**EDITORIAL**

Bariatric Surgery and Hypoglycemia
Bijan Ahrari, Samuel Dagogo-Jack

**REVIEW ARTICLE**

Asthma During Pregnancy: An Immunologic Perspective
Fawaz Azizieh, Raj Raghupathy

**ORIGINAL ARTICLES**

Intravenous Labetalol versus Oral Nifedipine in the Treatment of Severe Hypertension in Pregnancy
Ronita Devi Mayanglambam, Tempe Anjali

Total Hip Replacement in Nigeria: A Preliminary Report
Nwadingwge Cajetan Uwatoronye, Anyaehie Udo Ego, Katchy Uchenna Amaechi

Towards Prevention of Diabetes in Offsprings of Type 2 Diabetic Patients
Amal I El-Sharakawy, Abdulrahman A Abdulla, Fatimah Bendhifari

Stereotactic Surgery: Diagnostic and Therapeutic Role in the Management of Brain Disorders and Our Experience at Ibn Sina Hospital
Hasan Khajah, Aftab Khan, Yousaf Al Awadi, Abbas Ramadon

Synergy between Dendritic Cell-Based Vaccine and Anti-CD137 Monoclonal Antibody in the Treatment of Mouse Renal Cell Carcinoma
Si-Ming Wei, Zhi-Zhong Yan, Jian Zhou

The Effect of Gene Polymorphisms (ENOS G894T, PON1 and Catalase -262C→T) on Fertility and Sperm Parameters in Turkish Men with Clinical Varicocele: A Pilot Study
Cavit Ceylan, Gulay G Ceylan, Hakan Artas, Erdogan Aglamis, Can Ates, Huseyin Yuce

**INSIGHT**

Ward Mechanical Ventilation (WMV) Audit
Sulaiman Khadadah, Maryam Al-Ali, Mohamed Bahzad

**CASE REPORTS**

Unusual Presentation of Duplex Collecting System: A Case Report
Mukesh Kumar Vijay, Preeti Vijay, Pramod Kumar Sharma

Double Appendix: Report of a Case
Naorem Gopendro Singh, Hisham Kantoush, Mirza Kahvic

Oncocytic and Clear Cell Areas in a Solid Pseudopapillary Tumor of the Pancreas: A Case Report
Anuradha C K Rao, Manna Vailathan, Padmapriya Jaiprakash

Celiac Disease as Uncommon Cause of Death in Type 1 Diabetes Mellitus: A Case Study
Yasser Mohamed Abd Elraouf Ibrahim

Squamous Cell Carcinoma of the Penis: Magnetic Resonance Imaging Findings
Ibrahim Hamad, Hasan Almutairi, Muneera Al-Adwani

Unstable Carpometacarpal Dislocation of Ulnar Four Fingers – An Easily Overlooked Injury
Kumar Ashok, Singh Pritish, Badole Chandrashekhar

Prostatic Adenocarcinoma and Chronic Lymphocytic Leukemia: A Case Report
Abdul-Razzaq A Wraikat, Tariq N Aladily
LETTER TO THE EDITOR

Individual Cyclooxygenase-2 Inhibitors on the Risk of Peptic Ulcer Disease: A Population-Based Cohort in Taiwan 347
Shih-Wei Lai, Kuan-Fu Liao, Hsueh-Chou Lai, Chih-Hsin Muo, Fung-Chang Sung, Pei-Chun Chen

SELECTED ABSTRACTS OF ARTICLES PUBLISHED ELSEWHERE BY AUTHORS IN KUWAIT 349

FORTHCOMING CONFERENCES AND MEETINGS 353

WHO-FACTS SHEET 362
1. Diabetes
2. Epilepsy
3. Maternal Mortality
4. Diarrheal Disease

YEARLY TITLE INDEX 368
YEARLY AUTHOR INDEX 370

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Bariatric Surgery and Hypoglycemia

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Obesity is a major public health problem in the developed and developing regions of the world. Using a body mass index (weight in kg divided by height in meter squared) of 30 kg/m² or greater as the cut-off, recent estimates indicate that 36% of adults in the United States are obese[1]. The prevalence of severe or morbid obesity defined as BMI greater than 40 kg/m² is rising twice as fast as that of obesity and is currently close to 6% of US adult population. Obesity is associated with increased risk of morbidity and mortality from cardiovascular disease, diabetes, respiratory diseases, musculoskeletal disorders and neoplastic diseases, among others[2]. Management of obesity continues to be challenging, and traditional options based on dietary and lifestyle modifications seldom result in sustained weight loss. Compared with the proliferation of agents for diabetes therapy, the pace of drug development for obesity has been markedly slower. Moreover, the available agents are of limited efficacy[3], especially with regard to making an impact on morbid obesity.

Superficial interventions such as liposuction and removal of subcutaneous abdominal adipose tissue do not alter cardio-metabolic risks[4]. By contrast, gastric bypass surgery offers long-term weight loss associated with significant reduction of comorbidities associated with morbid obesity[5]. Complete resolution of diabetes occurs in 80% of patients while an additional number of patients see significant improvement in diabetes[6,7]. This happens through both weight-dependent as well as weight-independent mechanisms including alteration in bile flow, reduction of gastric size, anatomical gut rearrangement, vagal manipulation, and alterations in enteric hormones[6]. In addition, hyperlipidemia, hypertension and obstructive sleep apnea improve in 70%, 62% and 84% of patients respectively[5]. A large cohort study showed a 40% reduction in mortality from all causes associated with bariatric surgery[6].

Unfortunately, the cosmetic and cardio-metabolic benefits of bariatric surgery are achieved at a price of significant post-operative morbidity and sometimes mortality. However, the outcomes of bariatric surgery are generally improving over time with the use of more advanced surgical procedures, more careful selection of surgical candidates, and the use of specialized surgery centers. The overall 30-day mortality for bariatric surgical procedures is less than one percent[8]. Some of the more common complications of bariatric surgery include ventral and internal hernias, metabolic and nutritional derangements, marginal ulcers, short bowel syndrome, dumping syndrome and cholelithiasis[10].

An uncommon but potentially serious adverse effect of bariatric surgery is recurrent severe hypoglycemia. As is well-known, hypoglycemia is rare among non-diabetic persons[11]. Although mild asymptomatic hypoglycemia can be as seen in up to 50% of post-bypass patients, severe hypoglycemia accompanied by neuroglycopenic symptoms occurs in less than 1% of bariatric surgery patients[6,12]. The presentation of mild episodes of hypoglycemia is similar to that of the late phase of dumping syndrome and usually responds to dietary modifications[9]. Although much less frequent, episodes of severe hypoglycemia can have dramatic clinical presentations, including confusion, seizure and coma. Impaired cognitive function, altered neuromuscular reflexes, and diminished capacity for judgment resulting from neuroglycopenia can lead to automobile accidents and machinery injuries. In a nationwide Swedish case-control study (one case for every 10 matched population control subjects) of persons who had undergone gastric bypass (n = 5,040), vertical banded gastroplasty (n = 4,366), or
gastric banding (n = 2,917) for obesity, the relative risk of severe hypoglycemia was five-fold higher in the gastric bypass patients compared with controls[12]. However, it is noteworthy (and reassuring) that the absolute rate of post-bariatric hypoglycemia was low (< 1%). Furthermore, the Roux-en-Y gastric bypass procedure was more frequently associated with hypoglycemia than other forms of bariatric surgery, including vertical banding gastroplasty and gastric banding[12]. The median time from surgery to hypoglycemic symptoms in the Swedish survey was 2.7 years, consistent with the post-operative latency of 1 - 5 years reported in other series[5,13-15]. Of note, the frequency of accidental deaths was higher in post-bariatric surgery patients than in reference cohorts, which may indicate undiagnosed hypoglycemia and possible underestimation of the number of patients with hypoglycemia[12].

Classically, hypoglycemia in post-gastric bypass patients occurs postprandially or during the postabsorptive period (as opposed to during fasting). Post-gastric bypass hypoglycemia usually is associated with the concurrence of low serum glucose levels (typically < 60 mg/dl) and inappropriately elevated or measurable levels of insulin and C-peptide. The mechanisms behind post-gastric bypass hyperinsulinemic hypoglycemia are not well-understood. In 2005, Service et al reported a series of six patients with symptomatic postprandial hyperinsulinemic hypoglycemia that developed on average 30 months after gastric bypass surgery[16]. Insulinoma was ruled out using imaging studies and selective arterial calcium stimulation test[16]. These patients then underwent either extensive or spleen-preserving distal pancreatectomy, and islet specimens were obtained for histological study. The pancreatic islet sections obtained from the patients reported by Service et al showed evidence of nesidioblastosis (hypertrophic beta cells, with enlarged or normal-appearing islets; small scattered clusters of endocrine cells; and ductuloinsular complexes)[16]. The authors thus concluded that insulin hypersecretion from nesidioblasts was responsible for post-gastric bypass hypoglycemia in their patients[16]. However, re-examination of the pancreatic histology by Meier et al raised doubts about the presence of true nesidioblasts[17]. Instead, evidence of increased beta cell nuclear diameter was observed in post-gastric bypass patients compared with controls[17]. Thus, the hypoglycemia in such patients could have arisen from a combination of exaggerated “dumping” syndrome and increased insulin secretion per beta cell.

Another mechanism proposed for the insulin hypersecretion and possible islet cell proliferation was enhanced glucagon-like peptide 1 (GLP-1) secretion from L cells in distal ileum, resulting from the rapid transit of nutrients following gastric bypass surgery[16]. Indeed, studies identified exaggerated GLP-1 response and attendant insulintropic and glucagonostatic effects as mechanisms for post-gastric bypass hypoglycemia[18,19]. Since the mechanisms underlying post-bariatric hypoglycemia are not fully understood, a standard approach to management has not yet been developed. Mild hypoglycemia may be evaluated and treated in an outpatient setting. However severe hypoglycemia likely requires hospitalization and evaluation to rule out etiologies such as insulinoma. Without randomized controlled studies, the therapeutic approach to severe post-bariatric surgery hypoglycemia has been empirical. Management usually begins with dietary modification, including frequent small meals with low carbohydrate content. Pharmacological approaches that have had variable success include diazoxide, acarbose, octreotide, and calcium channel blockers[6, 13, 20]. For patients with refractory hypoglycemia, surgical intervention may be warranted, either to reverse the gastric restriction procedure or reduce the mass of insulin-secreting pancreatic tissue[8-7, 14-16].

