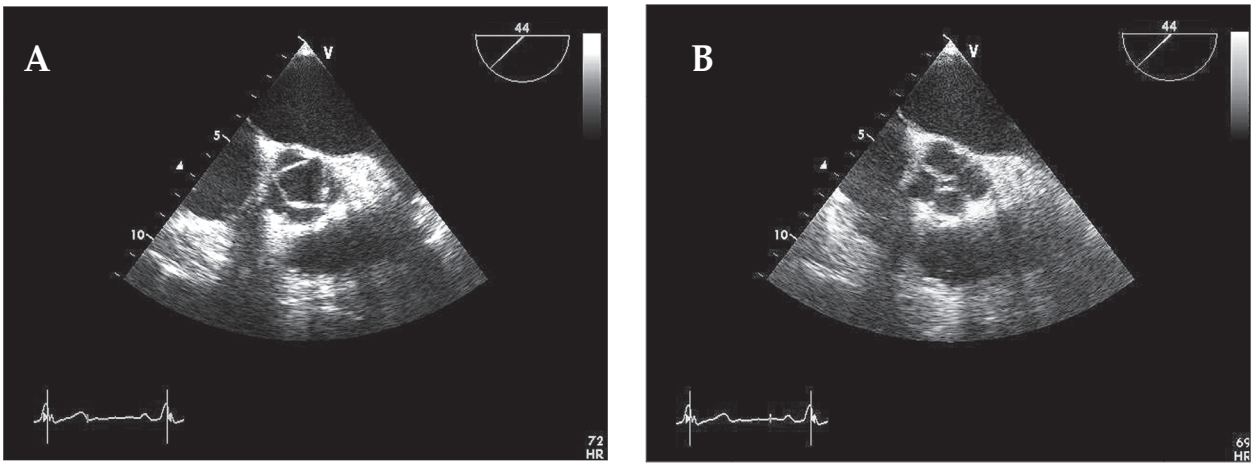

Fig. 1A,B: Transesophageal echocardiogram (TEE) short axis views in the vicinity of the aortic valve plane showing a quadricuspid aortic valve. **(A)** Left in systole and **(B)** right in diastole

left ventricular outflow tract ratio = 50%, regurgitant volume = 53 ml/beat, regurgitant fraction = 41%, regurgitant orifice area = 0.22 cm^2 with normal ascending aorta dimension.

DISCUSSION

QAV is a very rare congenital anomaly with an incidence of 0.008% at autopsy and 1% in patients presenting for AV surgery[1]. Embryologically, the aortic valve is formed when the truncus arteriosus partitions into the aortic and pulmonic valves. In the walls of the aortic and pulmonic trunks[3] small pads of connective tissue develop to form the primordia of the semilunar cusps. The mechanism of this congenital malformation is not fully known. One of the leading hypotheses is an abnormal septation of embryological truncus arteriosus[4].

When deviations from this symmetric arrangement occur, the semilunar valves may have 2, 4 or even 5 cusps[5]. QAV may be isolated or associated with other congenital cardiac abnormalities, including coronary ostium displacement or obstruction, altered coronary artery anatomy, ventricular septal defect, patent ductus arteriosus, subaortic fibromuscular stenosis, and malformations of the mitral valve[6].

The hemodynamic status of a QAV may be related to its morphology. Hurwitz and Roberts' have classified such valves into seven types, depending on the size and degree of equality of the four cusps. The most common type is the one with three large cusps and one small cusp[7].

The natural history of QAV is largely unknown, but valve regurgitation requiring surgical treatment is relatively frequent[2, 4]. A QAV will not necessarily cause hemodynamic compromise. Nevertheless, approximately 44% of these valves will exhibit a hemodynamic abnormality, AI being the most common finding[7].

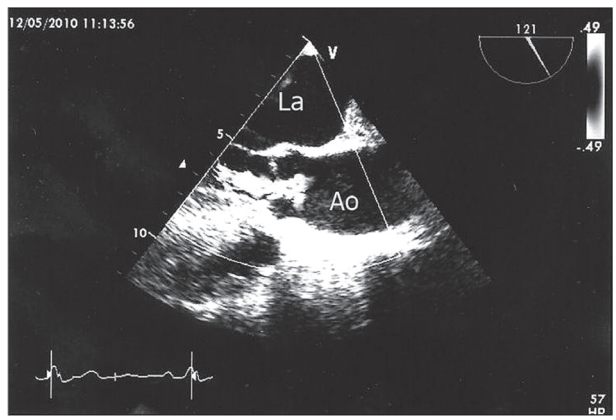

Fig. 2: Transesophageal echocardiogram (long axis view) of the quadricuspid aortic valve and ascending aorta (Ao) during diastole, with incomplete cusp closure and moderate AR. La = left atrium; Ao = aorta

The risk of infective endocarditis in patients with QAV is low in valves with four equal cusps, because of the lack of asymmetry or flow disturbance. In valves with unequal cusps, however, uneven distribution of stress and incomplete juxtaposition during diastole may lead to progressive aortic insufficiency and gradual deterioration over the years, generating speculation that patients who have valves with unequal cusps may be at higher risk for endocarditis[8].

The prevalence of QAV is too low to study the diagnostic accuracy of transthoracic versus transoesophageal echocardiography in the detection of this malformation.

Asymptomatic patients with QAV deserve close follow-up. If aortic regurgitation and / or stenosis are present, the standard surgical indications for valve replacement and / or repair apply. If the patient presents with AI, without significant stenosis, aortic valve repair can be attempted.

Prognosis is the same after treatment with aortic valve replacement or repair. Prognosis varies

depending on method, repair technique, type of valve used in replacement, and comorbidities[2].

Aortic regurgitation in conjunction with a QAV is mostly treated by valve replacement. But this exposes the relatively young patients to the typical valve related complications such as thromboembolism, bleeding, prosthetic valve degeneration and infective endocarditis with a cumulative risk of approximately 5% patients / year[9,10]. Reconstruction of the aortic valve seems to be superior to valve replacement with regard to valve-related complications and could be an attractive alternative[11]. In order to develop a uniform repair technique, it is essential to identify the mechanism of aortic regurgitation.

CONCLUSION

QAV is a rare congenital aortic valve anomaly. TEE can be used to differentiate the typical and other variant forms of QAV and quantify the degree of AR, if TTE images were suboptimal.

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Letter to the Editor

PirB may be a New Approach that Targets for Nogo-Related Genes with Schizophrenia

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Kuwait Medical Journal 2013, 45 (2): 158

Schizophrenia is characterized by distorted thinking and perception and tends to run a chronic course[1], with a presumed etiology in abnormal neurodevelopment attributable to combined effects of environmental and genetic risk factors[2]. It is clear that genetic factors play a very important role in the risk of schizophrenia.

In addition, many studies have suggested that myelin dysfunction may be causally involved in the pathogenesis of schizophrenia[2,3]. Indeed, Nogo-A, myelin-associated glycoprotein (MAG) has been linked to the increased risks of schizophrenia[2,4], which further support the disturbed myelin system theory of schizophrenia. Because Nogo, MAG and oligodendrocyte myelin glycoprotein (OMG) all bind to the common receptor, Nogo-66 receptor 1 (RTN4R), Nogo-66 receptor (NgR) genes among various genetic linkages to schizophrenia have also been identified[5,6]. Finally, NgR is related to improving recovery from stroke and spinal cord injury *via* axonal sprouting and regeneration[6]. Paired-immunoglobulin-like receptor B (PirB) is a receptor for major histocompatibility complex class I antigen (MHC-I). These molecules restrict synaptic plasticity and motor learning in the healthy brain. Thus, a recent report suggests that therapies for stroke are through targeting MHCI and PirB[7]. Additionally, PirB, which has been implicated in nervous system plasticity, is a high-affinity receptor for Nogo, MAG, and OMgp[8].

Due to the common characteristics of binding to the MAG, shared by PirB and NgR, PirB may be involved in the risk of Nogo-related genes of schizophrenia. Thus, it is reasonable to hypothesize that aberrant PirB gene may be another genetic risk factors, which contributes to the development of schizophrenia.

It is thus possible that in the near future some medications may emerge that can correct any disruption of PirB gene expressions in schizophrenia patients and make them achieve a higher quality of life.

ACKNOWLEDGMENTS

This study was supported by Scientific Research Initiation Foundation of Wenzhou Medical College (No. QTJL 0009) and Science and Technology Funding of Wenzhou (Y 20110093)

Conflict of interest statement: We declare there is no financial support or relationship that may pose conflict of interest.

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Letter to the Editor

Chronic Osteomyelitis and Hepatocellular Carcinoma: An Observation in Taiwan

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Kuwait Medical Journal 2013, 45 (2): 159 - 160

Accumulating evidence shows that in addition to chronic hepatitis B infection and chronic hepatitis C infection, hepatocellular carcinoma can be caused by non-viral etiologies[1,2]. On the other hand, substantial evidence shows that chronic inflammation may be caused by infections, chemical irritants, or physical factors and might correlate with increased risk of human cancer in various organs[3-5]. Chronic osteomyelitis is a chronic inflammatory disease which is mainly caused by bacterial infection and it is relatively difficult to treat because of frequent relapses[6]. Therefore, we hypothesize that there could be an association between chronic osteomyelitis and risk of hepatocellular carcinoma and this may be mediated by chronic inflammation.

In order to investigate this issue, we conducted a cohort study by analyzing the database from the Taiwan National Health Insurance program. The details of insurance program can be found in previous studies[7-9]. This cohort study included 21,604 subjects aged 20 years or older with new diagnosis of chronic osteomyelitis as cases (14,206 men and 7,398 women, mean age 55.4 ± 19.5 years) (based on International Classification of Diseases, 9th Revision-Clinical Modification, ICD-9 codes 730.1), and 86416 subjects without chronic osteomyelitis before the index date as controls (56,824 men and 29,592 women from 1997 to 2010). The index date was defined as the date of diagnosing chronic osteomyelitis. Both groups were frequency matched for gender, age (every 5 years), index-year and index-month, with case / control ratio = 1:4.

The chronic osteomyelitis group had higher incidence of hepatocellular carcinoma than the non-osteomyelitis group (1.53 Vs 1.21 per 1000 person-years). After controlling for confounding factors, the hazard ratio of hepatocellular carcinoma was 0.95 in chronic osteomyelitis group, compared to non-osteomyelitis group (95% confidence interval 0.79 - 1.15).

Despite emerging evidence suggesting that chronic inflammation might be involved in cancer development[3-5], no association could be found between chronic osteomyelitis and hepatocellular carcinoma in this present study. Till now, there is no evidence that chronic osteomyelitis might directly affect the liver and there are no available studies to compare with. Of course, it is only a real liver disease (which can be of various etiologies), and not just any other chronic systemic inflammation, that could have the potential to cause chronic inflammation and directly damage the liver. Therefore, the hypothesis that any other chronic systemic inflammation could increase the risk of hepatocellular carcinoma is clearly not sound at all. Furthermore, the liver most likely participates in the acute phase response related to the inflammation as per its physiological role.

ACKNOWLEDGEMENTS

Funding: This study was supported in part by Taiwan Department of Health Clinical Trial and Research Center of Excellence (DOH102-TD-B-111-004).The funding agency did not influence the study design,

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data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest: The authors disclose no conflicts of interest.

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Letter to the Editor

Time to Stop

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Kuwait Medical Journal 2013, 45 (3): 161 - 162

Unselective cardiopulmonary resuscitation (CPR) in Kuwait needs to stop. Very few countries worldwide still practice unselective CPR on their in-patient hospital population and Kuwait is one of those few. The practice of employing CPR has changed drastically over the past fifty years in both Islamic and non-Islamic countries in that it is no longer performed on all patients and especially not in all hospital patients that develop cardiac arrest[1]. We are lagging behind. Medical history is being resurrected through the practice of "slow / light codes" which highlight the conflict in physician's beliefs and practice, similar to what happened in the early 1970s in the western world when CPR was performed less selectively[2].

The evidence for the change in practice around the world has stemmed from over fifty years of cumulative CPR experience all over the world[2,3]. It has become evident that the outcome of CPR is dependant on the co-morbidity of the patient[2-4]. Patients with metastatic cancer, renal failure, stroke and cirrhosis frequently do not survive resuscitation and of those that do the outcome in terms of subsequent morbidity and mortality is extremely poor[4-7]. This raises both ethical questions and questions regarding the futility of extreme measures.