In summary, severe hyperinsulinemic hypoglycemia is a rare but serious sequel of gastric bypass surgery. It usually presents a few years after the surgery and is accompanied by neuroglycopenic symptoms including confusion, seizure, syncope or coma. Future studies should be directed at unraveling the mechanisms, identifying risk factors, and developing optimal surveillance and management strategies for post-gastric bypass hypoglycemia. While awaiting the results of definitive studies on the subject, clinicians should be cognizant of the risk of hypoglycemia, educate gastric bypass patients on the warning symptoms of impending hypoglycemia and appropriate corrective measures.

REFERENCES

Review Article

Asthma during Pregnancy: An Immunologic Perspective

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ABSTRACT

Asthma is one of the most common medical conditions to complicate pregnancy and represents a significant public health issue. Increased maternal complications and adverse fetal outcomes are associated with asthma during pregnancy. Since asthma can adversely affect the outcome of pregnancy, it is important for us to understand the mechanisms underlying asthma during pregnancy. In general, asthma is characterized by an up-regulated systemic production of T-helper 2 (Th2) cytokines. Pregnancy also brings about changes in maternal immune status making it polarized towards the Th2 phenotype.

Based on these considerations, we hypothesize that pregnancy-induced immune alterations may modify allergic mechanisms of asthma and that systemic Th2 cytokine and chemokine polarization does occur among asthmatics to a greater extent during pregnancy. We suggest that this is associated with exacerbation of asthma during pregnancy. The pathophysiology of asthma during pregnancy and the interrelationship between these two conditions are reviewed here.

KEY WORDS: allergy, cytokines, Th1, Th2

INTRODUCTION

Asthma is one of the most common medical conditions in the world. It is also the most common condition affecting the lungs during pregnancy. About 7-12% of pregnant women may be affected by asthma, making asthma one of the most important medical conditions complicating pregnancy[1-3]. Asthma influences the outcome of pregnancy; it is considered to be a risk factor for several maternal and fetal complications, such as asthma exacerbations, hospitalizations because of asthma attacks, pre-eclampsia, preterm delivery, cesarean delivery, gestational hypertension, low birth weight and a higher risk of perinatal mortality[4,5]. Conversely, pregnancy also influences the severity of asthma; during pregnancy, approximately one third of asthmatic women experience exacerbation of their symptoms[6,7]. Women who have more severe asthma before pregnancy appear more likely to experience worsening asthma during pregnancy[8,9]; prospective studies have shown that asthma is more likely to deteriorate during pregnancy in women with severe asthma than in those with mild asthma[10,11]. Maintenance of optimal asthma control during pregnancy reduces maternal and fetal risk for complications[11].

Two questions about the interaction of asthma and pregnancy are raised by clinicians and patients alike: (i) How does pregnancy affect asthma? (ii) How does asthma affect the outcome of pregnancy? Asthma is an immunologic disease, and pregnancy brings about changes in the immune system. Thus, it is of interest to view asthma during pregnancy from an immunologic perspective.

While the underlying immunologic mechanisms of the interactions between asthma and pregnancy are not fully understood, this review summarizes current knowledge about the immunology of asthma and the immunology of pregnancy, and suggests possible mechanisms for immunological interactions between asthma and pregnancy.

ASTHMA

The immune system surely does a splendid job of protecting us from infectious diseases (much of the time!). However, inappropriate responses of this system can lead to disease. Allergies and asthma are common among the outcome of immune dysfunction. Discomfort or even distress from common allergies may seem minor compared to life-threatening problems such as cancer or cardiovascular diseases,
but asthma is a serious problem that can cause severe difficulties in breathing. The real significance of asthma is demonstrated by the number of visits to the doctor and to the emergency room and days spent in the hospital\[10\]; in fact, the number of visits to the doctor for hypertension or for pregnancy or general examination is each fewer than the number of visits for asthma. Indeed, the single most common reason for a visit to the emergency room in the Western world is an asthma attack.

Asthma is a worldwide disease and a common one. With about 5% of the population in Western countries affected, there is no reason to assume that the incidence of asthma is lower in Kuwait and the Arabian Gulf. In fact, despite low allergen exposure, the pattern of childhood asthma in Kuwait follows that described in Western communities\[12,13\]. In Kuwait, the average annual admission rate for asthma per 100,000 people was 217 in the 1992-1994 period and the mean annual death rate per 100,000 people was about 1.6. The number of Kuwaiti patients being admitted for asthma has increased\[13\]. A survey made by the Asthma Insights and Reality in the Gulf and Near East (AIRGNE) of Jordan, Kuwait, Lebanon, Oman and the UAE in 2009 showed that the comparative population prevalence of diagnosed current asthma was high, ranging from 23% in Kuwait to 32% in Lebanon\[14\].

IMMUNOPATHOGENESIS OF ASTHMA

Asthma, also known as reversible obstructive airway disease, is characterized by hyperresponsiveness of the tracheobronchial tree to respiratory irritants and bronchoconstrictor chemicals producing attacks of wheezing, dyspnea, chest tightness and cough. This chronic respiratory disease is characterized by episodes of inflammation and narrowing of small airways in response to triggers of asthma. Asthma can be triggered by a variety of factors including allergens, infections, exercise, abrupt changes in the weather and exposure to airway irritants such as tobacco smoke. Asthma attacks can vary from mild to life-threatening.

Asthma can be due to either an allergic response or a non-allergic response. Asthma due to an allergic response is also known as allergic asthma, extrinsic asthma, atopic asthma or immunologic asthma. 50% of asthma cases are “allergic-asthma”\[4\]. Allergic asthma is triggered by air-borne or blood-borne allergens such as pollen, dust, fumes, insect products or viral products. Non-allergic asthma, also known as intrinsic or idiopathic asthma, is induced by cold or exercise, apparently independently of allergens. However, regardless of the presence or absence of allergy, all asthmatic patients have the cardinal features of airway hyperreactivity, airway obstruction and eosinophilia.

Allergic asthma in genetically susceptible individuals is a result of dysregulated immune responses to common environmental antigens. The pathogenesis of asthma involves cytokine production from T helper 2 (Th2) lymphocytes that in turn orchestrate the allergic inflammatory response. Upon recognition of an allergen, Th2 cells produce cytokines that induce IgE synthesis, activate eosinophils and mast cells, and up-regulate expression of adhesion molecules on endothelial and epithelial cells. Eosinophils are a key component of chronic allergic disease and contribute to many of the pathological processes of asthma producing molecules that stimulate vasomotor activity, bronchoconstriction and mucus secretion. They also produce a variety of pro-inflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin (IL)-1 and IL-6. Anti-allergen IgE antibodies first bind to mast cells; subsequent exposure to the allergen triggers an IgE-mediated release of mediators that may cause an asthmatic attack. IgE-sensitized mast cells and basophils secrete several mediators such as histamine, leukotrienes and prostaglandins which lead to bronchoconstriction, vasodilation and build-up of mucus. Subsequently, other mediators including eosinophil-chemotactic factor, platelet-activating factor and the cytokines IL-4, IL-5 and TNFα are released; these mediators increase endothelial cell adhesion and recruit inflammatory cells such as eosinophils and neutrophils into the bronchial tissue.

As Th2 reactivity is critical to the development of asthma, it is pertinent to elaborate on Th1/Th2 dichotomy at this point.

TH1 AND TH2 REACTIVITY

One of the most significant advances in our understanding of immune responses has been the delineation of the Th1/Th2 paradigm, which provides a framework for understanding how the immune system directs responses to different types of pathogens and antigens. The two major subsets of CD4+ T helper cells, Th1 and Th2, have different patterns of cytokine production and different roles in immune responses. Each subset induces functions that are effective at handling certain types of pathogens, but can be ineffective, or may even have pathological effects if made in response to other types of pathogens\[15, 16\]. Th1 cells secrete IFNγ, TNFβ, IL-2 and TNFα, the so called Th1-type cytokines. Th1-type cytokines activate cell-mediated reactions important in resistance to infection by intracellular pathogens, and in cytotoxic and delayed-type hypersensitivity (DTH) reactions. Th2 cells, on the other hand, secrete IL-4, IL-5, IL-6, IL-10 and IL-13; these Th2-type cytokines promote robust antibody production and are therefore commonly found in association with strong antibody responses that are important in combating infections with extracellular organisms. Which type of reactivity, Th1 or Th2 is activated first may influence the subsequent.
outcome; if a particular T cell subset is activated first or preferentially in a response, it can suppress the development of the other subset. The overall effect is that responses are often dominated by either humoral (Th2) or cell-mediated (Th1) immunity.

ASTHMA IS A TH2-MEDIATED REACTIVITY

The generation of Th2 cells and the development of Th2-type reactivity are crucially dependent on the cytokine IL-4. Th2 development is greatly favored once a threshold level of IL-4 is reached. Th2 cells provide help to B cells and promote the production of relatively large amounts of IgE, IgM and non-complement fixing IgG. In addition, Th2 cells cause mast cell growth via the production of IL-4, IL-10 and IL-13 and stimulate eosinophil activation via IL-5. It should be emphasized that Th2 cells support allergic reactions via the production of the quintessential Th2 cytokines, IL-4 and IL-5, and also IL-13. The co-culture of CD4+ T cells with peripheral blood monocytes from atopic asthmatic subjects results in enhanced production of IL-4 and IL-5. The Th2 cytokine IL-4 thus plays prominent and indispensable roles in the activation of mast cells as shown in Fig. 2. Levels of the Th2 cytokine IL-13 are increased in the airway mucosa of patients with asthma and challenge with allergen results in increased levels of IL-13 in addition to IL-4. The administration of IL-13 to mice increases airway eosinophilia and bronchial hyperresponsiveness. IL-13 induces inflammation by stimulating the expression of chemokines (i.e., cytokines that are chemotactic for immune cells) such as eotaxin from cells in the airways and also induces airway hyperresponsiveness and hypersecretion of mucous in the airway epithelium. Atopic asthma is characterized by increased production of Th2 cytokines; some studies have also reported up-regulation of systemic Th2 cytokine production associated with increased symptoms of allergy.

Allergy is thus a Th2 phenomenon, and Th2 cytokines are intimately involved in the stimulation of allergy (Fig. 1 and 2) while Th1 cytokines are actually antagonistic to allergy.

In addition to Th2-type cytokines, other cytokines such as IL-8 are also implicated in the development of asthma and in the chronic inflammatory processes of asthma by contributing to the release of inflammatory mediators such as histamine, airway remodeling, bronchoconstriction and bronchial hyperresponsiveness. Chemokines are important in asthma, as they are involved in attracting leukocytes from the circulation into the airways. Particularly important among these are the chemokines RANTES,
Eotaxin and IP-10. RANTES is a powerful eosinophil chemoattractant[32] and induces respiratory burst in eosinophils[33]. In addition, RANTES is a very effective basophil attractant[34]. Eotaxin, a Th2 chemokine, is elevated in individuals with asthma and eosinophilia, and many studies have evaluated its role in local tissues[35].

DOES ASTHMA GET BETTER OR WORSE DURING PREGNANCY?

Asthma is the most common chronic condition to complicate pregnancy. During pregnancy, approximately one third of asthmatic women experience an exacerbation[6,7]. Women who have more severe asthma before pregnancy appear more likely to experience worsening asthma symptoms during pregnancy[6,8]; prospective studies have shown that asthma is more likely to deteriorate during pregnancy in women with severe asthma (52 - 65%) than in those with mild asthma (8 - 13%) [10,36].

What happens to asthmatic women when they get pregnant? Do the symptoms get better or do they get worse? The consensus is that one-third of females experience a worsening of asthma during pregnancy, one-third improve and one-third remain unchanged[8,37,39] (Fig. 3). It is unclear whether this is due to changes in asthma severity, changes in asthma control or exacerbations during pregnancy. A variety of methods have been used to obtain this data. Most studies have used subjective questionnaires to ascertain the global change in asthma experienced during pregnancy, while a few studies have obtained data from daily recordings of symptom or changes in treatment requirements. However, even though only a few studies have examined objective measures such as lung function by peak spirometry or airway hyperresponsiveness, the general trend seems to support the notion that asthma symptoms worsen in about 24 - 43% of asthmatic women during pregnancy, improve in about 14 - 42% of women and are unchanged in 24 - 43% of women.

For example, Williams examined hospital records and reported that asthma gets worse in 24% of pregnant women, remains the same in 34% and symptoms improve in 42% of pregnant women[40]. Similarly, Schatz et al evaluated asthma in 336 pregnant women based on the daily symptoms diaries as well as by subjective classification of overall changes and reported that asthma became worse in 35% of women, unchanged in 33% and improved in 28%[39]. The same evaluation based on the same criteria was reported more recently and the percentages were 36%, 26% and 34% respectively[41]. Based on questionnaires on symptoms and self-report of overall changes in breathing, many others reported that asthma in pregnant women got worse in 34 - 41%, remained the same in 24 - 31% and improved in 16%[3,42].

In subjects whose asthma worsened, a significant increase has been reported in the number of days of wheezing and interference with sleep and activity between 25 - 32 weeks gestation[38]. In asthmatic subjects who felt their asthma improved overall, there was a decrease in wheezing with little change in interference with sleep or activity between 25 - 32 weeks gestation. Most subjects who felt their asthma improved during pregnancy actually improved post-partum, with significantly fewer days of wheezing at 5 - 12 weeks post-partum compared with 29 - 32 weeks of gestation. Conversely, most subjects who felt their asthma improved during pregnancy later worsened after delivery, with significantly more days of interference of activity with sleep or activity between 29 - 36 weeks of gestation. In general, increased asthma severity during pregnancy is associated with greater morbidity in the mother and newborn[39].

In summary then, the paradigm has remained for decades that during pregnancy, asthma will worsen in one-third of women, remain the same in one-third and improve in one-third.

MECHANISMS OF PREGNANCY-INDUCED CHANGES IN ASTHMA

The mechanisms that contribute to changes in asthma during pregnancy are not well understood, although increases in maternal circulating hormones, altered 2-adrenoreceptor responsiveness or fetal sex have been suggested to be involved (Fig. 4). One could postulate that elevations in both estrogen and progesterone that occur particularly during the first trimester may contribute to the severity of asthma during pregnancy. Evidence for this can be found from the multiple studies that have reported associations between higher levels of hormones and asthma symptoms. For example, more frequent
Asthma symptoms have been reported in association with menstruation[43] and in association with hormone replacement therapy[44,45]. Increased progesterone levels, in both animals[46] and humans[44,45], have been associated with worsening asthma symptoms in several, but not all studies[47]. Both estrogen and progesterone have been shown to up-regulate Th2 cytokine production both in vitro[48,49] and in vivo[50].

The pregnancy-associated rise in serum-free cortisol may contribute to improvements in asthma during pregnancy[51], since cortisol has anti-inflammatory properties. In addition, estradiol and progesterone concentrations increase significantly during pregnancy[52]. Progesterone is known to contribute to increased ventilation during normal pregnancy[53] and is also a potent smooth muscle relaxant[54] and may, therefore, be expected to contribute to improved asthma during pregnancy. On the other hand, progesterone has been shown to induce Th2-type reactivity[54,55] and thus pregnancy-associated increase in progesterone levels may be postulated to result in an increased Th2-bias and thus increased severity of asthma.

Changes in β2-adrenergoreceptor responsiveness and airway inflammation as a result of circulating progesterone may also contribute to worsening asthma during pregnancy[56]. Alternations in asthma associated with changes in sex steroid production during the menstrual cycle have previously been observed[57], with up to 40% of females experiencing an exacerbation around the time of menstruation when progesterone and estradiol levels are low[58].

The season of pregnancy or delivery was not found to affect asthma progression[38], suggesting that allergen exposure may not play a role in asthma alterations with pregnancy. Kircher et al[60] suggest that factors, such as IgE, which affect both the upper and lower airways, may be important in changes that occur in asthma during pregnancy. Early studies by Gluck and Gluck[61] also showed a correlation between increased serum IgE and deteriorating asthma during pregnancy.

An observation that is worth mentioning here in terms of mechanisms and clinical relevance, is pertinent to the course of asthma during pregnancy. More severe asthma tends to worsen during pregnancy, whereas less severe asthma tends to remain unchanged or tends to improve[62]. The relationship between asthma severity classification and subsequent changes in asthma during pregnancy was assessed in a study on 1,700 pregnant asthmatics[37]. Exacerbations of asthma occurred in over half of all severe asthmatics, while only 12% of patients with mild asthma had exacerbations during pregnancy.

It is tempting to suggest that perhaps maternal immune factors, such as the prevailing Th2 versus Th1 cytokine profile, may be one of the determinants of whether an asthmatic woman will get better or worse when she gets pregnant. Is this possibly due to an already heavily Th2-biased immune system tilting towards a stronger Th2 bias during pregnancy?

IMPAKT OF ASTHMA ON PREGNANCY

In addition to the observed effects of pregnancy on asthma, it is also well-recognized that women with asthma are at increased risk of poor pregnancy outcomes[63]. Cases of severe life-threatening asthma requiring first trimester termination of pregnancy have been reported and an improvement in maternal asthma within 24 hours of termination has been observed[64]. Epidemiological studies have demonstrated that asthmatic females are at increased risk of many poor outcomes of pregnancy. Uncontrolled asthma in pregnant women can result in perinatal complications and exacerbations which can be life-threatening for the mother and fetus[65].

Increased maternal complications, including pre-eclampsia[66], gestational diabetes[67], preterm labor[68], intrauterine growth restriction[69], vaginal hemorrhage[60], placenta previa[60] and cesarean delivery[60] have been described. Adverse fetal outcomes include increased risk of perinatal mortality[60], intrauterine growth restriction[69] and low birth weight[60]. As early as in 1970, Gordon et al[60] reported a relatively large number of maternal or perinatal deaths in asthmatic patients, which were more likely to occur in severe asthmatics. A Californian perinatal database study comparing asthmatics to controls showed that asthmatics were more at risk of cesarean section, pre-term labour or delivery and pre-term premature rupture of the membranes. A cohort of almost 25,000 pregnant females in Canada found a significant association between pre-eclampsia and asthma[60]. Greenberger and Patterson[60] found
that those who had been hospitalized with status asthmaticus delivered neonates of reduced birth weight compared with those who were not hospitalized for asthma, suggesting that an acute attack of asthma may put the fetus at additional risk, particularly of intra-uterine growth restriction (IUGR).

However, it must be conceded that a few studies have not found such correlations. Apter et al[69] found no evidence of an increased rate of pre-eclampsia, pre-term delivery or IUGR in asthmatic adolescents compared with general estimates for adolescent pregnancies. However, these researchers did report that IUGR was significantly more likely in females with moderate or severe asthma, who required hospitalization during pregnancy, compared to subjects with mild asthma, who were not hospitalized for asthma during pregnancy. Similarly, Mabie et al[70] reported no increased rate of pre-term delivery or low birth weight among asthmatic females compared with general population rates, which were very high (17.7 and 6.3%, respectively). Likewise, Tata et al[71] reported an increase in risks of miscarriage and cesarean section in women with more severe asthma and previous asthma exacerbation, but not other complications.

Despite the few studies showing a lack of adverse consequences, a majority of the studies have demonstrated associations between asthma and pre-eclampsia, and asthma and low birth weight by both historical or prospective cohort and case-control studies. A meta-analysis of the association between asthma in pregnancy and low birth weight babies showed that there was a significantly increased risk of low birth-weight babies in asthmatic pregnancies and that there was no significant increase in the risk of low birth weight with asthma when inhaled corticosteroids (ICS) were used[80].