One cannot doubt the number of lives that have been saved through this development of modern medicine. It has certainly been shown to be effective in many people and perhaps this in itself is acting as a strong deterrent from simply letting go.

When reviewing data on CPR survival it is important to distinguish the population being studied. Inpatient cardiac arrests are a very different population compared to out of hospital cardiac arrest population[8]. The data for survival of inpatient cardiac arrest varies tremendously in the literature from 0% to an average range of 15 - 20%[5,8]. There are many reasons for these differences including the various definitions of cardiac arrest, survival and the selection of patients[9]. More importantly, if you look more closely at these studies you find that, most these patients that were studied were all "selected to receive resuscitation", and therefore automatically many of these studies excluded patients that where pre-determined not to receive any resuscitation![4,6].

Nonetheless even in these studies with "selected populations" patients with co-morbidities such as renal failure, metastatic disease and cirrhosis had statistically higher mortality compared to other patients, closer to 90%[4].

This again raises the question. Why do we still offer CPR unselectively to all in-patients without consideration? The answer appears to be highly complex and encompasses religious, ethical, medical and social misconceptions in Kuwait that have placed misguided legal constraints on doctors.

In actual fact, religiously and ethically there are no obligations to provide futile treatment to patients[10,11]. The proof of futility comes from years of experience as well as direct and indirect evidence that certain patients if resuscitated will likely not survive.

It is also unjust to offer resuscitation to all inpatients and then not offer them equal care because we are lacking in the resources to do so. We also know that our alternative to the ICU, *i.e.*, mechanical ventilation on the medical wards in Kuwait has a very high fatality and that it may actually do more harm than good to patients and their families[12]. Therefore, even if we do offer to resuscitate all patients, ethically, we cannot accept to ventilate them in the ward.

The law in Kuwait has constrained doctors to resuscitate all patients. The answer to why this law remains unchanged remains elusive in the face of overwhelming evidence that unselected CPR cannot

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ethically be sustained nor is it necessary. This has created a true ethical dilemma for physicians working in Kuwait. This is why we need to stop this practice and this is why the law needs to change.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2013, 45 (2): 163 - 166

Self-confidence of Medical Students in Performing Clinical Skills Acquired during Their Surgical Rotation. Assessing Clinical Skills Education in Kuwait

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Saudi Med J 2012; 33:1310-1316

Objective: To assess the self-confidence of clinical years' medical students in performing clinical skills/procedures
Methods: A cross-sectional study was conducted in April 2011 at the Department of Surgery, Faculty of Medicine, Health Sciences Center, Kuwait University, Safat, Kuwait. A questionnaire was used to collect data from students who had completed their surgical rotation of their first clinical year. The students reported their level of self-confidence in performing specific skills/procedures related to that rotation. Data were presented using frequencies and percentages. A total score of confidence was calculated for each student. The Mann-Whitney and Kruskal-Wallis tests were used to assess the association between the students` sociodemographic characteristics and confidence score.
Results: Of the 122 students invited to participate in the study, only 15 (12.3%) declined to comply. Most students reported high confidence level (more than 75%) in performing 7 of the 13 history taking/physical examination skills, and 2 of the 39 diagnostic/treatment procedure skills. The highest confidence level was in performing abdominal examination, while the lowest level was in care of Jackson-Pratt drain site and emptying the drain bulb. The total confidence score was significantly higher among males ($p = 0.021$), and students with higher monthly income ($p = 0.002$).
Conclusion: Medical students appeared to have poor self-confidence in performing clinical skills/procedures. Curriculum planners should explore potential reasons, and methods for the improvement of confidence level among medical students in performing skills/procedures they were expected to learn during their surgical rotation.

Seasonal Variations in the Atmospheric Concentrations of Polybrominated Diphenyl Ethers in Kuwait

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Sci Total Environ 2013 Apr 5;454-455C:534-541

The study reports fortnightly atmospheric concentrations of PBDEs concomitantly measured at an urban and a remote location over a twelve-month period in Kuwait to examine seasonal variability and urban-rural concentration gradients. The annual mean (and range) of ∑PBDE concentrations was 32 (3 - 208) pgm-3 at the remote site and 57 (0.3 - 445) pgm-3 at the urban site. Although not statistically significant, the median (29pgm-3) and mean (57pgm-3) concentrations at the urban location were higher than those measured at the remote location (18 and 29pgm-3 respectively), consistent with the view that urban centers are an important net source of these compounds to the environment. Although Clausius-Clapeyron

plots showed statistically significant correlations ($p < 0.05$) with temperature for low molecular weight congeners (BDEs 28, 47, 100), correlations with the ΣPBDE concentrations were not significant at both urban and remote sites. The seasonal variations in ΣPBDE concentrations were not markedly different at the urban location, but the median summer ΣPBDE concentration at the remote location was significantly higher than winter median ΣPBDE concentrations. The absence in seasonality at the urban location may be due to ongoing primary emissions in urban areas.

Phylogenetic Analysis of Partial L1 Gene of 10 Human Papillomavirus Types Isolated Most Commonly from Women with Normal and Abnormal Cervical Cytology in Kuwait

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Arch Virol 2013 Mar 17 [Epub ahead of print]

This study was undertaken to evaluate the presence of human papillomavirus (HPV) variants in cervical samples. L1 genetic variable region was studied in 10 HPV types: HPV 11, 16, 18, 33, 53, 54, 56, 61, 66 and 81. A total of 116 isolates were examined, including 47 HPVs isolated from women with normal cytology and 69 with abnormal cytology of different grades. HPV sequences were detected using MY09/MY11 consensus primers. Fifty silent and 65 missense mutations were detected. Two missense mutations were detected in HPV18, 3 in HPV56 and 17 in HPV61. The number of missense mutations per isolate ranged from 1 to 3, except in HPV54 and HPV61, where 7 and 11 missense mutations were found, respectively. Most of the isolates (52.3 %) with missense mutations were isolated from women with abnormal cervical samples. Low-grade squamous intraepithelial lesion cytology diagnosis dominated all cervical abnormalities. This study is the first on the identification of molecular variants in the Middle East and suggests the circulation of new HPV subtypes and variants in Kuwait, which needs to be confirmed by further analysis of the complete HPV genome.

In Vitro Susceptibility of Campylobacter Jejuni from Kuwait to Tigecycline & Other Antimicrobial Agents

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Indian J Med Res 2013; 137:187-190

Background & objectives: There is an increasing frequency of resistance of Campylobacter jejuni to antimicrobial agents making treatment difficult. In this study, the in vitro susceptibility of C. jejuni isolates collected over an eight year period was tested against tigecycline, a glycylcycline, the previously tested antimicrobial agents in Kuwait, ciprofloxacin, erythromycin and tetracycline, and other antimicrobial agents not previously tested in Kuwait, amoxicillin-clavulanic acid, gentamicin, imipenem and meropenem.
Methods: A total of 97 C. jejuni isolates from diarrhoeal stools of Kuwaiti patients during 2002 - 2010 were studied for susceptibility to the above antimicrobial agents by E test.
Results: Erythromycin resistance increased from 5.0 per cent in 2002 - 2003 to 13.8 per cent in 2007 - 2010. The figures for ciprofloxacin resistance for the same periods were 53 and 65.5 per cent, respectively. Tetracycline resistance increased from 40.0 per cent in 2003 - 2006 to 62.1 per cent in 2007 - 2010 ($P = 0.05$). However, all isolates were uniformly susceptible to tigecycline and other antimicrobial agents.

Interpretation & conclusions: There was a progressive increase in the prevalence of resistance to ciprofloxacin, erythromycin and tetracycline. As all isolates were uniformly susceptible to tigecycline, this antimicrobial agent can be considered as a potential candidate for treatment in clinical studies.

Viral Load of Human Papillomavirus in Women with Normal and Abnormal Cervical Cytology in Kuwait

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J Infect Dev Ctries 2013; 7:130-136

Introduction: Human papillomaviruses (HPV) are the most commonly known sexually transmitted agents. Almost all cases of cervical cancer are caused by persistent infection. This study was conducted to ascertain whether there is a difference in HPV load in cervical samples with normal and abnormal cervical cytology reports in Kuwait.
Methodology: HPV-positive abnormal ThinPrep samples (n = 206) and normal ThinPrep samples (n = 120) were taken from women attending gynecology clinics. Real-time PCR was used to measure the viral load for all HPV genotypes.
Results: The median normalized viral load in samples with normal and abnormal cytology reports was 0.86 × 10-7 and 4.66 × 10-7, respectively (p = 0.001). Median normalized viral load of high-risk (HR), intermediate-risk (IR) and low-risk (LR) HPV was 4.04 × 10-7, 0.71 × 10-7 and 2.38 × 10-7, respectively, (p = 0.002).
Conclusions: The findings suggest that, in the absence of a proper screening programme in Kuwait, quantification of HPV viral load could be considered as a surrogate virology test to identify women with abnormal cytology. Further population-based prospective studies are needed to include more women with high-grade and invasive carcinoma reports.

Molecular Identification and Antifungal Susceptibility Profile of Aspergillus Flavus Isolates Recovered from Clinical Specimens in Kuwait

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BMC Infect Dis 2013; 13:126

Background: Within the genus Aspergillus, A. flavus is the second most important species of clinical significance. It is predominantly associated with infections involving sinuses, eye and skin, mostly in geographic regions with hot and arid climate, including the Middle East. Recent reports on emergence of resistance to triazoles among Aspergillus spp. is a cause of concern for treatment of patients with invasive aspergillosis. In this study we present data on genetic characterization and antifungal susceptibility profile of clinical and environmental isolates of A. flavus.
Methods: Ninety-nine Aspergillus section Flavi isolates, originating from clinical (n = 92) and environmental (n = 7) sources, initially identified by morphological characteristics, were analyzed by partial sequencing of β-tubulin and calmodulin gene fragments and their susceptibilities to six antifungal agents was determined by Etest on RPMI1640 and Muller-Hinton agar media. Etest minimum inhibitory

concentrations (MICs) of amphotericin B and voriconazole were also compared with zone of inhibition diameters obtained by disc diffusion test on RPMI agar medium.
Results: The identity of all clinical and environmental isolates was confirmed as A. flavus species by combined analysis of β-tubulin and calmodulin genes. The mean MIC90 (μg/ml) values on RPMI medium for amphotericin B, voriconazole, posaconazole, anidulafungin, micafungin and caspofungin were 3, 0.25, 0.25, 0.002, 0.002 and 0.032, respectively. No environmental isolate exhibited MIC value of >2 μg/ml for amphotericin B. For clinical isolates, the zone of inhibition diameters for amphotericin B and voriconazole ranged from 7 - 16 mm and 24 - 34 mm, respectively. Linear regression analysis between Etest MIC values and disk diffusion diameters revealed a significant inverse correlation with amphotericin B ($p < 0.001$) and voriconazole ($p < 0.003$).
Conclusions: The β-tubulin and calmodulin gene sequences confirmed that all 92 clinical isolates identified phenotypically belonged to A. flavus taxon, thus suggesting that the other species within Aspergillus section Flavi are of little clinical significance. Triazoles and echinocandins showed very good in vitro activity against the A. flavus, however, 10% clinical isolates showed MICs of >2 μg/ml for amphotericin B.