There is therefore, a general agreement that severe asthma requiring corticosteroid therapy is associated with an increased incidence of low birth-weight babies and of preterm births[72-74]. Asthma, when not treated with inhaled steroids during pregnancy was associated with changes in placental function that affect fetal development which includes the hypothalamic-pituitary axis and growth[10]. In general, published data suggest that asthma severity, especially with suboptimal control, is associated with adverse pregnancy outcomes (Fig. 4)[72].

PREGNANCY: A Th2-TYPE SITUATION

The fetus can be viewed as a sort of a semi-allogeneic allograft that expresses paternal antigens, which under non-pregnant circumstances would result in the activation of a “rejection reaction”. However, it is postulated that a number of processes are activated in concert to protect the fetus and thus ensure its survival. These include the separation of the maternal and fetal circulations, masking of paternal antigens on the trophoblast, endocrinological inhibition of adverse maternal immune reactions and production of immunomodulatory factors by both the mother and fetus. In 1993, Wegmann et al proposed that a shift towards Th2-mediated immunity particularly at uterine sites during pregnancy inhibits Th1 immune responses and prevents the rejection of the fetus by the maternal immune system[75].

Humoral immune responses are enhanced during pregnancy, while cell-mediated immune responses and the course of cell-mediated autoimmune disorders are down-regulated. Clinical evidence indicates that pregnant women undergo immunological changes consistent with a weakening of Th1 responses and strengthening of Th2 responses[75,76] leading to the contention that successful pregnancy probably depends on preferential stimulation of Th2 cytokine-producing cells. Experiments on mice and evidence in humans indicate that humoral responses are enhanced during pregnancy, but that there is a down-regulation of cell-mediated reactivity, responses to intracellular infections and the course of cell-mediated autoimmune disorders. These observations are consistent with a dampening of pro-inflammatory or Th1 reactivity and augmentation of anti-inflammatory or Th2 immunity during pregnancy.

Dudley et al[77] found that cytokine responses by activated lymphocytes from pregnant mice are marked by a progressive decline in the production of the Th1 cytokine IL-2 and a concomitant increase in the levels of the Th2 cytokine IL-4. In humans, there are reports of significantly higher production of IL-10 (a Th2 cytokine) by mitogen-activated PBMC in pregnant women as compared with non-pregnant women[79]. Kruse et al[79] reported significantly reduced IL-2 and IFNγ mRNA expression during normal human pregnancy and a shift to a pronounced Th2 status. Using flow cytometric techniques on a single cell, significantly increased IL-4-producing CD4+ and CD8+ T cells were demonstrated in normal pregnant women as compared to non-pregnant women. In contrast, IFNγ- and IL-2-producing CD4+ and CD8+ T cells were significantly reduced in pregnancy, which is suggestive of a Th2 shift in pregnancy[80]. Thus, pregnancy is indeed a Th2-type phenomenon as proposed by Wegmann et al[75] and pregnancy seems to engender a shift towards Th2 bias[74].

Thus, the two broad lines of evidence described above show that both asthma and pregnancy are indeed Th2-type situations. Th2 cells and cytokines stimulate IgE production and are responsible for the activation of mast cells and inflammatory responses in asthma[17-21,23-26]. Likewise, pregnancy is associated with a dominance of Th2 reactivity and at the same time Th2 reactivity is conducive to successful pregnancy[75,76].
Interestingly, immune mechanisms involved in the maintenance of asthma-related symptoms are regulated by Th2-mediated mechanisms as in normal pregnancy which leads us to propose that pregnancy may worsen asthma by bringing about a stronger bias towards Th2 reactivity. However this rather simplistic notion is complicated by the fact that the disease becomes worse in only about a third of the patients and, not as one might predict, in all the patients.

**IMMUNE STATUS IN ASTHMATIC WOMEN WHO BECOME PREGNANT**

Pregnancy is proposed to be a state of wide-spread lymphocyte activation, but at the same time it may blunt lymphocyte activation which characterizes bronchial asthma. However, immunological changes in asthmatic women during pregnancy are not well elucidated. Tamasi et al. reported signs of pregnancy-induced attenuation of allergic responses in asthmatic pregnant women. Activated pools within CD4+ and CD8+ T cells were larger, and the number of natural killer T (NK-T) cells was increased both in non-pregnant asthmatic and in healthy pregnant subjects (compared to non-pregnant healthy controls), but in well-controlled pregnant asthmatics no further lymphocyte activation was observed, suggesting that the immunosuppressive effect of uncomplicated pregnancy may dull lymphocyte activation which characterizes asthma. In addition, as a sign of an enhanced T cell apoptosis, higher numbers of cytotoxic T cells was detected in healthy pregnant women than in healthy non-pregnant women, together with a positive correlation between cytotoxic T cell counts and birth weights in healthy but not in asthmatic pregnancies. On the other hand, in another study on poorly-controlled asthmatic pregnant women, a substantial number of peripheral IFN-γ-producing cells were detected, and a significant negative correlation was revealed between the number of IFN-γ-positive T cells and birth weight of newborns, suggesting that intrauterine growth restriction can be related to active, asthma-associated maternal immune reactions.

Bohacs et al. reported an increased prevalence of regulatory T (Treg) cells in peripheral blood of healthy pregnant women but a lower prevalence of Treg and an elevated prevalence of NK-T cells in pregnant asthmatic women compared to healthy pregnant women. They also reported lower effector/ memory ratios and higher naive T cell prevalence in asthmatic pregnant patients compared to non-pregnant asthmatics.

Analysis of immune cells in the maternal circulation indicates that circulating white cells are altered in asthmatics when compared to non-asthmatics and that these alterations may contribute to worsening asthma during pregnancy. Maternal circulating monocyte populations were significantly increased in pregnant asthmatic women not using inhaled steroids for the treatment of their disease. Monocytes play important inflammatory roles in asthma, as the precursors to macrophages and also through their interaction with Th2 lymphocytes, eosinophils and mast cells within the lung. Murphy et al. examined placental Th2:Th1 cytokine mRNA ratios and found a significant increase in placental Th2:Th1 cytokine mRNA ratios in females, as assessed by measuring TNFα (Th1) and IL-5 (Th2) mRNA.

**A CYTOKINE LINK BETWEEN ASTHMA AND PREGNANCY**

As pregnancy is a Th2-type situation, it is tempting to predict that symptoms in asthmatic women may become worse when they get pregnant, because asthma is also a Th2-type situation. It is a sort of an “immunological double whammy”! One might speculate that the Th2 predominance seen in pregnancy might worsen asthma situations; by corollary then, all asthmatic women should have worsened asthma symptoms when they become pregnant. However, this is not the case; the dogma holds that only about 33% of asthmatic women have worsened symptoms during pregnancy, while approximately 33% actually get better!

There is a lack of studies on longitudinal assessment of cytokine bias during and after pregnancy in asthmatics that become pregnant as also possible effects of changes in cytokine patterns on asthma symptoms during pregnancy. Rastogi et al. reported a non-significant trend towards decreased intracytoplasmic levels of IFNγ and increased IL-4 levels in pregnant asthmatics. Non-asthmatic pregnant women were not studied. Interestingly, these researchers demonstrated a decline in IP-10/eotaxin ratio over the course of pregnancy; this ratio was also shown to be associated with worse asthma symptoms. The levels of other cytokines were not estimated in this study. Clearly this aspect needs to be investigated further.

Tamasi et al. demonstrated increased levels of IFNγ-producing T cells in pregnant asthmatics as compared to non-pregnant asthmatics. IL-4-producing T cells were also increased in number though to a much lower extent, leading these researchers to conclude that pregnancy in asthmatics leads to a dominant IFNγ response. While these results are interesting, it should be noted that pregnant non-asthmatics were not compared, nor were other cytokines tested.

**CONCLUSION**

The jury is still out; as asthma is characterized by increased Th2 polarization, we suggest that pregnancy-associated Th2 polarization may contribute mechanistically to worse birth outcomes. Our
hypothesis is that asthmatic women who get worse during pregnancy have a different cytokine profile as compared to asthmatic women who get better during pregnancy. We suggest that some asthmatic women develop a substantially stronger Th2-bias during pregnancy as compared to other asthmatic women; and that the former subgroup would have worsened asthma symptoms than the latter due to the stronger Th2-bias. Further studies are needed to elucidate the relationship between immunological alterations in Th2 polarization and asthma symptoms during and following pregnancy. Closer monitoring with early identification and perhaps treatment of Th2 polarization may in turn lead to reduced asthma symptomatology and perhaps prevention of asthma-related adverse effects on the fetus.

ACKNOWLEDGMENTS

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Objective: To evaluate the efficacy of intravenous labetalol versus oral nifedipine in the treatment of severe hypertension with pregnancy. 

Design: Prospective, non-randomized

Setting: Department of Obstetrics and Gynecology, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India

Subjects and Methods: Fifty pregnant patients with severe hypertension (blood pressure ≥ 160/110 mmHg).

Intervention: The patients were consecutively given either intravenous labetalol or oral nifedipine.

Main Outcome Measures: The speed and adequacy of control of blood pressure was compared in both groups.

Results: Both drugs were effective in the control of blood pressure, but nifedipine caused significant reduction of blood pressure in 20 minutes with a single dose (i.e., with the first dose (p = 0.03). The diastolic blood pressure reduction was also significant with nifedipine (15.1 ± 6 Vs 8.3 ± 2 mmHg) (p = 0.03). Average time required was also less with nifedipine (24 ± 8.2 Vs 44.21 ± 26.31 minutes, p = 0.006).

Conclusions: Both drugs effectively controlled the blood pressure in severe hypertension in pregnancy. However, nifedipine faired better than labetalol in time taken, reduction of diastolic blood pressure and number of patients responding with first dose (i.e., in 20 minutes).

INTRODUCTION

Hypertension in pregnancy is one of the main causes of maternal deaths in both developed and developing countries[1]. The main goal of treatment of hypertension in pregnancy is to safeguard the mother from the development of acute complications like cerebro-vascular accidents, eclampsia, target organ damage and maternal mortality while delivering a healthy infant[2-3]. According to the consensus report on high blood pressure, the ideal antihypertensive drug should be potent and safe, rapidly acting, controllable and without detrimental maternal or fetal side effects[4]. Labetalol, an α and β adrenergic blocker, produces rapid dose dependant reduction in blood pressure by decreasing the peripheral vascular resistance without causing reflex tachycardia and fetal distress[5-7]. Labetalol does not reduce cerebral perfusion and utero-placental blood flow, it has an anti-platelet aggregation property[8] and a fetal lung maturation accelerating influence[9] and it also decreases proteinuria. American College of Obstetricians and Gynecologists currently recommend labetalol as one of the first line antihypertensive medications in pre-eclampsia[10]. Intravenous labetalol has been available in India only recently.

On the other hand, nifedipine (calcium channel blocker) is easily available in India and a less expensive drug which can also be used in the treatment of severe hypertension in pregnancy. However, concomitant use of nifedipine and magnesium sulphate is supposed to cause neuromuscular blockade[11], maternal hypotension and fetal distress. Additionally, nifedipine has tocolytic effect and reflex tachycardia.

The present study was undertaken to compare the efficacy of intravenous labetalol for the treatment of severe hypertension in pregnancy, with nifedipine administered orally.

SUBJECTS AND METHODS

After institutional and ethical committee approval, a non-randomized trial was conducted in the Department of Obstetrics and Gynecology, Maulana Azad Medical
College and associated Lok Nayak Hospital, New Delhi from December 2006 and December 2008.

The study included patients selected according to the criteria given below. Fifty patients were included in the study.

**Inclusion criteria**

Pregnancy more than or equal to 20 weeks of gestation, having severe hypertension i.e., systolic blood pressure (SBP) of at least 160 mmHg and / or diastolic blood pressure (DBP) of at least 110 mmHg with or without proteinuria were included.

**Exclusion criteria**

Patients with cardiac failure, history of bronchial asthma, bradycardia (pulse rate < 60 beats per minute), allergic diathesis and eclampsia were excluded.

After taking history, doing a complete examination and taking informed consent, either intravenous labetalol or oral nifedipine were given to the patients consecutively. Patients were divided into two groups (i.e., group A - labetalol and group B - nifedipine).

**Group A:** Twenty five patients received intravenous labetalol (n = 25), 20 mg intravenous bolus dose initially, (if not effective within 20 minutes) followed by escalating doses of 40 mg (2nd dose), 80 mg (3rd dose), 80 mg (4th dose), and then 80 mg (5th dose) every 20 minutes until the therapeutic blood pressure goal of SBP < 160 mmHg and DBP < 110 mmHg was achieved or up to a maximum dose of 300 mg or five doses (Fig. 1).

**Group B:** Twenty five patients received oral nifedipine (n = 25), 10 mg oral dose initially, with repeated doses of 20 mg every 20 minutes until the therapeutic goal (SBP < 160 mmHg and DBP of < 110 mmHg) was achieved or up to a maximum dose of 90 mg or five doses (Fig. 1).

The patients were then put on oral maintenance dose of either oral labetalol 100 mg twice daily or oral nifedipine 10 mg twice daily in addition to a fixed dose of 250 mg thrice daily of α-methyl dopa to start with. The dose of labetalol and nifedipine were titrated to a maximum of 1200 mg of labetalol or 60 mg of nifedipine in divided doses in the two groups respectively.

The outcome measures were assessed in terms of the control of the blood pressure i.e., SBP < 160 mmHg and DBP < 110 mmHg. The time taken for the control of blood pressure, the number of doses required was noted and the patients were observed during the first two hours.

**Statistical analysis**

Student’s t test was applied for comparing age, fall in diastolic blood pressure, fall in systolic blood pressure and average time required to control blood pressure between the two groups. Fisher’s Z-test was used for comparing the proportion of blood pressure controlled in the two groups by single dose of individual drug. A p-value of < 0.05 was regarded as statistically significant

**RESULTS**

Table 1 shows the demographic data of the two treatment groups. There were no significant differences in ages between the two groups. The mean age at presentation was 24.5 years in group A and 25.35 years in group B. Seventy five per cent of patients were

<table>
<thead>
<tr>
<th>Patient classification</th>
<th>Group A (Labetalol) n = 25</th>
<th>Group B (Nifedipine) n = 25</th>
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<tr>
<td>Mean age (years)</td>
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<td>25.35 ± 3.74</td>
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![Flow chart showing methodology](image-url)
nulliparous in the group A and 45% of patients were para 1 in the group B. Most of the patients in both the groups were unbooked. Nineteen patients (76%) of group A and 17 patients (68%) of group B were pre-eclamptic patients (Table 1). The blood pressure control was achieved in both the groups fairly well. In nifedipine group, the control of blood pressure was achieved in all the patients. In labetalol group, blood pressure was controlled in 24 out of 25 patients, one patient who was not controlled with full dose, received nitroglycerin for control of hypertension. However, the number of patients controlled with the first dose of the drug was lower in labetalol group as compared to nifedipine group (10 / 25 Vs 20 / 25, p = 0.03). Mean doses requirement of labetalol and nifedipine were 113.4 ± 20 mg and 20.5 ± 10 mg respectively. Mean SBP reduction of labetalol and nifedipine at first 20 minutes were 14.4 ± 6 mmHg and 18.3 ± 5 mmHg respectively and there was no significant difference (p = 0.257) in SBP reduction in both the groups. There was significant difference (p = 0.03) in reduction of DBP in first 20 minutes between nifedipine (15.1 ± 6 mmHg) and labetalol (8.3 ± 2 mmHg) groups (Table 2). The average time required for control of blood pressure was 44.2 ± 26.31 and 24 ± 8.2 minutes in labetalol and nifedipine groups respectively and there was significant difference in between the two groups (p = 0.006) (Table 3).

**DISCUSSION**

Hypertension is one of the most common problems arising during the pregnancy complicating up to 15% of all pregnancies, and within this disorder, approximately one in four patients will experience an episode of severe hypertension[12]. Treatment of severe hypertension in pregnancy is mandatory as it decreases the incidence of maternal intracranial hemorrhage, hypertensive encephalopathy, abruptio placenta and maternal mortality. The maternal mortality from hypertensive disease has been studied for its attributing factors[13]. There is general agreement that rapid lowering of high blood pressure can reduce the maternal risk[14-16].

Labetalol and nifedipine, both are found to be safe drugs for the treatment of severe hypertension in pregnancy from the previous studies[17-20]. Previous reports[21,22] have indicated that there was apprehension in nifedipine use as the sublingual variety caused more sudden decrease in blood pressure, resulting thereby in overshoot hypotension and ischemia there upon. The oral variety does not seem to have this[23] effect as found in our study. There were minimal side effects in our patients with the use of either drug. No patient had sudden hypotension below 100 mmHg systolic during the initial two hours of treatment. Nifedipine achieved adequate control of blood pressure with only one dose in 20 / 25 patients whereas in the labetalol group only 10 / 25 patients achieved the control of blood pressure with one dose, and this difference was statistically significant (p = 0.03). Both drugs lowered the SBP in the first 20 minutes by 14.4 ± 6 mmHg and 18.3 ± 5 mmHg in labetalol and nifedipine group respectively and there was no statistically significant difference between the two groups. However, there was significant fall in the blood pressure particularly diastolic with nifedipine as compared to labetalol in the first 20 minutes. This is substantiated in other studies by Vermillion et al[20] and by Raheem et al[24]; these authors found that the use of nifedipine was associated with increase in urine output in addition to rapid control over blood pressure as compared to labetalol. Whether rapid fall in blood pressure is beneficial or not is unclear, particularly if it is not causing cerebral hypoperfusion or overshoot hypotension or any other adverse effects on the fetus or the mother.

Nevertheless, the importance of close monitoring of blood pressure every 20 minutes or earlier as need arises has to be emphasized as the patient can have hypotension if the drugs are not adequately titrated.

If the trends of blood pressure over two hours are carefully observed, it is evident that both drugs achieved fair control of blood pressure in our study.

### Table 2: Effects of drugs on blood pressure

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<th>Group B (Nifedipine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>24 / 25</td>
<td>25 / 25</td>
</tr>
<tr>
<td>Not adequate</td>
<td>1 / 25</td>
<td>0</td>
</tr>
<tr>
<td>Doses required to get the therapeutic blood pressure goal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st dose</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>2nd dose</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3rd dose</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>4th dose</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5th dose</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Successful treatment with first dose</td>
<td>10 (p = 0.03)</td>
<td>20 (p = 0.0007)</td>
</tr>
<tr>
<td>Amount of drug required (mg)</td>
<td>113.4 ± 20</td>
<td>20.5 ± 10</td>
</tr>
<tr>
<td>Fall in blood pressure in first 20 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>14.4 ± 6</td>
<td>18.3 ± 5 (p = 0.257)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>8.3 ± 2</td>
<td>15.1 ± 6 (p = 0.03)</td>
</tr>
</tbody>
</table>

### Table 3: Average time for control of blood pressure in minutes

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients who got BP controlled</th>
<th>Mean (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (Labetalol) n = 25</td>
<td>24</td>
<td>44.21 ± 26.3</td>
</tr>
<tr>
<td>Group B (Nifedipine) n = 25</td>
<td>25</td>
<td>24 ± 8.2 (p = 0.006)</td>
</tr>
</tbody>
</table>
Therefore, either drug can be used successfully in the control of hypertension in pregnancy. The use of nifedipine for control of severe hypertension in pregnancy had been proven in earlier studies as well. However, labetalol may be advantageous in delirious patient because of its intravenous route.

CONCLUSION
Both drugs effectively controlled the blood pressure in severe hypertension in pregnancy. However, nifedipine fared better than labetalol in time taken, reduction of DBP and number of patients responding with first dose (i.e., in 20 minutes).