Combined Ciprofloxacin and Amikacin Prophylaxis in the Prevention of Septicemia after Transrectal Ultrasound Guided Biopsy of the Prostate

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J Urol 2013; 189:911-915

Purpose: A steady increase in the incidence of septicemia after prostate biopsy in our unit between 2001 and 2005 prompted us to review our prophylactic antibiotic regimen. We compared the incidence of septicemia in patients undergoing prostate biopsy between 2001 and 2005 when only oral ciprofloxacin was used prophylactically (group 1) to the incidence among patients undergoing biopsy between 2006 and 2010 when a single dose of intravenous amikacin was added to ciprofloxacin (group 2).
Materials and Methods: In group 1, the 300 patients were given 500 mg oral ciprofloxacin twice daily 1 day before and for 2 days after the biopsy while in group 2 the 897 patients, in addition to the ciprofloxacin previously mentioned, received 500 mg intravenous amikacin 30 minutes before the biopsy. Patients admitted to the hospital with septicemia after prostate biopsy had urine and blood culture and sensitivity tests. The number of patients in whom septicemia developed in each group after prostate biopsy and the microorganisms isolated from the urine and blood of such patients were compared using the chi-square test.
Results: Septicemia was seen in 24 of 300 (8%) and 15 of 897 (1.7%) patients in groups 1 and 2, respectively ($p < 0.001$). In group 1 the rate of septicemia after prostate biopsy was 2.1% and 13% in 2001 and 2005, respectively ($p < 0.001$). In group 2 the rate of septicemia was 1.5% in 2006 and 1.6% in 2010 ($p < 0.25$). Escherichia coli resistant to quinolones was responsible for 33 of 39 (84.6%) septicemic cases.
Conclusions: The addition of amikacin to ciprofloxacin prophylaxis significantly reduces the incidence of septicemia after prostate biopsy.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013; 45 (2): 167 - 180

Abdominal and Pelvic Imaging 2013: A Practical Multi-Modality Review Course of Gi and Gu Radiology
Jun 17 - 19, 2013
United States / Massachusetts / Boston
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600, Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

Cutting Edge **Laryngology** 2013
Jun 17 - 19, 2013
United Kingdom / London
Contact: Nicole Nielsen, Organiser Secretariat, Kenes UK
Phone: 011-44-20-7380-8030
Email: nnielsen@kenes.com

Human Genomics and Personalized Medicine
Jun 17 - 21, 2013
Sweden / Stockholm
Contact: Keystone Symposia on Molecular and Cellular Biology
Phone: 800-253-0685 or 970-262-1230
Fax: 970-262-1525
Email: info@keystonesymposia.org

IPEG 22nd Annual Congress for **Endosurgery** In Children
Jun 17 - 22, 2013
China / Beijing
Contact: Meeting Registrar, International Pediatric Endosurgery Group
Phone: 310-437-0553 ext. 128
Email: registration@ipeg.org

Principles and Practice of **Pain Medicine**
Jun 17 - 21, 2013
United States / Massachusetts / Cambridge, MA
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600, Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

13th International Conference of **Forensic Mental Health** Services
Jun 18 - 21, 2013
Netherlands / Maastricht
Contact: International Association of Forensic Mental Health Services
Tel: 604-924-5026; Fax: 604-924-5027
E-mail: tmoropito@iafmhs.org

Core Skills in **Laparoscopic Surgery**
Jun 18 - 20, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Dizziness: A Multidisciplinary Approach
Jun 18 - 21, 2013
United Kingdom / London
Contact: Kate Eykamp, Course Organiser, University College London
Phone: 011-44-20-3448-3275
Email: kate.eykamp@uclh.nhs.uk

11th World Congress of **Perinatal Medicine**
Jun 19 - 22, 2013
Russia / Moscow
Contact: MCA Events
Phone: 011-39-2-3493-4404, Fax: 011-39-2-3493-4397
Email: info@mcaevents.org

53rd INPC - International **Neuropsychiatric** Pula Congress
Jun 19 - 22, 2013
Croatia / Pula
Contact: INPC Secretariat, INPC Secretariat, Society for Neuropsychiatry
Phone: 011-385-1-638-6191, Fax: 011-385-1-638-6191
Email: info@pula-cong.com

BMJ Masterclasses: **Dermatology and Ophthalmology** Update
Jun 19, 2013
United Kingdom / Leeds
Contact: Sara Potter, Marketing Assistant, BMJ Masterclasses
Phone: 011-44-20-7874-0706
Email: info.masterclasses@bmjgroup.com

16th Annual **Cardiothoracic Update** and TEE Board Review
Jun 20 - 23, 2013
United States / South Carolina / Hilton Head Island
Contact: Duke CME, Duke University School of Medicine
Phone: 919-401-1200
Email: cme@mc.duke.edu

19th Conference of International Union Against **Tuberculosis and Lung Disease** (The Union) Africa Region
Jun 20 - 22, 2013
Rwanda / Kigali, Rwanda
Contact: The Union, Africa Region
Phone: 011-250-7-8841-0827
Email: kigali2013@theunion.org

6th International **Nasopharyngeal Carcinoma** Symposium
Jun 20 - 22, 2013
Turkey / Istanbul
Contact: Esra Unlugencoglu, Project Executive, Ea Organization
Phone: 011-90-216-465-3540
Fax: 011-90-216-465-4048
Email: pco@eaorganizasyon.com.tr

Dermatologic Procedures
Jun 20 - 21, 2013
United States / California / Newport Beach
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631
Fax: 512-329-0442
Email: julie@npinstitute.com

EASL Special Conference: **Liver Cancer** Management
Jun 20 - 22, 2013
Turkey / Istanbul
Contact: EASL Office
Phone: 011-41-22-807-0360
Fax: 011-41-22-328-0724
Email: easloffice@easloffice.eu

X-Ray Interpretation
Jun 20 - 21, 2013
United States / California / Newport Beach
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631
Fax: 512-329-0442
Email: julie@npinstitute.com

10th National Neuroscience Conference on **Epilepsy In Children**
Jun 21, 2013
United Kingdom / London
Contact: MA Healthcare Limited
Phone: 011-44-20-7501-6762; Fax: 011-44-20-7978-8319
Email: conferences@markallengroup.com

1st International Forum **"Ballistic Head and Neck Injuries"** on Military Medicine
June 21 – 22, 2013
Germany / Dillingen on the Danube / Bavaria
Contact: Heike Lange, Geschaftsfuhrung, BETA Verlag & Marketinggesellschaft mbH, Celsiusstrabe 43, 53125 Bonn. www.diforum.de
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2nd Annual Internal **Derangements of Joints** - Brazil
Jun 21 - 23, 2013
Brazil / Sao Paulo
Contact: iiCME, Inc.
Phone: 205-467-0290; Fax: 205-467-0195
Email: iicmemail@gmail.com

6th International Conference on **Neonatal and Childhood Pulmonary Vascular Disease**
Jun 21 - 22, 2013
United States / California / San Francisco
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-4251; Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Colonoscopy
Jun 21 - 22, 2013
United States / California / Newport Beach
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

International Symposium on Prostate, Androgens and **Men's Sexual Health**
Jun 21 - 23, 2013
Germany / Berlin
Contact: Ms. Silke Weerts, CPO Hanser Service
Phone: 011-49-40-670-8820
Email: issmessm@cpo-hanser.de

Musculoskeletal Ultrasound Course for Rheumatologists with Interventional **Cadaver Workshop**—Intermediate
Jun 21 - 23, 2013
United States / Illinois / Rosemont
Contact: American College of Rheumatology
Phone: 800-636-4766 (US & Canada) or 415-979-2265
Fax: 415-293-5231
Email: ACRProfMtgs@cmrus.com

20th Annual International **Stress and Behavior Neuroscience and Biopsychiatry** Conference (North America)
Jun 22 - 24, 2013
United States / Louisiana / New Orleans
Contact: NA Nutsa, Conference Secretary, International Stress and Behavior Society
Phone: 240-899-9571
Email: isbs.congress@gmail.com

World **Allergy and Asthma** Congress
Jun 22 - 26, 2013
Italy / Milan
Contact: European Academy of Allergy & Clinical Immunology HQ
Phone: 011-41-44-205-5533
Fax: 011-41-44-205-5539
Email: events@eaaci.org

12th World Congress in **Fetal Medicine** 2013
Jun 23 - 27, 2013
Spain / Marbella
Contact: Kristis, Fetal Medicine Foundation
Email: kristis@fetalmedicine.com

2013 Annual Meeting of the Society for **Behavioral Neuroendocrinology**
Jun 23 - 26, 2013
United States / Georgia / Atlanta
Contact: Society for Behavioral Neuroendocrinology
Phone: 847-517-7225
Fax: 847-517-7229
Email: info@sbn.org

30th International **Epilepsy** Congress
Jun 23 - 27, 2013
Canada / Quebec / Montreal
Contact: Congress Secretariat
Phone: 011-353-1-205-6720
Fax: 011-353-1-205-6156
Email: montreal@epilepsycongress.org

12th International Workshop on **Developmental Nephrology**
Jun 24 - 26, 2013
United Kingdom / Edinburgh
Contact: Jordan Kreidberg, Harvard Medical School
Email: Jordan.Kreidburg@childrens.harvard.edu
Website: http://ipna-online.org/iwdn/

2013 **Cancer and Metabolism**
Jun 24 - 25
Netherlands / Amsterdam
Contact: Conference Secretariat, Abcam plc
Phone: 877-749-8807
Email: events@abcam.com

RCOG World Congress in **Obstetrics and Gynaecology** 2013
Jun 24 - 26, 2013
United Kingdom / Liverpool
Contact: Michelle Maginn, RCOG World Congress 2013 Secretariat, Hampton Medical Conferences Ltd
Phone: 011-44-20-8979-8300; Fax: 011-44-20-8979-6700
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Specialty Skills n **Vascular Surgery**
Jun 24 - 25, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

6th Congress of the International Society of **Vascular Behavioural and Cognitive Disorders**
Jun 25 - 28, 2013
Canada / Ontario / Toronto
Contact: Conference Secretariat, International Conference Services
Phone: 604-681-2153; Fax: 604-681-1049

Clinical Skills in **Spinal Assessment** And Management
Jun 25 - 26, 2013
United Kingdom / London
Contact:Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

International **Behavioral Neuroscience** Society Annual Meeting 2013
Jun 25 - 30, 2013
Ireland / Malahide
Contact: IBNS Central Office
Phone: 830-796-9393; Fax: 830-796-9394
Email: ibns@ibnshomepage.org

Advanced Skills in **Vascular Surgery**
Jun 26 - 28, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Care of the **Critically Ill** Surgical Patient (CCRISP)
Jun 26 - 28, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Hot Topics in **Infection and Immunity** in Children
Jun 26 - 28, 2013
United Kingdom / Oxford
Contact: Course Administrator, University of Oxford Department of Paediatrics
Phone: 011-44-18-6585-7466
Email: iic@paediatrics.ox.ac.uk

ISMRM Workshop on **Multiple Sclerosis** as a Whole-Brain Disease
Jun 26 - 28, 2013
United Kingdom / London
Contact: International Society for Magnetic Resonance in Medicine
Email: info@ismrm.org

4th **Critical Care** Conference in Thailand 2013
Jun 27 - 29, 2013
Thailand / Pataya
Contact: Mr. Withun Bunsiri, The Thai Society of Critical Care Medicine (TSCCM)
Phone: 011-66-2-714-2590; Fax: 011-66-2-714-2656
Email: tsccmconference@gmail.com

5th International Congress of **Molecular Medicine**
Jun 27 - 30, 2013
Turkey / Elazig City
Contact: Conplus, Conplus Kongre ve Organizasyon, Turkish Society of Molecular Medicine
Phone: 011-90-216-541-0054; Fax: 011-90-216-541-0108
Email: molecular2013@conplus.org

9th World Congress of **Cosmetic Dermatology**
Jun 27 - 30, 2013
Greece / Athens Dermatology
Contact: Congress Organizing Bureau, Erasmus Conferences Tours & Travel
Phone: 011-30-210-741-4700; Fax: 011-30-210-725-7532
Email: info@wcocd2013.com

American Academy of **Anti-Aging Medicine** Chicago Conference
Jun 27 - 28, 2013
United States / Illinois / Chicago
Contact: American Academy of Anti-Aging Medicine
Phone: 888-997-0112 or 561-997-0112

Congenital, Structural and Valvular Interventions (**CSI**) 2013
Jun 27 - 29, 2013
Germany / Frankfurt
Contact: Alexander Sommerauer, Congress Organization, cme4u GmbH
Phone: 011-49-69-8999-0507; Fax: 011-49-69-2562-8658
Email: info@cme4u.org

Core Skills in **Laparoscopic Surgery** Course
Jun 27 - 28, 2013
United Kingdom / Dundee
Contact: Susan McComiskie, Secretary, Cuschieri Skills Centre, University of Dundee
Phone: 011-44-13-8238-3400; Fax: 011-44-13-8264-6042
Email: s.mccomiskie@dundee.ac.uk