REFERENCES
ABSTRACT

Objectives: The first total hip replacement (THR) in Nigeria was performed in 1974. But due to infrastructural decay in public institutions, arthroplasty outcome was poor. National Orthopedic Hospital, Enugu (NOHE) - a regional trauma and orthopedic centre took the initiative in 2008. This paper presents our preliminary results and lists our challenges in establishing this service in a resource-constrained economy.

Design: Prospective

Setting: NOHE, Nigeria

Subjects: Fifty-two patients who had primary hip arthroplasty between November 2008 and November 2010.

Method: Details of demographic data, joints affected, etiology, co-morbidities, anesthesia, postoperative treatment, complications, and follow-up were recorded, analyzed and challenges noted.

Intervention: Total hip replacement

Main Outcome Measures: Improvement in patient’s function and re-operation rate.

Result: Fifty-four THRs were done in fifty-two patients. Twenty nine (53.7%) patients were male. The mean age was 52 ± 2.4 years. Two patients had staged bilateral hip replacement. Twenty five (48.1%) patients had primary osteoarthritis. The commonest complaint at presentation was incapacitating hip pain. Half of the patients 26 (49.9%) had this pain for over four year. Trauma related secondary arthritis was responsible for 21 cases and old unreduced hip dislocation in five (9.6%) patients. Six patients had previous hip surgeries. Implant dislocation occurred in three (5.5%) patients. The functional status improved in all patients as shown by Harris Hip scores.

Conclusion: There is an absolute need to develop arthroplasty service in Nigeria. A good number of the cases were complex primary arthroplasties. Most of the patients were relatively young and will outlive their implant.

INTRODUCTION

Total hip replacement (THR) is undoubtedly the most successful procedure in orthopedics\(^1\). It brings a new lease of life by pain relief and improvement in hip function in patients with advanced osteoarthritis when conservative management has failed.

Since the work of Sir John Charnley on the hip arthroplasty in 1960’s, a lot of advances have been seen in this field of orthopedics\(^2,3\). The first THR in Nigeria was performed in 1974 at the University of Nigeria Teaching Hospital, Enugu. But due to sustained infrastructural decay in public institutions, the specialty of arthroplasty was poorly developed even though indications were there. Hitherto, few patients (who could afford it) were referred abroad. This practice over the years was associated with many problems; huge capital flight, poor patient follow-up and persistent underdevelopment of the specialty. The vast majority of patients with end stage osteoarthritis (OA) were either left to live with their pain and deformity or were offered arthrodesis or excision arthroplasty.

National Orthopedic Hospital, Enugu (NOHE) - a regional trauma and orthopedic training center took the initiative in 2008. To the best of our knowledge, no coordinated institutional arthroplasty center exists in Nigeria. The objectives of this paper were to present our preliminary results and to share our challenges in establishing this service in a resource-constrained economy.

SUBJECTS AND METHODS

This was a prospective study of 54 consecutive THRs done from November 2008 to November 2010. Details such as demographic data, joints affected, etiology, co-morbidities, anesthesia, postoperative treatment, complications, and follow-up were collected prospectively. The functional level of each patient was assessed pre and postoperatively, at six months...
and one year using Harris hip score. All patients had preoperative and immediate postoperative X-ray evaluation. The preoperative X-rays were classified based on Kellgren and Lawrence scale for primary osteoarthritis and Ficat and Arlet for avascular necrosis (AVN). The X-ray evaluation was repeated at three months, six months and one year follow-up as the case may be. All the operations were through anterolateral approach. The implant consisted of hydroxyapatite coated titanium femoral stem, 28 mm cobalt based alloy head and 28 mm UHMWP on metal shell (Corail Duraloc, DePuy International). All patients received prophylatic antibiotics - ceftriazone and metronidazole. Enoxaparin 40 mg daily for five days and compression bandaging were used for deep vein thrombosis (DVT) prophylaxis and the patients were mobilized on the first day post surgery. The major outcome measures were improvement in patient’s function and reoperation rate. Data analysis was done with SPSS software version 11. Descriptive statistics are provided. The study was approved by ethical committee of the hospital.

RESULTS
A total of 54 total hip replacement surgeries were done in 52 patients in two years. All the patients were pooled in a unit to create volume. Two patients had bilateral total hip replacements within three months. Twenty-nine (53.7%) were male while 25 (46.2%) were female, giving a male to female ratio of 1.2:1 (Fig. 1). Their ages ranged from 18 to 78 years with an overall mean of 52 ± 2.4 years (Table 1). Twenty-four were on the left side and 30 on the right side. The most common complaint at presentation was incapacitating joint pain. About half the patients (26, 49.9%) had this pain for over four years (Table 1).

![Genderwise distribution of patients](image1)

**Table 1: Duration of symptoms**

<table>
<thead>
<tr>
<th>Duration of symptom</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain &lt; 1 year</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Pain 1 - 3 years</td>
<td>23 (44.2)</td>
</tr>
<tr>
<td>Pain 4 - 6 years</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Pain 7 - 10 years</td>
<td>11 (21.1)</td>
</tr>
<tr>
<td>Pain &gt; 10 years</td>
<td>5 (9.6)</td>
</tr>
</tbody>
</table>

![Bilateral severe OA hip](image2)

Twenty-five (48.1%) patients had primary osteoarthritis that had progressed to advanced stage 4 (Kellgen and Lawrence scale) (Fig. 2). Trauma related secondary arthritis was responsible for 21 (40.4%) cases with poorly managed hip fractures accounting for 16 (30.8%) cases and old unreduced hip dislocation accounting for five (9.6%) cases (Table 2). Three of the patients with poorly managed hip fractures had failed angle blade plates. A total of six patients had previous hip surgeries (Table 3). The five patients...
with old unreduced posterior hip dislocation had posterior wall defect and false acetabulum. All cases presented to our center more than one year after initial injury and treatment by traditional bone setters with uncontained femoral heads; all underwent one-stage total hip arthroplasty. This group of patients was also younger with a mean age of 42 ± 2.3 years.

Avascular necrosis of the head of femur from sickle cell disease was noted in four (7.7%) patients. They were all stage IV (Ficat and Arlet staging, Fig. 3). Their mean age was 28 ± 3.4 years. All the sicklers had dense bone sclerosis and near obliteration of the proximal femoral medullary canal intraoperatively. One patient had femoral perforation during reaming. We did not observe painful postoperative sickling crises. All patients had oxygen saturation monitored during the surgery.

Patients had an average pre-operative Harris hip score of 45 (range of 35 - 47). Twenty-three patients had co-morbidities. The most common associated medical problem was uncontrolled hypertension in 14 patients. The others were diabetes mellitus in four, asthma in one and peptic ulcer disease in four patients. All the co-morbidities were well-controlled with medication before the THR.

Regional block was employed in all the surgeries except in five cases of failed spinal which were then converted to general anesthesia. Intra-operative blood loss varied from 400 ml – 1000 ml (mean blood loss 800 ml). Five patients received intraoperative blood transfusion, while seven others had postoperative blood transfusion in the ward.

All the patients were given intravenous antibiotics, ceftriaxone and metronidazole for five days. They also received parenteral analgesics for 48 hours before shifting to oral drugs. Enoxaparin 40 mg daily was given for five days and compression bandaging was used for DVT prophylaxis and the patients were mobilized on the first day post surgery.

The most important complication observed was implant dislocation in three (5.5%) patients. This was due to component mal-positioning. Two hips dislocated while in the hospital and one at home. Three of them had component repositioning and remained stable (Table 4).

Thirty one patients were discharged in the second week after surgery while the remaining twenty-one were discharged in the third week. In this group of patients, due to a longstanding pathology, rehabilitation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girdlestone excision arthroplasty</td>
<td>2</td>
</tr>
<tr>
<td>Angle blade plating</td>
<td>3</td>
</tr>
<tr>
<td>Hemiarthroplasty</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency (n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post spinal headache</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>Superficial wound infection- stitch sinus</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Dislocated implant</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Trochanteric fracture</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (3.7)</td>
</tr>
</tbody>
</table>
was slow. They were discharged on partial weight bearing with bilateral axillary crutches.

Follow up is on-going. Harris hip score at six months and one year post surgery improved to 90 in thirty five patients and 80 - 89 in seventeen patients. Most of them were satisfied with their progress so far. There was no mortality recorded.

DISCUSSION

Total joint replacement is a well-established procedure for the hip joint in the developed world. Although other joints have been replaced with variable outcome, hip replacement has been adjudged the most successful orthopedic operation[1].

In Nigeria, THR is at its infancy[4] although the first THR in Nigeria was done in 1974. The subspecialty could not advance due to sustained infrastructural decay in public institutions and the huge capital overlay made it an impossible venture for most private practitioners. Nigeria is a country of 150 million people with varying health needs. In this study, our patient population was a mixed bag of primary osteoarthritis (OA), post-traumatic secondary OA, sickle cell disease (SCD) etc., and they were relatively young.

We found the mean age of our patients to be 52 ± 2.4 years (range 18 - 78 years) . The import of having relatively younger patients is that many of them will outlive their implant and require revision. It has been shown that patients younger than 50 years at the time of surgery have a greater chance of requiring a revision than of dying; those around 58 years of age have a 50:50 chance of needing a revision and in those older than 62 years the prosthesis will normally outlast the patient. Patients over 77 years old have a greater than 90% chance of dying than requiring a revision whereas those around 47 years are on an average twice more likely to require a revision than die[5]. What this means for our region is that revision surgery should develop alongside primary arthroplasty.

Trauma is a known cause of morbidity and mortality in people under sixty years of age. In our environment there are many confounding factors to effective trauma care. Topmost among them are poverty, influence of traditional bone setters and faith healers. These were major reasons why hip dislocations were left unreduced for a reasonable length of time as observed in the study (Fig. 4).