Hip and Knee Conference 2013
Jun 27 , 2013
United Kingdom / London
Contact: Jacques Clarkson, Registration Manager, Orthopaedic Product News
Phone: 011-44-14-2385-1150
Email: jacques.clarkson@barkerbrooks.co.uk

World **Hypertension** Congress
Jun 27 - 30, 2013
Turkey / Istanbul
Contact: Esra Unlugencoglu, Project Executive, Ea Organization
Phone: 011-90-216-465-3540; Fax: 011-90-216-465-4048
Email: pco@eaorganizasyon.com.tr

12th International **Facial Nerve** Symposium
Jun 28 - Jul 1, 2013
United States / Massachusetts / Boston
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600
Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

2013 **Cardiothoracic Imaging** Update In Quebec City
Jun 28 - 30, 201
Canada / Quebec / Quebec City
Contact: Department of Radiology, University of Ottawa
Phone: 613-737-8899 ext. 74044
Email: info@ottawaradcme.com

Comprehensive Minimally Invasive **Gynecologic Surgery**
Jun 28 - 29, 2013
United States / Nevada / Las Vegas
Contact: Innovations in Medical Education and Training
Phone: 856-427-6200; Fax: 732-204-0124
Email: contact@imetcme.com

12th International Congress on **Pediatric Pulmonology**
Jun 29 - Jul 1, 2013
Spain / Valenci
Contact: Anne Flore Bidart, MD, Congress Secretariat, Mediaxa
Phone: 011-33-4-9703-8597; Fax: 011-33-4-9703-8598
Email: info-cipp@mediaxa.com

2013 PNS Biennial Meeting of the **Peripheral Nerve** Society
Jun 29 - Jul 3, 2013
France / Saint-Malo
Contact: Secretariat, Le Public Système PCO
Phone: 011-33-1-7094-6535, Fax: 011-33-1-7094-6501

Multidisciplinary Management of **Head and Neck Oncology**
Jun 30 - Jul 3, 2013
Hungary / Budapest
Contact: European Society for Radiotherapy and Oncology
Phone: 011-32-2-775-9340; Fax: 011-32-2-779-5494
Email: education@estro.org

Primary Care: Addressing Issues of Aging Patients 9-Night Baltic Cruise
Jun 30 - Jul 9, 2013
Denmark / Copenhagen
Contact: Continuing Education, Inc.
Phone: 800-422-0711 or 727-526-1571
Email: 063013Aging@continuingeducation.net

Paediatric **Rheumatology**
Jul 1 - 3, 2013
United Kingdom / London
Contact: ICH Events, UCL Institute of Child Health
Phone: 011-44-20-7905-2699
Email: info@ichevents.com

2013 **Musculoskeletal Imaging** Update In Montreal
Jul 2 - 4, 2013
Canada / Quebec / Montreal
Contact: Department of Radiology, University of Ottawa
Phone: 613-737-8899 ext. 74044
Email: info@ottawaradcme.com

15th World Congress on **Gastrointestinal Cancer**
Jul 3 - 6, 2013
Spain / Barcelona
Contact: Imedex
Phone: 770-751-7332; Fax: 770-751-7334
Email: meetings@imedex.com

7th London Emergency **Ultrasound** Level 2 Course
Jul 3 - 4, 2013
United Kingdom / London
Contact: Luis G Macchiavello, Director, Infomed Research and Training
Phone: 011-44-20-8123-0021; Fax: 011-44-20-8290-6917
Email: courses@infomedltd.co.uk

Cell Culture
Jul 3 - 4 , 2013
United Kingdom / London
Contact: Fateja Begum, SMi Group
Phone: 011-44-20-7827-6184
Email: fbegum@smi-online.co.uk

Cognitive Remediation Therapy Training
Jul 3 - 4 , 2013
United Kingdom / London
Contact: Geraldine Davis, King's College London
Phone: 011-44-20-7848-5040
Email: geraldine.davis@kcl.ac.uk

Introduction to CBT for **Occupational Health** Professionals
Jul 3 – 4, 2013
United Kingdom / Birmingham
Contact: CPD Training Team, Institute of Occupational and Environmental Medicine, University of Birmingham
Phone: 011-44-12-1414-6013 / 6014
Fax: 011-44-12-1414-6217
Email: occhealth@contacts.bham.ac.uk

4th Congress of the **Psoriasis** International Network
Jul 4 - 6 2013
France / Paris Dermatology
Contact: MCI Paris
Phone: 011-33-1-5385-8259; Fax: 011-33-1-5385-8283
Email: pso2013@mci-group.com

Advanced **MR Imaging** of the Musculoskeletal System
Jul 4 - 6, 2013
Malta / Msida
Contact:European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

Minimally Invasive **Oesophagectomy**
Jul 4 - 5, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, IMACS Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: najma.amir@nhs.net

Summer Seminar: **Psychopharmacology**, 2013
Jul 5 - 7, 2013
United States / Maine / Martha's Vineyard
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600; Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

12th Congress of the **Cell Transplant** Society - CTS 2013
Jul 7 - 11, 2013
Italy / Milan
Contact: CTS 2013 Secretariat, c/o The Transplantation Society
Phone: 514-874-1717; Fax: 514-874-1716
Email: info@cts2013.org

International Congress on **Naturopathic Medicine**
Jul 7 - 9, 2013
France / Paris
Contact: Shirley Dinenson, Conference secretariat, Paragon Conventions
Phone: 011-41-22-533-0948; Fax: 011-41-22-580-2953
Email: sdinenson@paragon-conventions.com

Echocardiography: Hands-On Cardiac Ultrasound Imaging And Doppler
Jul 8 - 13, 2013
United States / Texas / Dallas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 or 972-353-3200; Fax: 817-577-4250

Hands-on **Abdominal Ultrasound Imaging** For Primary Care Mds and Clinicians
Jul 8 - 11, 2013
United States / Texas / Dallas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 or 972-353-3200; Fax: 817-577-4250

Hands-on **Obstetric and Pelvic Ultrasound Imaging**
Jul 8 - 12, 2013
United States / Texas / Dallas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 or 972-353-3200; Fax: 817-577-4250

How to Do Research on **Therapeutic Interventions:** Protocol Preparation
Jul 8 - 12, 2013
United Kingdom / Oxford
Contact: Sarah Kelly, Department for Continuing Education, University of Oxford
Phone: 011-44-18-6528-6955
Email: exptherr@conted.ox.ac.uk

Laryngectomy: Rehabilitation and Surgical Voice Restoration (Advanced Level)
Jul 8 - 12, 2013
United Kingdom / London
Contact: Centre for Continuing Professional Development, Imperial College London
Phone: 011-44-20-7594-6882
Email: cpd@imperial.ac.uk

Symposia at Sea: **Head and Neck Oncology** 2013
Jul 9 - 19, 2013
Italy / Rome
Contact: Educational Symposia
Phone: 800-338-5901 or 813-806-1000; Fax: 800-344-0668 or 813-806-1001

2nd World Congress on **Thyroid Cancer**
Jul 10 - 14, 2013
Canada / Ontario / Toronto
Contact: Conference Secretariat, The Bayley Group
Phone: 888-527-3434 or 519-263-5050
Email: info@thyroidworldcongress.com

Breast Cancer, New Horizons, Current Controversies
Jul 11 - 13, 2013
United States /Massachusetts / Boston
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600; Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

Topics in **Anesthesia**
Jul 11 - 14, 2013
United States / California / Anaheim
Contact: Northwest Anesthesia Seminars, Inc.
Phone: 509-547-7065; Fax: 509-547-1265
Email: info@nwas.com

Topics in **Anesthesia + ACLS + NRP + PALS**
Jul 11 - 14, 2013
United States /Missouri / Branson
Contact: Northwest Anesthesia Seminars, Inc.
Phone: 509-547-7065; Fax: 509-547-1265
Email: info@nwas.com

Update on **Psoriatic Arthritis**
Jul 11, 2013
Canada / Ontario / Toronto
Contact: Continuing Education and Professional Development, University of Toronto
Phone: 416-978-2719
Email: info-MED1360@cepdtoronto.ca

Hands-on **Transvaginal Pelvic Ultrasound** Imaging
Jul 12, 2013
United States / Texas / Dallas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 or 972-353-3200; Fax: 817-577-4250

2013 **Idiopathic Pulmonary Fibrosis** Conference: Improving Clinical Outcomes
Jul 13, 2013
United States / Missouri / Kansas City
Contact: Marla Sutton, MS, Senior Program Manager, University of Kansas Medical Center
Phone: 913-588-4487
Email: msutton@kumc.edu

7th International Pediatric Transplant Association (Ipta) Congress on **Pediatric Transplantation**: Building Bridges
Jul 13 - 16, 2013
Poland / Warsaw
Contact: Meredith Weiner, Meeting Manager, IPTA
Phone: 856-439-0500 ext. 4419
Email: mweiner@ahint.com

2013 **STI and AIDS** World Congress
Jul 14 - 17, 2013
Austria / Vienna
Contact: Alissa McGregor, Conference Office, Vienna Medical Academy
Phone: 011-43-1-405-1383 ext. 11
Fax: 011-43-1-407-8274
Email: STIvienna2013@medacad.org

49th Annual **Internal Medicine** Program
Jul 14, 2013
United States / Colorado / Estes Park
Contact: Pam Welker, Administrator and Conference Manager, University of Colorado
Phone: 303-724-3551
Email: Pam.Welker@UCDenver.edu

17th International Congress of Comparative **Endocrinology** (ICCE 2013)
Jul 15 - 19, 2013
Spain / Barcelona Endocrinology
Contact: Mondial & Cititravel Congresos
Phone: 011-34-932-212-955; Fax: 011-34-934-592-059
Email: icce2013@mondial-congress.com

2013 **Osteoporosis**
Jul 16, 2013
United Kingdom / London
Contact: MA Healthcare Limited
Phone: 011-44-20-7501-6762; Fax: 011-44-20-7978-8319
Email: conferences@markallengroup.com

5th World **Glaucoma** Congress
Jul 17 - 20, 2013
United States / British Columbia / Vancouver
Contact: MCI Amsterdam
Phone: 011-31-20-679-3411
Email: wgc-2013-info@mci-group.com

8th World Congress of **Melanoma**
Jul 17 - 20, 2013
Germany / Hamburg
Contact: MCI Deutschland GmbH
Phone: 011-49-30-204-590; Fax: 011-49-30-204-5950
Email: congress@worldmelanoma2013.com

Renal Biopsy in Medical Diseases of the Kidneys
Jul 17 - 20, 2013
United States / New York / New York Pathology
Contact: Laura Yasso, Program Manager, Columbia University College of Physicians & Surgeons
Phone: 212-305-3334; Fax: 212-305-5740
Email: cme@columbia.edu

Difficult **Airway Management**: A Critical Care Approach
Jul 19 - 21, 2013
United States /Illinois / Northbrook
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

2013 International Society for **Pediatric and Adolescent Diabetes** Science School for Physicians
Jul 22 - 26, 2013
Australia / Sydney
Contact: Assoc Prof Maria Craig, Convenor, The Children's Hospital at Westmead
Email: m.craig@unsw.edu.au

40th Annual **Renal Disease** and Electrolyte Disorders
Jul 22, 2013
United States / Colorado / Aspen
Contact: Pam Welker, Administrator and Conference Manager, University of Colorado
Phone: 303-724-3551
Email: Pam.Welker@UCDenver.edu

Laparoscopic **Cholecystectomy**
Jul 22, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, IMACS Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: najma.amir@nhs.net

Focus on the **Female Patient**
Jul 24 - 27, 2013
United States /South Carolina / Kiawah Island
Contact: Vicki Baugh, Coordinator, Professional Development, Southern Medical Association
Phone: 800-423-4992
Fax: 205-945-1548
Email: vbaugh@sma.org

Osteoporosis: Diagnosis, Management And Prevention
Jul 24 - 27, 2013
United States /South Carolina / Kiawah Island
Contact: Vicki Baugh, Coordinator, Professional Development, Southern Medical Association
Phone: 800-423-4992; Fax: 205-945-1548
Email: vbaugh@sma.org

Transcranial Doppler Course
Jul 24 - 26, 2013
United States / California / Los Angeles
Contact: Office of Continuing Medical Education, UC Los Angeles
Phone: 310-794-2620 Fax: 310-794-2624

18th World Congress on **Heart Disease**
Jul 26 - 29, 2013
United States / British Columbia / Vancouver
Contact: Asher Kimchi, MD, Chairman, International Academy of Cardiology
Phone: 310-657-8777; Fax: 310-659-4781
Email: klimedco@ucla.edu

Mechanical Ventilation: Advanced Critical Care Management
Jul 26 - 28, 2013
United States / Illinois / Northbrook
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

Multidisciplinary **Cancer Management** Course (Mcmc)
Jul 26 - 28
Mexico / La Paz
Contact: American Society of Clinical Oncology
Phone: 888-282-2552 or 571-483-1300
Email: mcmc@asco.org

3rd International Conference on **Vaccines and Vaccination**
Jul 29 - 31, 2013
United States / Nevada / Las Vegas
Contact: Conference Secretariat, OMICS Group Conferences
Phone: 800-216-6499 (USA & Canada) l 1-800-651-097 (Australia) l 0805-080048 (Europe)
Fax: 650-618-1414
Email: vaccines2013@omicsgroup.com

Society of **Neurointerventional Surgery** 10th Annual Meeting
Jul 29 - Aug 1, 2013
Florida / Miami
Contact: Society of NeuroInterventional Surgery
Phone: 703-691-2272; Fax: 703-537-0650

Summer Seminar: **Cognitive-Behavioral Therapy** and Dialectical Behavior Therapy: A Clinical Update
Jul 29 - Aug 2, 2013
United States / Massachusetts / Cape Cod
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600;Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

Occupational Contact **Dermatitis And Skin** Surveillance
Jul 31 - Aug 1, 2013
United Kingdom / Birmingham
Contact: CPD Training Team, Institute of Occupational and Environmental Medicine, University of Birmingham
Phone: 011-44-12-1414-6013 / 6014
Fax: 011-44-12-1414-6217
Email: occhealth@contacts.bham.ac.uk

Essentials of **Bronchoscopy**
Aug 1 - 2, 2013
United States / Illinois / Northbrook
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

Neurosurgery Update 2013
Aug 1 - 3, 2013
United States / California / Napa
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-4251; Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Neurotrauma 2013
Aug 4 - 7, 2013
United States / Tennessee / Nashville
Contact: Karen Gottlieb, Conference Organizer, TLC Events Group
Phone: 305-661-5581
Email: nns@neurotrauma.org

Skin Problems and Diseases
Aug 7 – 10, 2013
South Carolina / Hilton Head Island Family Medicine
Contact: American Academy of Family Physicians
Phone: 800-274-2237 or 913-906-6000
Fax: 913-906-6075

2013 **Cardio-Pulmonary Update** Mediterranean Cruise
Aug 9 - 21, 2013
Spain / Barcelona
Contact: CMEatSea
Phone: 888-523-3732 or 604-684-9283

Echocardiography: Hands-On Cardiac Ultrasound Imaging And Doppler
Aug 12 - 17, 2013
United States / Texas / Dallas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 or 972-353-3200
Fax: 817-577-4250

Hands-On **Peripheral Venous and Arterial Ultrasound Imaging** Including Vascular Access
Aug 12 - 14, 2013
United States / Texas / Dallas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 or 972-353-3200; Fax: 817-577-4250

Neuro / ENT in Santa Fe
Aug 12 - 15, 2013
United States / New Mexico / Santa Fe
Contact: iiCME, Inc.
Phone: 205-467-0290; Fax: 205-467-0195
Email: iicmemail@gmail.com

Orthopedics for the Office 1 - **Joint Injections**
Aug 15 - 16, 2013
United States / Illinois / Chicago
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

Anti-Aging Medicine: Advances in **Hormone Replacement**
Aug 17 - 18, 2013
United States / Illinois / Chicago
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631
Fax: 512-329-0442
Email: julie@npinstitute.com

Cosmetic and Anti-Aging Medicine; Treating Senescence & Dermatological Disorders
Aug 17 - 18, 2013
United States / Illinois / Chicago
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

15th International Congress of **Immunology**
Aug 22 - 27, 2013
Italy / Milan
Contact: Triumph C&C
Phone: 011-39-6-355-301; Fax: 011-39-6-3553-0262
Email: ici2013@triumphgroup.it

9th Singapore International Congress of **Obstetrics and Gynaecology** (9SICOG 2013)
Aug 22 - 24, 2013
Singapore / Singapore
Contact: 9SICOG 2013 Secretariat, 9SICOG 2013 Secretariat, 9SICOG 2013 Secretariat
Email: secretariat.sicog@ubm.com

Internal Derangements of Joints: Sydney, Australia
Aug 23 - 26, 2013
Australia / Sydney
Contact: IICME, Inc.
Phone: 205-467-0290; Fax: 205-467-0195
Email: iicmemail@gmail.com

2013 International Symposium on **Auditory and Audiological** Research (ISAAR)
Aug 28 - 30, 2013
Denmark / Nyborg
Contact: Torben Poulsen, ISAAR
Email: tp@elektro.dtu.dk

25th International Course on **Endoscopic Surgery of the Paranasal Sinuses and Skull** Base
Aug 28 - 31, 2013
Belgium / Ghent
Contact: Conference Secretariat, Semico n.v.
Fax: 011-32-9-233-8597
Email: FESS@semico.be

Central Nervous System II
Aug 31 - Sep 4, 2013
Romania / Bucharest
Contact: Walter Rijsselaere, Department of Radiology, UZ Brussel
Phone: 011-32-2-477-5322; Fax: 011-32-2-477-5362
Email: walter.rijsselaere@uzbrussel.be

Gynecology, Obstetrics, and Women's Health Series 2013
Sep 4, 2013
United States / Michigan / Detroit
Contact: Tonya Hibbett, CME Representative, Henry Ford Health System
Phone: 313-916-8208
Email: thibbet1@hfhs.org

8th Asia Pacific **IAP** Congress
Sep 5 - 8, 2013
South Korea / Busan
Contact: Ms. Chloe JO, APIAP 2013 Secretariat
Phone: 011-82-2-6000-2502; Fax: 011-82-2-6000-2501
Email: abstract@apiap2013.org

Advanced **MR Imaging** in Paediatric Radiology
Sep 5 - 7, 2013
Austria / Graz
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

GERD: **Gastroesophageal Reflux** Disease
Sep 5, 2013
Austria / Graz
Contact: Guenter J. Krejs, MD, Professor of Medicine, Medical University Graz
Phone: 011-43-316-3851-3030;Fax: 011-43-316-3851-7560
Email: guenter.krejs@medunigraz.at

Masterclass: **Train The Trainer** - A Creative Approach To Training
Sep 5, 2013
United Kingdom / London
Contact: Kerry Tarant, Programme Director, Healthcare Conferences UK
Phone: 011-44-19-3242-9933
Fax: 011-44-19-3288-0402
Email: kerry@healthcareconferencesuk.co.uk

9th Annual Conference of Indian Society for **Bone and Mineral** Research (ISBMR)
Sep 6 - 7, 2013
India / Srinagar
Contact: Indian Society for Bone & Mineral Research
Email: isbmrindia@gmail.com

Eosinophilic Esophagitis: A Novel Chronic-Inflammatory Disease Of The Gi Tract
Sep 6 - 7, 2013
Austria / Graz
Contact: Prof. Dr. Alex Straumann, Chairman, Swiss EoE Research Group
Phone: 011-41-62-212-5577; Fax: 011-41-62-212-5564
Email: alex.straumann@hin.ch

SGI Summit Turkey 2013: Innovations in **Obstetrics and Gynecology**
Sep 6 - 8, 2013
Turkey / Istanbul
Contact: Rauf K?nay, Organization Secretariat, Serenas International Tourism Congress Organization Services
Email: info@sgiturkey2013.org

2013 **Breast Cancer** Symposium
Sep 7 - 9, 2013
United States / California / San Francisco
Contact: American Society of Clinical Oncology
Phone: 888-282-2552 or 571-483-1300

New Advances in **Inflammatory Bowel Disease** 2013
Sep 7 - 8, 2013
United States / California / San Diego
Contact: Scripps Health
Phone: 858-652-5400; Fax: 858-652-5565
Email: med.edu@scrippshealth.org

Suturing, Basic
Sep 7 - 8, 2013
United States / Massachusetts / Boston
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

Ultrasound: Musculoskeletal
Sep 7 - 8, 2013
United States / Massachusetts / Boston
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

Wisconsin Society of **Anesthesiologists** 2013 Annual Meeting
Sep 7 - 8, 2013
United States / Wisconsin / Milwaukee
Contact: Wisconsin Society of Anesthesiologists
Phone: 414-389-8616; Fax: 414-276-7704
Email: info@thewsa.org
Website: http://www.wsaonline.org/cms/content/view/21/40/

14th Congress of the European Society for Biomedical Research on **Alcoholism**: ESBRA 2013
Sep 8 - 11, 2013
Poland / Warsaw
Contact: Ewa Pankowska, Conference Office, Batumi Conference & Event Agency
Phone: 011-48-22-885-8947; Fax: 011-48-22-885-6261
Email: biuro@batumi.pl

15th Wfns World Congress of **Neurosurgery**
Sep 8 - 13, 2013
South Korea / Seoul
Contact: Secretariat, The Plan Co.
Phone: 011-82-2-538-2042 ext. 3; Fax: 011-82-2-538-1540
Email: info@wfns2013.org

Abdomen and **Urogenital MRI**
Sep 9 - 11, 2013
Italy / Palermo
Contact: Organizing Secretariat, A.S.C. Servizi
Phone: 011-39-91 656-3617; Fax: 011-39-91-645-4952
Email: ascongr@tin.it

Colonoscopy, Advanced
Sep 9, 2013
United States / Massachusetts / Boston
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

Laparoscopic **Antireflux Surgery**
Sep 12 - 13, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, IMACS Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: najma.amir@nhs.net

International **Liver Cancer** Association 7th Annual Conference: Ilca 2013
Sep 13 - 15, 2013
United States / District Of Columbia / Washington
Contact: International Liver Cancer Association
Phone: 011-32-2-789-2345; Fax: 011-32-2-743-1550
Email: info@ilca-online.org

11th World Congress of the International **Cartilage Repair** Society: ICRS 2013
Sep 15 - 18, 2013
Turkey / Izmir
Contact: Mr. Stephan Seiler, Executive Director, Cartilage Executive Office (CEO) GmbH
Phone: 011-41-44-503-7370; Fax: 011-41-44-503-7372
Email: sseiler@cartilage.org

2nd International Conference on Immunometabolism: **Molecular and Cellular Immunology** of Metabolism
Sep 15 - 20, 2013
Greece / Rhodes
Contact: Aegean Conferences, Inc.
Phone: 610-527-7630; Fax: 610-527-7631

Comprehensive Review of **Musculoskeletal MRI**
Sep 15 - Aug 18, 2013
California / Half Moon Bay
United States / Contact: Debbie Griffin, Department of Radiology, Duke University School of Medicine
Email: deborah.griffin@duke.edu
Website: http://radiology.duke.edu/modules/dept_rad_visitingfellow/index.php?id=1

Stem Cells in Translation
Sep 15 - 18, 2013
Italy / Florence
Contact: International Society for Stem Cell Research
Phone: 224-592-5700; Fax: 224-365-0004
Email: isscr@isscr.org

Anticoagulation Management in Primary Care
Sep 16 - 18, 2013
United Kingdom / Birmingham
Contact: Amy Partleton, Centre for Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

Benign **Abdominal Surgery** - Open And Laparoscopic
Sep 16 - 17, 2013
United Kingdom / London
Contact: Royal College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6200
Email: events@rcog.org.uk

Neuroradiology Post Graduate Course - **Head and Neck Radiology**
Sep 16 - 20, 2013
United States / Massachusetts / Cambridge, Ma
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600; Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

2013 **Childhood Infections**
Sep 17, 2013
United Kingdom / London
Contact: MA Healthcare Limited
Phone: 011-44-20-7501-6762; Fax: 011-44-20-7978-8319
Email: conferences@markallengroup.com

2013 **Neuroradiology** Review
Sep 18 - 23, 2013
United States / California / Long Beach
Contact: Johns Hopkins University School of Medicine
Phone: 410-502-9634