SCD is prevalent in Nigeria[6]. Children with SCD were hitherto regarded as curse from the ‘spirit world’ and therefore were not adequately cared for. But with better understanding and awareness of genetic basis for this condition and improvement in their care some are surviving into adulthood. For these young SCD patients, development of AVN of the hip is one of the most limiting factors in their lives in terms of pain, level of activity, and function. We observed this in our cases. The treatment of these young patients is therefore, particularly important not only for socio-economic and humanitarian reasons, but also because of their improved life expectancy[7,8]. The cases in this study had severe adductor contractures. In addition, sclerotic proximal femur made reaming very difficult and could hardly accept anything above size 8 stem. Those who may have this patient population must be aware of this and make adequate arrangement for different implant sizes.

Primary OA was a common etiological factor, but not as common as in studies from the western world[9]. A number of factors may be responsible for this; Nigeria, although an oil producing country ranks low in human development index - life expectancy is low (47.56 years), and far below the usual age for primary osteoarthritis; high illiteracy rate results in lack of awareness about availability of service and low gross
national income per capita of $2,069 compared to the cost of arthroplasty\[9\]. These factors either collectively or singly may account for the low number. Some of the patients with primary OA have some features of AVN from prolonged steroid ingestion to relieve pain.

We observed male preponderance in this study. This is different from reports in literatures which show female preponderance\[8\]. There is scepticism on the part of our female folks on new procedures especially when it entails excision of a part and replacement with a foreign material.

Pain relief is the primary indication for THR\[4\]. In this study, pain was the most common indication for surgery. Most of our patients were virtually on daily non-steroidal anti-inflammatory drugs for over four years. This was at a great cost for the four patients that developed peptic ulcer disease.

Simultaneous arthroplasties are increasingly being performed during one single anesthetic event\[10\]. Two patients in this study had bilateral arthroplasty as staged operations. We were particularly worried about the effect of prolonged anesthesia and wound infection. The interval between the operations was three months. This was particularly beneficial to the patients who paid out of their pockets.

Regional (spinal) anesthesia was generally well-tolerated. This is particularly useful in the resource-scarce environment that we worked in; however, the incidence of post-spinal headache was high. This is similar to other reports\[11\].

We gave all our patients extended antibiotic therapy for two reasons. We were ‘paranoid’ about infection. Our theatre does not have laminar air-flow system and the same theatre is used for routine clean orthopedic cases. We believe that in addition to the general measures of ensuring clean theatre environment, 3 - 4 days antibiotic therapy is necessary until the procedure is well-standardized and facilities upgraded. No case of serious infection was observed in the cases so far.

Also, the length of hospital stay was long. A number of reasons were responsible for this. We were unsure of the home environment for most patients. The team of physiotherapists needed the time to guide the patients before discharge. Secondly, some of the difficult case had marked muscle wasting and required considerable time for rehabilitation post operation.

The need for deep vein thrombosis (DVT) surveillance and prophylaxis is well established in THR. However, the critical issue is the duration\[12\]. We gave our patients enoxaparin 40 mg daily for five days and continued with compression bandaging and low-dose aspirin. This corresponds to the time most of them were fully ambulant. The reason for this short duration regime was cost. We observed no case of overt DVT.

This was surprisingly similar to the low incidence reported in other studies with extended duration of treatment\[13\], but quite different from studies in the African-Americans\[14\]. References on the incidence of venous thrombo-embolism (VTE) among the blacks are commonly taken from studies on African-Americans, because there is dearth of studies among the native sub-Saharan black Africans. Our observation may be due to a number of factors. Immobility remains one of the most important factors for the development of DVT. Preoperatively, all our patients maintained their mobility despite extreme pathology and they were able to mobilize within the first two days post surgery. Secondly, most of our patients continued with low dose aspirin and compression bandaging even after enoxaparin was discontinued. Although there is strong evidence that the prevalence of VTE varies significantly among different ethnic / racial groups, the genetic, physiologic and clinical basis for these differences remain largely undefined\[15\]. Our finding supports the need to determine gene polymorphisms associated with VTE in Africans\[16\].

Posterior implant dislocation was the only major adverse event recorded and the only reason for re-operation in two patients and re-admission and re-operation in one patient. It was noted that the patients whose implants dislocated were those that had old unreduced posterior dislocation of the hip with posterior wall defect and false acetabulum as well. No mortality was recorded in this study supporting the low mortality rate associated with this procedure\[17\].

Technical difficulties encountered were due to the fact that our patients presented very late and so had bone defects, contractures about the joint, disuse muscles atrophy, limb length discrepancy, etc. The contractures make for difficult surgery with need to do a lot of soft tissue releases, thereby increasing post operative blood loss and operating time.

Some patients who had prior surgeries like girdlestone arthroplasty or had hardware in situ following a failed internal fixation of proximal femoral fracture presented a lot of surgical challenges. Indeed, some of these cases qualify for revision or complex primary arthroplasty. As reported by Sathappan, complex primary total hip arthroplasty (THA) is defined as primary THA in patients with compromised bony or soft-tissue states, including but not limited to dysplastic hip, ankylosed hip, prior hip fracture, protrusio acetabuli, certain neuromuscular conditions, skeletal dysplasia, and previous bony procedures about the hip\[18\].

For the conversion of Girdlestone excision arthroplasty to THR, locating the original acetabulum without image intensifier was technically challenging. The dense fibrous tissue was also very bloody. This could therefore, be regarded as a revision hip.

Conversion to total hip arthroplasty is generally accepted as the most successful procedure for failure
of fixation devices in hip fractures[19]. All the affected patients had a one stage procedure: implant removal and THR.

Some of the cases had major bone defect that required bone grafting. In absence of a bone bank, we overcame this problem by morselizing whatever is left of the femoral head, which in some cases was badly degenerated and collapsed.

Blood loss during surgery is often related to the difficulties encountered. Significant proportion of our cases was complex primary and six of them had previous surgical intervention with dense fibrosis. The average blood loss (both intra-operative and post-operative period) for our patients was 800 ml. This compares favourably with values in the literature[20].

CONCLUSION

There is an absolute need to sustain the development of arthroplasty service in Nigeria as shown by the variety of cases presented. A good number of the cases are complex primary arthroplasty and most of the patients are relatively young and will outlive their implant and therefore, require revision. Therefore, in addition to development of primary procedures, investment in capacity building for revision procedures should be started now to bridge the gap.

ACKNOWLEDGMENT

The authors are grateful to the Medical Director, Dr CB Eze, who made it possible for the development of this new specialty at the NOHE. Also, we own a debt of gratitude to Dr Sam Orakwe, Dr Ike Nwachukwu and Johnson & Johnson for providing the initial technical support.

Conflict of interest: The authors do not have any financial relationship with any of the companies manufacturing any of the products mentioned in this study. It was not supported by external funding of any sort.

REFERENCES

Towards Prevention of Diabetes in Offsprings of Type 2 Diabetic Patients

Amal I El-Sharakawy, Abdulrahman A Abdulla, Fatimah Bendhifari
Al-Yarmouk Health Center, Kuwait

ABSTRACT

Objectives: To reveal the extent of advice given about prevention of diabetes by diabetic parents to their children who had not developed diabetes yet, and reveal its relation to risk perception, and other parental factors related to diabetes

Design: Observational cross-sectional prospective

Setting: Al-Yarmouk Primary Health Care Center, Kuwait

Subjects and Methods: Two hundred type 2 diabetic patients with non-diabetic children were recruited for this study. A self-administered questionnaire was used to collect data.

Main Outcome Measure: The nature of advice given by diabetic parents to their non-diabetic children about adopting a healthy lifestyle to prevent or delay onset of diabetes

Results: Only 40.5% of diabetic patients advised their children to adopt a healthy behavior that may prevent development of type 2 diabetes. Giving advice was significantly associated with young age, not suffering from complications related to diabetes, recognizing the importance of giving advice and identifying unbalanced diet as a risk for diabetes. More than half the studied group recognized lack of exercise (63%), overeating (70%), and heredity (56.5%) as etiological factors for diabetes, while 48% recognized unbalanced diet, and only 3% could recognize the risk of diabetes among offspring.

Conclusion: A comprehensive behavioral, social, and physical environment approach is required to improve risk perception of etiological factors of type 2 diabetes especially unbalanced diet, to enable parents to provide an advice to their children about healthy behavior needed to prevent diabetes.

INTRODUCTION

Diabetes (DM) is considered a major public health problem not only because of its association with multiple medical complications, but also because of a continuously alarming rise in prevalence rate[1]. Its impact extends beyond the individual to affect health systems, social systems, and greatly undermines the economic resources of the whole country. The highest increase in the rates of the disease is observed mainly in the rapidly developing countries as the disease is mainly associated with changes in lifestyles, economic development and population growth[2]. Recent studies in Kuwait reveal a prevalence rate of 14.6%. During 2010, Kuwait ranked seventh for diabetes prevalence among the 216 countries for which data are available all over the world[3]. What adds to the complexity of the problem is the reported finding by the International Diabetes Federation (IDF) that an estimated 93.9% increase in the rates of DM in the Middle East-North Africa region during the period 2010-2030 is expected[3]. The high prevalence of type 2 diabetes in Kuwait, as well as other countries of Co-operation Council for the Arab States of the Gulf (GCC), is associated with higher prevalence of risk factors for this disease.

Multiple risk factors interact to lead to development of type 2 diabetes. These factors involve mainly genetic and environmental factors. One primary risk factor is a family history of diabetes. A considerable amount of evidence demonstrated that familial aggregation of diabetes is associated with an inherited defective gene that renders the individuals at a higher risk of diabetes[4]. Other environmental and behavioral risk factors suggested by the IDF include physical activity that is closely linked to overweight and obesity. Other non-modifiable factors included age, race, ethnicity, and gestational diabetes[4].

Efforts directed towards prevention or delaying onset of diabetes among the high-risk group depends mainly on changing or controlling the modifiable behavioral risk factors of type 2 diabetes, namely, amount of daily activity or exercise, balanced eating, and amount of daily consumed food[5]. Diabetic
parents can play an important role in implementing the preventive programs dealing with these risk factors through communicating the concepts and importance of adopting these healthy behaviors to their children who are actually at a higher risk of developing type 2 diabetes\[2\]. However, they have first to recognize the etiological factors of type 2 diabetes and then advise their children to adopt these behaviors\[8\]. Review of the available literature did not reveal any studies carried out in Kuwait on this subject. Thus the current study was planned to reveal the extent of giving advice about prevention of diabetes given by diabetic parents to their children who had not developed diabetes yet, and reveal its relation to recognizing the etiological risk factors, risk perception, and other parental factors related to diabetes.