How To **Write A Scientific Paper**
Sep 18 - 20, 2013
Malta / Qawra
Contact: Malta Institute for Medical Education
Email: info@maltime.com

Advanced **Head and Neck Mr Imaging**
Sep 19 - 21, 2013
Poland / Krakow
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

Advanced **MR Imaging** of the Chest
Sep 19 - 21, 2013
Spain / Valencia
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

ESGAR **Liver Imaging** Workshop 2013
Sep 19 - 20, 2013
Sweden / Stockholm
Contact: European Society of Gastrointestinal and Abdominal Radiology
Phone: 011-43-1-535-8927; Fax: 011-43-1-535-7037
Email: office@esgar.org

Focused **Thoracic and Vascular Ultrasound**
Sep 19 – 20, 2013
United States / Illinois / Wheeling
Contact: American College of Chest Physicians
Phone: 847-498-1400
Fax: 847-498-5460

4th International Conference on **Stem Cells and Cancer** (ICSCC-2013): Proliferation, Differentiation and Apoptosis
Oct 19 - 22, 2013
India / Mumbai, Maharashtra
Contact person: Prof. Dr. Sheo Mohan Singh
Website: http://www.icscc.in/

Simultaneous **Multi-Slice/Multiband Imaging**
Sep 19 - 21, 2013
Germany / Essen
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

2013 Fetal and **Women's Imaging**
Sep 20 - 22, 2013
United States / Washington / Seattle
Contact: World Class CME
Phone: 980-819-5095
Fax: 980-819-5099
Email: office@worldclasscme.com

Challenges in **Obstetrics and Gynecology** Eastern Mediterranean Cruise
Sep 20 - 30, 2013
Italy / Rome
Contact: Jim Goodrich, CEO, Symposia Medicus
Phone: 800-327-3161 or 925-969-1789
Fax: 925-969-1795
Email: info@symposiamedicus.org

Clinical Pediatrics Conference
Sep 20 - 22, 2013
Canada / British Columbia / Vancouver
Contact: Dana Smith, Clinical Pediatrics
Email: admin@clinicalpeds.com

Diabetic Foot Study Group 2013 Annual Scientific Meeting
Sep 20 - 22, 2013
Spain / Sitges
Contact: Eve Stamm, DFSG Secretary, Diabetic Foot Study Group
Phone: 011-49-21-145-1165
Email: evestamm@aol.com

Innovations in **Aesthetic Breast Surgery**
Sep 20 - 21, 2013
United States / Oklahoma / Tulsa
Contact: Cynthia Strohschein, Director of Marketing, American Academy of Cosmetic Surgery
Phone: 312-981-6760; Fax: 312-981-6787
Email: ahoward@cosmeticsuregry.org

21st World Congress of **Neurology**
Sep 21 - 26, 2013
Austria / Vienna
Contact: Rene Chait, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: wcn@kenes.com

7th World Congress on **Itch**
Sep 21 - 23, 2013
United States / Massachusetts / Boston
Contact: Agri Meetings, Agri Meetings, Agri Meetings
Phone: 978-304-0935; Fax: 978-304-0936
Email: info@agrimeetings.com

Critical Care Echocardiography
Sep 21 - 22, 2013
United States / Illinois / Wheeling
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

7th **Leukocyte Signal** Transduction Workshop
Sep 22 - 27, 2013
Greece / Corfu
Contact: Aegean Conferences, Inc.
Phone: 610-527-7630; Fax: 610-527-7631

Radiology in St. Petersburg, Russia
Sep 22 - 28, 2013
Russia / St. Petersburg
Contact: Radiology International
Phone: 860-225-1700; Fax: 860-356-0922
Email: info@radiologyintl.com

Intrapartum **Fetal Surveillance**
Sep 23, 2013
United Kingdom / London
Contact: Royal College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6200
Email: events@rcog.org.uk

Lung Transplantation - Minimally Invasive Surgery
Sep 23 - 24, 2013
France / Elancourt
Contact: ESTS Secretariat, European Society of Thoracic Surgeons
Fax: 011-44-13-9243-0671
Email: sue@ests.org.uk

Medical **Ethics**
Sep 23 - 27, 2013
United Kingdom / London
Contact: Centre For Continuing Professional Development, Imperial College London
Phone: 011-44-20-7594-6882
Email: cpd@imperial.ac.uk

14th World Congress of the International **Pancreas and Islet Transplant** Association: IPITA 2013
Sep 24 - 27, 2013
United States / California / Monterey
Contact: Secretariat Office, The Transplantation Society
Phone: 514-874-1717; Fax: 514-874-1716
Email: info@ipita2013.org

Counselling and Psychotherapy in Family Medicine
Sep 27 - Jun 8, 2013
Canada / Ontario / Toronto
Contact: Continuing Education & Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719; Fax: 416-971-2200
Email: info-FCM1310@cepdtoronto.ca

Cancer Medicine and **Hematology**
Sep 29 - Oct 4, 2013
United States / Massachusetts / Boston
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600; Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

16th International Congress of the International **Psychogeriatric** Association
Oct 1 - 4, 2013
South Korea / Seoul
Contact: IPA 2013 Secretariat, Secretariat, International Psychogeriatric Association, Korean Association for Geriatric Psychiatry
Phone: 011-82-2-566-5920; Fax: 011-82-2-566-6087
Email: seoul@ipa2013.com

3rd World **Parkinson** Congress
Oct 1 – 4, 2013
Canada / Quebec / Montreal
Contact: World Parkinson Congress
Email: info@worldpdcongress.org

2013 World Congress of **Liposuction**
Oct 2 - 5, 2013
United States / New York / New York
Phone: 312-981-6760
Fax: 312-981-6787
Email: info@cosmeticsurgery.org

Advanced Techniques in **Benign Oesophago Gastric Surgery**
Oct 3 - 4, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, IMACS Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: najma.amir@nhs.net

Pediatric and Adolescent **Gynecology**
Oct 3 - 4, 2013
United States / Massachusetts / Boston
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600
Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

2013 Multi Modality **Gynecological and Obstetric Imaging**
Oct 4 - 6, 2013
Canada / Quebec / Montebello
Contact: Department of Radiology, University of Ottawa
Phone: 613-737-8899 ext. 74044
Email: info@ottawaradcme.com

Liver Diseases In 2013: Advances in Pathogenesis and Treatment
Oct 4 - 5, 2013
United Kingdom / London
Contact: Prof. Dr. Roger William Chapman, John Radcliffe Hospital
Phone: 011-44-18-6522-0618; Fax: 011-44-18-6575-1100
Email: roger.chapman@ndm.ox.ac.uk

Musculoskeletal Medicine
Sep 25, 2013
United Kingdom / Manchester
Contact: BMJ Masterclasses
Phone: 011-44-20-7387-4410; Fax: 011-44-20-7383-6974

2013 **Viral Hepatitis** Congress
Sep 26 - 28, 2013
Germany / Frankfurt
Contact: Sophie Lea, Senior Account Director, KP360
Phone: 011-44-16-2566-4392
Email: hep@kp360group.com

Laparoscopic Exploration of Common **Bile Duct and Intraoperative Choledochoscopy**
Sep 26, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, IMACS Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: najma.amir@nhs.net

69th Korean Congress of **Radiology**
Oct 9 - 12, 2013
South Korea / Seoul
Contact: Secretariat, InSession International Convention Services, Inc.
Phone: 011-82-2-3452-7240
Fax: 011-82-2-521-8683
Email: info@kcr4u.org

Brain Injuries
Oct 9 - 12, 2013
United States / District of Columbia / Washington
Contact: Contemporary Forums
Phone: 800-377-7707

2013 International Society for **Hip Arthroscopy**
Oct 10 - 12, 2013
Germany / Munich
Contact: Intercongress GmbH
Email: isha@intercongress.de

2nd International Congress on Controversies in **Stem Cell Transplantation and Cellular Therapies**
Oct 10 - 13, 2013
Germany / Berlin
Contact: Congress Secretariat, ComtecMed
Email: costem@comtecmed.com

Diabetic **Limb Salvage** 2013
Oct 10 - 12, 2013
United States / District of Columbia / Washington
Contact: International Conference Management
Phone: 337-235-6606
Fax: 337-235-7300
Email: info@dlsconference.com

GBCC 2013 (Global **Breast Cancer** Conference 2013)
Oct 10 - 12, 2013
South Korea / Seoul
Contact: Jay Hwang, Secretariat for GBCC2013, INTERCOM
Phone: 011-82-2-501-7065
Email: gbcc@intercom.co.kr

21st Annual Perspectives in Total **Joint Arthroplasty:** Updates in Hip Replacement
Oct 11 - 12, 2013
United States / Kansas / Falls River
Contact: International Congress for Joint Reconstruction
Phone: 760-942-7859
Email: info@icjr.net

1st Annual World Congress of **Geriatrics and Gerontology** 2013 (WCGG-2013)
Oct 12 - 15, 2013
China / Dalian
Contact: Julia Wang, BIT Congress Inc.
Phone: 011-86-411-8457-5669 ext. 873; Fax: 011-86-411-8457-5669 ext. 873
Email: julia@wcgg-bit.com

8th World Congress of **Immunopathology, Respiratory Allergy and Asthma**
Oct 12 - 15, 2013
United Arab Emirates / Dubai
Contact: World Immunopathology Organization
Phone: 011-7-495-735-1414; Fax: 011-7-495-735-1414
Email: info@wipocis.org
Website: http://wipocis.org/Page314.html

Acute **Cardiac Care** 2013
Oct 12 - 14, 2013
Spain / Madrid
Contact: European Society of Cardiology
Phone: 011-33-4-9294-7600; Fax: 011-33-4-9294-8622

10th International Congress on **Coronary Heart Disease**
Oct 13 - 16, 2013
Italy / Florence
Contact: Tammy Lessick, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: iccad@kenes.com

29th Annual Echocardiography in **Pediatric and Adult Congenital Heart Disease** Symposium
Oct 13 -16, 2013
United States / Minnesota / Rochester (Mn)
Contact: Sheila Fick, Education Specialist, Mayo Clinic
Phone: 507-284-0536; Fax: 507-266-7403
Email: cvcme@mayo.edu

Advanced **Critical Care and Trauma**
Oct 13 - 16, 2013
United States / Nevada / Las Vegas
Contact: Contemporary Forums
Phone: 800-377-7707

Stem Cells in Science and Medicine
Oct 14 - 17, 2013
China / Suzhou
Contact: International Society for Stem Cell Research
Phone: 224-592-5700; Fax: 224-365-0004
Email: isscr@isscr.org

WHO-Facts Sheet

1. Noncommunicable Diseases
2. Deafness and Hearing Loss
3. Climate Change and Health
4. Your Blood Pressure Risk
5. Congenital Anomalies

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013, 45 (2): 181 - 188

1. NONCOMMUNICABLE DISEASES

Overview

Noncommunicable diseases (NCDs), also known as chronic diseases, are not passed from person to person. They are of long duration and generally slow progression. The four main types of noncommunicable diseases are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes.

NCDs already disproportionately affect low- and middle-income countries where nearly 80% of NCD deaths – 29 million – occur. They are the leading causes of death in all regions except Africa, but current projections indicate that by 2020 the largest increases in NCD deaths will occur in Africa. In African nations deaths from, NCDs are projected to exceed the combined deaths of communicable and nutritional diseases and maternal and perinatal deaths as the most common causes of death by 2030.

KEY FACTS

- Noncommunicable diseases (NCDs) kill more than 36 million people each year.
- Nearly 80% of NCD deaths - 29 million - occur in low- and middle-income countries.
- More than nine million of all deaths attributed to NCDs occur before the age of 60; 90% of these "premature" deaths occurred in low- and middle-income countries.
- Cardiovascular diseases account for most NCD deaths, or 17.3 million people annually, followed by cancers (7.6 million), respiratory diseases (4.2 million), and diabetes (1.3 million - based on data from death certificates).
- These four groups of diseases account for around 80% of all NCD deaths.
- They share four risk factors: tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets.

Who is at risk of such diseases?

All age groups and all regions are affected by NCDs. NCDs are often associated with older age groups, but evidence shows that more than nine million of all deaths attributed to noncommunicable diseases (NCDs) occur before the age of 60. Of these "premature" deaths, 90% occurred in low- and middle-income countries. Children, adults and the elderly are all vulnerable to the risk factors that contribute to noncommunicable diseases, whether from unhealthy diets, physical inactivity, exposure to tobacco smoke or the effects of the harmful use of alcohol.

These diseases are driven by forces that include ageing, rapid unplanned urbanization, and the globalization of unhealthy lifestyles. For example, globalization of unhealthy lifestyles like unhealthy diets may show up in individuals as raised blood pressure, increased blood glucose, elevated blood lipids, overweight and obesity. These are called 'intermediate risk factors' which can lead to cardiovascular disease, a NCD.

Risk factors

Modifiable behavioural risk factors: Tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol increase the risk of or cause most NCDs.

- Tobacco accounts for almost six million deaths every year (including over 600,000 deaths from exposure to second-hand smoke), and is projected

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to increase to eight million by 2030.
- About 3.2 million deaths annually can be attributed to insufficient physical activity.
- Approximately 1.7 million deaths are attributable to low fruit and vegetable consumption.
- Half of the 2.3 million (This figure takes into account the estimated beneficial impact of low levels of alcohol use on some diseases in some population groups) annual deaths from harmful drinking are from NCDs.

Metabolic/physiological risk factors: These behaviours lead to four key metabolic/physiological changes that increase the risk of NCDs: raised blood pressure, overweight/obesity, hyperglycemia (high blood glucose levels) and hyperlipidemia (high levels of fat in the blood).

In terms of attributable deaths, the leading NCD risk factor globally is elevated blood pressure (to which 16.5% of global deaths are attributed) (1) followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and overweight and obesity (5%). Low- and middle-income countries are witnessing the fastest rise in overweight young children.

What are the socioeconomic impacts of NCDs?

NCDs threaten progress towards the UN Millennium Development Goals. Poverty is closely linked with NCDs. The rapid rise in NCDs is predicted to impede poverty reduction initiatives in low-income countries, particularly by forcing up household costs associated with health care. Vulnerable and socially disadvantaged people get sicker and die sooner than people of higher social positions, especially because they are at greater risk of being exposed to harmful products, such as tobacco or unhealthy food, and have limited access to health services.

In low-resource settings, health-care costs for cardiovascular diseases, cancers, diabetes or chronic lung diseases can quickly drain household resources, driving families into poverty. The exorbitant costs of NCDs, including often lengthy and expensive treatment and loss of breadwinners, are forcing millions of people into poverty annually, stifling development.

In many countries, harmful drinking and unhealthy diet and lifestyles occur both in higher and lower income groups. However, high-income groups can access services and products that protect them from the greatest risks while lower-income groups can often not afford such products and services.

Prevention and control of NCDs

To lessen the impact of NCDs on individuals and society, a comprehensive approach is needed that requires all sectors, including health, finance, foreign affairs, education, agriculture, planning and others, to work together to reduce the risks associated with NCDs, as well as promote the interventions to prevent and control them.

An important way to reduce NCDs is to focus on lessening the risk factors associated with these diseases. Low-cost solutions exist to reduce the common modifiable risk factors (mainly tobacco use, unhealthy diet and physical inactivity, and the harmful use of alcohol) and map the epidemic of NCDs and their risk factors.

Other ways to reduce NCDs are high impact essential NCD interventions that can be delivered through a primary health-care approach to strengthen early detection and timely treatment. Evidence shows that such interventions are excellent economic investments because, if applied to patients early, can reduce the need for more expensive treatment. These measures can be implemented in various resource levels.

Lower-income countries generally have lower capacity for the prevention and control of noncommunicable diseases. High-income countries are nearly four times more likely to have NCD services covered by health insurance than low-income countries. Countries with inadequate health insurance coverage are unlikely to provide universal access to essential NCD interventions.

2. DEAFNESS AND HEARING LOSS

Overview

Over 5% of the world's population – 360 million people – has disabling hearing loss (328 million adults and 32 million children). Disabling hearing loss refers to hearing loss greater than 40dB in the better hearing ear in adults and a hearing loss greater than 30dB in the better hearing ear in children. The majority of these people live in low- and middle-income countries.

Approximately one-third of people over 65 years of age are affected by disabling hearing loss. The prevalence in this age group is greatest in South Asia, Asia Pacific and sub-Saharan Africa.

KEY FACTS
- 360 million people worldwide have disabling hearing loss* (*Refers to hearing loss greater than 40dB in the better hearing ear in adults and a hearing loss greater than 30dB in the better hearing ear in children).
- Hearing loss may be inherited, caused by maternal rubella or complications at birth, certain infectious diseases such as meningitis, chronic ear infections, use of ototoxic drugs, exposure to excessive noise and ageing.

- Half of all cases of hearing loss are avoidable through primary prevention.
- People with hearing loss can benefit from devices such as hearing aids, assistive devices and cochlear implants, and from captioning, sign language training, educational and social support.
- Current production of hearing aids meets less than 10% of global need.
- WHO is assisting countries in developing programmes for primary ear and hearing care that are integrated into the primary health-care system of the country.

Hearing loss and deafness

A person who is not able to hear as well as someone with normal hearing – hearing thresholds of 25dB or better in both ears – is said to have hearing loss. Hearing loss may be mild, moderate, severe or profound. It can affect one ear or both ears, and leads to difficulty in hearing conversational speech or loud sounds.

'Hard of hearing' refers to people with hearing loss ranging from mild to severe. They usually communicate through spoken language and can benefit from hearing aids, captioning and assistive listening devices. People with more significant hearing losses may benefit from cochlear implants.

'Deaf' people mostly have profound hearing loss, which implies very little or no hearing. They often use sign language for communication.

Causes of hearing loss and deafness

The causes of hearing loss and deafness can be divided into congenital causes and acquired causes.

Congenital causes

Congenital causes lead to hearing loss being present at or acquired soon after birth. Hearing loss can be caused by hereditary and non-hereditary genetic factors or by certain complications during pregnancy and childbirth, including:

- maternal rubella, syphilis or certain other infections during pregnancy;
- low birth weight;
- birth asphyxia (a lack of oxygen at the time of birth);
- inappropriate use of ototoxic drugs (such as aminoglycosides, cytotoxic drugs, antimalarial drugs and diuretics) during pregnancy; and
- severe jaundice in the neonatal period, which can damage the hearing nerve in a newborn infant.

Acquired causes

Acquired causes lead to hearing loss at any age.

- Infectious diseases such as meningitis, measles and mumps can lead to hearing loss, mostly in childhood, but also later in life.
- Chronic ear infection, which commonly presents as discharging ears, can lead to hearing loss. In certain cases this condition can also lead to serious, life-threatening complications, such as brain abscesses or meningitis.
- Collection of fluid in the ear (otitis media) can cause hearing loss.
- Use of ototoxic drugs at any age, such as some antibiotic and antimalarial medicines for example, can damage the inner ear.
- Head injury or injury to the ear can cause hearing loss.
- Excessive noise, including working with noisy machinery, and exposure to loud music or other loud noises, such as gunfire or explosions, can harm a person's hearing.
- Age-related hearing loss (presbycusis) is caused by degeneration of sensory cells.
- Wax or foreign bodies blocking the ear canal can cause hearing loss at any age. Such hearing loss is usually mild and can be readily corrected.

Among children, chronic otitis media is the leading cause of hearing loss.

Impact of hearing loss

Functional impact: One of the main impacts of hearing loss is on the individual's ability to communicate with others. Spoken language development is often delayed in children with deafness.

Hearing loss and ear diseases such as otitis media can have a significantly adverse effect on the academic performance of children. However, when opportunities are provided for people with hearing loss to communicate they can participate on an equal basis with others. The communication may be through spoken/ written language or through sign language.

Social and emotional impact: Limited access to services and exclusion from communication can have a significant impact on everyday life, causing feelings of loneliness, isolation and frustration, particularly among older people with hearing loss.

If a person with congenital deafness has not been given the opportunity to learn sign language as a child, they may feel excluded from social interaction.

Economic impact: In developing countries, children with hearing loss and deafness rarely receive any schooling. Adults with hearing loss also have a much higher unemployment rate. Among those who are employed, a higher percentage of people with hearing loss are in the lower grades of employment compared with the general workforce. Improving access to education and vocational rehabilitation services, and raising awareness especially among employers, would decrease unemployment rates among adults with hearing loss.

In addition to the economic impact of hearing loss at an individual level, hearing loss substantially affects social and economic development in communities and countries.

Prevention

Half of all cases of hearing loss can be prevented through primary prevention. Some simple strategies for prevention include:

- immunizing children against childhood diseases, including measles, meningitis, rubella and mumps;
- immunizing adolescent girls and women of reproductive age against rubella before pregnancy;
- screening for and treating syphilis and other infections in pregnant women;
- improving antenatal and perinatal care, including promotion of safe childbirth;
- avoiding the use of ototoxic drugs, unless prescribed and monitored by a qualified physician;
- referring babies with high risk factors (such as those with a family history of deafness, those born with low birth weight, birth asphyxia, jaundice or meningitis) for early assessment of hearing, prompt diagnosis and appropriate management, as required; and
- reducing exposure (both occupational and recreational) to loud noises by creating awareness, using personal protective devices, and developing and implementing suitable legislation.

Hearing loss due to otitis media can be prevented by healthy ear and hearing care practices. It can be suitably dealt with through early detection, followed by appropriate medical or surgical interventions.

Identification and management

A large percentage of people living with hearing loss can benefit from early identification and intervention, and appropriate management.

In infants and young children with hearing loss, early identification and management through infant hearing screening programes can improve the linguistic and educational outcomes for the child. Children with deafness should be given the opportunity to learn sign language along with their families. Pre-school, school and occupational screening for ear diseases and hearing loss can also be effective for early identification and management of hearing loss.

People with hearing loss can benefit from the use of hearing devices, such as hearing aids, assistive listening devices and cochlear implants. They may also benefit from speech therapy, aural rehabilitation and other related services. However, current production of hearing aids meets less than 10% of global need. In developing countries, fewer than one out of 40 people who need a hearing aid have one. Making properly-fitted, affordable hearing aids and providing accessible follow-up services in all parts of the world will benefit many people with hearing loss.

People who develop hearing loss can learn to communicate through development of lip-reading skills, use of written or printed text, and sign language. Teaching in sign language will benefit children with hearing loss, while provision of captioning and sign language interpretation on television will facilitate access to information.

Officially recognizing national sign languages and increasing the availability of sign language interpreters are important actions to improve access to sign language services. Human rights legislation and other protections can also help ensure better inclusion for people with hearing loss.

For more information contact: WHO Media centre.
Telephone: +41 22 791 2222.
E-mail: mediainquiries@who.int

3. CLIMATE CHANGE AND HEALTH

KEY FACTS

- Climate change affects the social and environmental determinants of health – clean air, safe drinking water, sufficient food and secure shelter.
- Global warming that has occurred since the 1970s caused over 140 000 excess deaths annually by the year 2004.
- The direct damage costs to health (i.e. excluding costs in health-determining sectors such as agriculture and water and sanitation), is estimated to be between US$ 2-4 billion / year by 2030.
- Many of the major killers such as diarrhoeal diseases, malnutrition, malaria and dengue are highly climate-sensitive and are expected to worsen as the climate changes.
- Areas with weak health infrastructure – mostly in developing countries – will be the least able to cope without assistance to prepare and respond.
- Reducing emissions of greenhouse gases through better transport, food and energy-use choices can result in improved health.

Climate change

Over the last 50 years, human activities – particularly the burning of fossil fuels – have released sufficient quantities of carbon dioxide and other greenhouse gases to trap additional heat in the lower atmosphere and affect the global climate.

In the last 100 years, the world has warmed by approximately 0.75 ºC. Over the last 25 years, the rate

of global warming has accelerated, at over 0.18 ºC per decade.

Sea levels are rising, glaciers are melting and precipitation patterns are changing. Extreme weather events are becoming more intense and frequent.

What is the impact of climate change on health?

Although global warming may bring some localized benefits, such as fewer winter deaths in temperate climates and increased food production in certain areas, the overall health effects of a changing climate are likely to be overwhelmingly negative. Climate change affects social determinants of health – clean air, safe drinking water, sufficient food and secure shelter.

Extreme heat

Extreme high air temperatures contribute directly to deaths from cardiovascular and respiratory disease, particularly among elderly people. High temperatures also raise the levels of ozone and other pollutants in the air that exacerbate cardiovascular and respiratory disease. Urban air pollution causes about 1.2 million deaths every year.

Pollen and other aeroallergen levels are also higher in extreme heat. These can trigger asthma, which affects around 300 million people. Ongoing temperature increases are expected to increase this burden.

Natural disasters and variable rainfall patterns

Globally, the number of reported weather-related natural disasters has more than tripled since the 1960s. Every year, these disasters result in over 60,000 deaths, mainly in developing countries.

Rising sea levels and increasingly extreme weather events will destroy homes, medical facilities and other essential services. More than half of the world's population lives within 60 km of the sea. People may be forced to move, which in turn heightens the risk of a range of health effects, from mental disorders to communicable diseases.

Increasingly variable rainfall patterns are likely to affect the supply of fresh water. A lack of safe water can compromise hygiene and increase the risk of diarrhoeal disease, which kills 2.2 million people every year and in extreme cases, water scarcity leads to drought and famine. By the 2090s, climate change is expected to widen the area affected by drought, double it's frequency and increase their average duration six-fold.

Floods are also increasing in frequency and intensity. Floods contaminate freshwater supplies, heighten the risk of water-borne diseases, and create breeding grounds for disease-carrying insects such as mosquitoes. They also cause drownings and physical injuries, damage homes and disrupt the supply of medical and health services. Rising temperatures and variable precipitation are likely to decrease the production of staple foods in many of the poorest regions – by up to 50% by 2020. This will increase the prevalence of malnutrition and undernutrition, which currently cause 3.5 million deaths every year.

Patterns of infection

Climatic conditions strongly affect water-borne diseases and diseases transmitted through insects, snails or other cold blooded animals. Changes in climate are likely to lengthen the transmission seasons of important vector-borne diseases and to alter their geographic range. Malaria is strongly influenced by climate. Transmitted by Anopheles mosquitoes, malaria kills almost one million people every year – mainly African children under five years old. The Aedes mosquito vector of dengue is also highly sensitive to climate conditions. Studies suggest that climate change could expose an additional two billion people to dengue transmission by the 2080s6.

Who is at risk?

All populations will be affected by climate change, but some are more vulnerable than others. People living in small island developing states and other coastal regions, megacities, and mountainous and polar regions are particularly vulnerable.

Children – in particular, children living in poor countries – are among the most vulnerable to the resulting health risks and will be exposed longer to the health consequences. The health effects are also expected to be more severe for elderly people and people with infirmities or pre-existing medical conditions. Areas with weak health infrastructure – mostly in developing countries – will be the least able to cope without assistance to prepare and respond.

4. YOUR BLOOD PRESSURE RISK

Overview

Worldwide, high blood pressure is estimated to affect more than one in three adults aged 25 and over, or about one billion people. More than one in three adults worldwide have raised blood pressure – a condition that causes around half of all deaths from stroke and heart disease – which together make up the world's number one cause of premature death and disability. Researchers estimate that high blood pressure contributes to nearly 9.4 million deaths from cardiovascular disease each year. It also increases the risk of conditions such as kidney failure and blindness.

What is raised blood pressure (hypertension)?

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels

have persistently raised pressure. Blood is carried from the heart to all parts of the body in the vessels. Each time the heart beats, it pumps blood into the vessels. Blood pressure is created by the force of blood pushing against the walls of blood vessels (arteries) as it is pumped by the heart. The higher the pressure the harder the heart has to pump.

Normal adult blood pressure is defined as a blood pressure of 120 mmHg when the heart beats (systolic) and a blood pressure of 80 mmHg when the heart relaxes (diastolic). When systolic blood pressure is equal to or above 140 mmHg and/or a diastolic blood pressure equal to or above 90 mmHg the blood pressure is considered to be raised or high. Sometimes hypertension causes symptoms such as headache, shortness of breath, dizziness, chest pain, palpitations of the heart and nose bleeds. However, most people with hypertension have no symptoms at all.

Why is raised blood pressure dangerous?

The higher the blood pressure, the higher the risk of damage to the heart and blood vessels in major organs such as the brain and kidneys.

If left uncontrolled, hypertension can lead to a heart attack, an enlargement of the heart and eventually heart failure. Blood vessels may develop bulges (aneurysms) and weak spots that make them more likely to clog and burst. The pressure in the blood vessels can cause blood to leak out into the brain and cause a stroke. Hypertension can also lead to kidney failure, blindness, and cognitive impairment.

The health consequences of hypertension can be compounded by other factors that increase the odds of heart attack, stroke and kidney failure. These factors include tobacco use, unhealthy diet, harmful use of alcohol, lack of physical inactivity, and exposure to persistent stress as well as obesity, high cholesterol and diabetes mellitus.

How can raised blood pressure be prevented and treated?

All adults should have their blood pressure checked. If blood pressure is high, they need the advice of a health worker.

For some people, lifestyle changes are sufficient to control blood pressure such as stopping tobacco use, eating healthily, exercising regularly and avoiding the harmful use of alcohol. Reduction in salt intake can help. For others, these changes are insufficient and they need prescription medication to control blood pressure.

Adults can support treatment by adhering to the prescribed medication, by monitoring their health. People with high blood pressure who also have high blood sugar or elevated blood cholesterol face even higher risk of heart attacks and stroke. Therefore, it is important that regular checks for blood sugar, blood cholesterol and urine albumin take place.

Steps to minimize blood pressure

Here are five concrete steps to minimize the odds of developing high blood pressure and its adverse consequences.

- Healthy diet:
  - o promoting a healthy lifestyle with emphasis on proper nutrition for infants and young people;
  - o reducing salt intake to less than 5 g of salt per day (just under a teaspoon);
  - o eating five servings of fruit and vegetables a day;
  - o reducing saturated and total fat intake.
- Avoiding harmful use of alcohol i.e., limit intake to no more than one standard drink a day
- Physical activity:
  - o regular physical activity and promotion of physical activity for children and young people (at least 30 minutes a day).
  - o maintaining a normal weight: every 5 kg of excess weight lost can reduce systolic blood pressure by 2 to 10 points.
- Stopping tobacco use and exposure to tobacco products
- Managing stress in healthy way such as through meditation, appropriate physical exercise, and positive social contact.

Prevention and control of high blood pressure

Detecting high blood pressure is the first step in preventing and controlling it. When people know their blood pressure level, they can take steps to control it. Overall, high-income countries have a lower prevalence of hypertension (35% of adults) than low -and -middle income groups (40% of adults) – due to successful multisectoral public policies, and better access to health care. Many people with high blood pressure in developing countries remain undiagnosed, and so miss out on treatment that could significantly reduce their risk of death and disability from heart disease and stroke.

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5. CONGENITAL ANOMALIES

Definition

Congenital anomalies are also known as birth defects, congenital disorders or congenital

malformations. Congenital anomalies can be defined as structural or functional anomalies, including metabolic disorders, which are present at the time of birth.

KEY FACTS

- Congenital anomalies (also referred as birth defects) affect approximately one in 33 infants and result in approximately 3.2 million birth defect-related disabilities every year.
- An estimated 270 000 newborns die during the first 28 days of life every year from congenital anomalies.
- Congenital anomalies may result in long-term disability, which may have significant impacts on individuals, families, health-care systems and societies.
- The most common serious congenital disorders are heart defects, neural tube defects and Down syndrome.
- Congenital anomalies may have a genetic, infectious or environmental origin; although in most of the cases it is difficult identify their cause.
- About 110,000 cases of babies born with congenital rubella syndrome can be prevented through timely vaccination of the mothers during childhood and the reproductive years.
- Many birth anomalies can be prevented and treated. An adequate intake of folic acid, iodine, vaccination, and adequate antenatal care are key.

Congenital anomalies and preterm birth are important causes of childhood death, chronic illness, and disability in many countries.

Causes of 3.1 million neonatal deaths in 193 countries in 2010

Source: Adapted from WHO. Born too soon. The global action report on preterm birth. Geneva, World Health Organization, 2012

Causes and risk factors

Approximately 50% of all congenital anomalies, however, cannot be assigned to a specific cause. However some causes or risk factors have been associated to congenital anomalies.

Socioeconomic factors

Although it may be an indirect determinant, congenital anomalies are more frequent among resource constrained families and countries. It is estimated that about 94% of serious birth defects occur in middle- and low-income countries, where mothers are more susceptible to macronutrient and micronutrient malnutrition and may have increased exposure to any agent or factor that induces or increases the incidence of abnormal prenatal development, particularly infection and alcohol. Advanced maternal age also increases the risk of some chromosomal abnormalities including Down syndrome.

Genetic factors

Consanguinity (relationship by blood) increases the prevalence of rare genetic congenital anomalies and nearly doubles the risk for neonatal and childhood death, intellectual disability and serious birth anomalies in first cousin unions. Some ethnic communities, e.g., Ashkenazi Jews or Finns, have comparatively high prevalence of rare genetic mutations, leading to a higher risk of congenital anomalies.

Infections

Maternal infections such as syphilis and rubella are a significant cause of birth defects in low- and middle-income countries.

Maternal nutritional status

Iodine deficiency, folate insufficiency, overweight, or conditions like diabetes mellitus are linked to some congenital anomalies. For example folate insufficiency increases the risk of having a baby with neural tube defects.

Environmental factors

Maternal exposure to pesticides, medicinal and recreational drugs, alcohol, tobacco, certain chemicals, high doses of vitamin A during the early pregnancy, and high doses of radiation increase the risk of having a baby with congenital anomalies. Working or living near or in waste sites, smelters, or mines may also be a risk factor.

Prevention

Preventive public health measures administered through pre- and peri-conception and prenatal health care services decrease the frequency of certain congenital anomalies. Primary prevention of congenital anomalies involves:

- Improving the diet of women throughout their reproductive years, ensuring an adequate dietary intake of vitamins and minerals such as folic acid and iodine, and restricting harmful substances, particularly the abuse of alcohol. Controlling pre-conceptional and gestational diabetes through counselling, weight management, diet and the administration of insulin when needed.
- Avoiding exposure to hazardous environmental substances (e.g., heavy metals, pesticides, some medicinal drugs) during pregnancy.
- Improving vaccination coverage, especially with rubella virus, for children and women. This can be prevented through childhood vaccination. The

rubella vaccine can also be given at least one month prior to pregnancy to women who are not already immune.
- Increasing and strengthening education to health staff and others interested in promoting birth defects prevention.

Detection

Pre- and peri-conceptional care includes basic reproductive health practices as well as medical genetic screening. Screening can be conducted during the following three periods:
- Preconception screening is used to identify persons at risk for specific disorders or at risk for passing one on to their children. The strategy includes the use of family histories and carrier screening, and is particularly valuable in countries where consanguineous marriage is common.
- Antenatal screening includes screening for advanced maternal age, Rhesus blood group incompatibility, and carrier screening. Ultrasound can be used to detect Down syndrome during the first trimester and serious fetal anomalies during the second trimester; maternal serum screening can also be used for detection of Down syndrome and neural tube defects during the first and second trimesters.
- Newborn screening includes clinical examination and screening for haematological, metabolic, and hormonal disorders. Screening for deafness and heart defects as well as early detection of birth defects can facilitate life-saving treatments and prevent the progression towards some physical, intellectual, visual or auditory disabilities.

Treatment and care

In countries with well-established health services, structural birth defects can be corrected with paediatric surgery and early treatment can be administered to children with functional problems such as thalassaemia (inherited recessive blood disorders), sickle cell disorders and congenital hypothyroidism.

The GAVI Alliance, of which WHO is a partner, is assisting developing countries in improving control and elimination of rubella and congenital rubella syndrome through immunization.

WHO develops normative tools, including guidelines and a global plan of action, to strengthen medical care and rehabilitation services to support the implementation of the Convention on the Rights of Persons with Disabilities. Similarly WHO supports countries to integrate medical care and rehabilitation services into overall primary health care, supports the development of community-based rehabilitation programmes and facilitates the strengthening of specialized rehabilitation centres and their links with