**Study hypothesis**
Recognition by diabetic parents of etiological factors of diabetes and their risk perception as well as their physical health status would affect their ability to advise their children about adopting a healthy lifestyle to avoid development of diabetes.

**SUBJECTS AND METHODS**
An observational cross-sectional study design was adopted for this purpose. The study was carried out at the Al-Yarmouk Health Center, Kuwait. All patients with type 2 diabetes aged less than 75 years and having non-diabetic children aged between 20 and 50 years were candidates for this study. Those suffering from mental retardation were excluded. Out of all diabetic patients attending the health center, only those fulfilling the entry criteria were included. A total of 231 eligible diabetic patients were recruited during the study period. Out of these, 31 patients refused to share in the study giving a response rate of 86.6%. The study covered the period from December 2011 to April 2012.

**Tools of the study**
A specially designed questionnaire was prepared for this study. It consisted of three parts. Part one dealt with socio-demographic characteristics of patients and included: age, sex, nationality, educational level, family history of diabetes, and living with offspring in the same house. Part two consisted of four questions in addition to measuring weight and height and calculation of body mass index. These four questions covered the physical status of the patient, namely, duration of diabetes, type and form of treatment, whether suffering from complications of diabetes, and hospitalization related to the disease. Part three of the questionnaire dealt with risk perception about diabetes. Four questions dealt with recognizing etiological factors of diabetes, namely, inactivity (lack of exercise), overeating, unbalanced diet and heredity.

In addition one question dealt with risk of suffering from diabetes for offsprings with diabetic or non-diabetic parents. The main outcome question of this study was whether the parents actually advised their children to adopt a healthy lifestyle behavior. Their opinion about the necessity of giving their children an advice about adopting healthy behavior was also verified.

A pilot study was carried out on 20 diabetic patients (not included in the final study) to test the clarity and applicability of the study tools.

**Data Management**
A pre-coded sheet was used. Data were fed to the computer directly from the questionnaire. The Excel program was used for data entry. Data entry was verified before analysis. Body mass index was calculated according to the following formula: weight [kg] / (height [meter])\(^2\). The WHO recommendation for classification of BMI was adopted with the following cut off points: < 18.5 (underweight), 18.5 < 25 (normal weight), 25 < 30 (overweight), ≥ 30 (obese)\[9\].

**Statistical analysis**
Before analysis; data were imported to the Statistical Package for Social Sciences (SPSS) version 17 which was used for both data analysis and tabular presentation. The following statistical measures were utilized:

- **Descriptive measures:** count, percentage, arithmetic mean, and standard deviation
- **Analytic measures:** Mann-Whitney test was used for quantitative variables with non-normal distribution

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 (42.0)</td>
</tr>
<tr>
<td>Female</td>
<td>116 (58.0)</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
</tr>
<tr>
<td>Kuwaiti</td>
<td>151 (75.5)</td>
</tr>
<tr>
<td>Non-Kuwaiti</td>
<td>49 (24.5)</td>
</tr>
<tr>
<td>Educational certificate</td>
<td></td>
</tr>
<tr>
<td>Less than secondary</td>
<td>83 (41.5)</td>
</tr>
<tr>
<td>Secondary</td>
<td>42 (21.0)</td>
</tr>
<tr>
<td>University</td>
<td>70 (35.0)</td>
</tr>
<tr>
<td>Postgraduate (master/doctorate)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Under insulin treatment</td>
<td>45 (22.5)</td>
</tr>
<tr>
<td>Experiencing complications of diabetes</td>
<td>127 (63.5)</td>
</tr>
<tr>
<td>Hospital admission related to diabetes</td>
<td>44 (22.0)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>159 (79.5)</td>
</tr>
<tr>
<td>Living with their offspring</td>
<td>162 (81.0)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>56.4 (10.7)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>31.2 (6.6)</td>
</tr>
<tr>
<td>Duration of diabetes in years</td>
<td>8.6 (7.6)</td>
</tr>
</tbody>
</table>
while Student t test was used for quantitative variables with normal distribution. Odds ratio (OR), 95% CI (confidence interval), and Mantel Haenszel Chi square were used for studying association. Also Chi square was used to compare qualitative variables of socio-demographic characteristics. Multiple logistic regression technique was used to identify significant predictors of advising offspring after adjusting for the confounding effect of other variables. The level of significance selected for this study was a p-value of ≤ 0.05.

All the necessary approvals for carrying out the research were obtained. The Ethical Committee of the Kuwaiti Health Science Center and Kuwait Institute for Medical Specializations (KIMS) approved the research.

**RESULTS**

Table 1 shows characteristics of the studied population. The majority were female (58.0%), Kuwaiti (75.5%) holding less than a university certificate (65.6%). The mean age of the whole group was 56.4 ± 10.7 years, with a mean body mass index indicating obesity (31.2 ± 6.6 kg/m²), and suffering from diabetes for a mean period of 8.6 ± 7.6 years. Most of the studied diabetics were living with their offspring (81.0%) and had a positive family history of diabetes (79.5%). Although, only 22.0% were receiving insulin yet 63.5% suffered from one or more complications of diabetes. Those admitted to hospital due complications of diabetes constituted 22.0% of the sample.

<table>
<thead>
<tr>
<th>Parental factors</th>
<th>Yes n (%)</th>
<th>No n (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>39 (46.4)</td>
<td>45 (53.6)</td>
<td>1.53 (0.86 - 2.71)</td>
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<tr>
<td>Female</td>
<td>42 (36.2)</td>
<td>74 (63.8)</td>
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<td>Kuwait</td>
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<td>88 (58.3)</td>
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<td>Education</td>
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<tr>
<td>University +</td>
<td>38 (50.7)</td>
<td>37 (49.3)</td>
<td>1.96 (1.09 - 3.51)</td>
<td>0.0236*</td>
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<td>&lt; University</td>
<td>43 (34.4)</td>
<td>82 (65.6)</td>
<td></td>
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<tr>
<td>Obese</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (38.1)</td>
<td>65 (61.9)</td>
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<td>No</td>
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<td>54 (56.8)</td>
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<tr>
<td>Yes</td>
<td>31 (24.4)</td>
<td>96 (75.6)</td>
<td>0.15 (0.08 - 0.28)</td>
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<td>50 (68.5)</td>
<td>23 (31.5)</td>
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<td>102 (64.2)</td>
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<td>24 (58.5)</td>
<td>17 (41.5)</td>
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<td>Living with their offspring</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>67 (41.4)</td>
<td>95 (58.6)</td>
<td>1.20 (0.58 - 2.51)</td>
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<td>No</td>
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<td>24 (63.2)</td>
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<tr>
<td>Mean ± SD</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.2 ± 8.7</td>
<td>59.2 ± 11.1</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>8.5 ± 7.7</td>
<td>8.7 ± 7.6</td>
<td></td>
<td>0.959</td>
</tr>
</tbody>
</table>

* Significant : p ≤ 0.05; OR = Odds ratio; CI = Confidence interval
Table 2 reveals attitude of diabetics and their actual provision of advice to their offspring about prevention of diabetes. Just a total of 81 (40.5%) out of the studied diabetic subjects actually advised them about how to adopt preventive measures, while two thirds (66.5%) recognized that it is necessary to give advice to their offsprings.

Table 3 portrays the relationship between giving advice about diabetes to offspring and parental factors. Those holding a university or higher certificate were more significantly likely to give advice to their offspring (OR = 1.96, 95% CI = 1.09 – 3.51, p = 0.0236). Those experiencing diabetic complications significantly tended not to advice their offspring as only 24.4% of them passed on this advice compared with 68.5% of those without complications (OR = 0.15, 95% CI = 0.08 – 0.28, p < 0.001). The same trend was noticed for those with positive family history of diabetes as only 35.8% of those with positive family history advised their offspring about diabetes prevention compared with 58.5% of those with negative family history of diabetes (OR = 0.39, 95% CI = 0.19 – 0.79, p = 0.0085). Diabetic patients giving advice to their offspring were significantly younger than those not giving advice (52.2 ± 8.7 compared with 59.2 ± 11.1 years, p < 0.001). Sex, obesity, regimen of treatment, hospital admission related to diabetes, living with offspring and duration of diabetes were not significantly associated with advising offspring about prevention of development of diabetes.

Table 4 reveals the relationship between actually advising children about prevention of and recognition of etiological factors of diabetes. Univariate analysis showed that recognizing lack of exercise (OR = 2.53, 95% CI = 1.36 – 4.71, p = 0.003), unbalanced diet (OR = 2.37, 95% CI = 1.26 – 4.46, p = 0.0069), risk perception of diabetes (OR = 7.87, 95% CI = 0.90 – 68.66, p = 0.0291), and necessity of giving advice about diabetes prevention to offspring (OR = 47.55, 95% CI = 11.16 – 202.49, p < 0.001) are significantly associated with actually advising offsprings about diabetes. The only etiological factor that was not significantly associated with advising offspring was overeating (OR = 1.39, 95% CI = 0.74 – 2.61, p = 0.3008).

Diabetic patients giving advice to their offspring were significantly younger than those not giving advice (52.2 ± 8.7 compared with 59.2 ± 11.1 years, p < 0.001). Sex, obesity, regimen of treatment, hospital admission related to diabetes, living with offspring and duration of diabetes were not significantly associated with advising offspring about prevention of development of diabetes.

Table 5 reveals the relationship between actually advising children about prevention of and recognition of etiological factors of diabetes. Univariate analysis showed that recognizing lack of exercise (OR = 2.53, 95% CI = 1.36 – 4.71, p = 0.003), unbalanced diet (OR = 2.37, 95% CI = 1.26 – 4.46, p = 0.0069), risk perception of diabetes (OR = 7.87, 95% CI = 0.90 – 68.66, p = 0.0291), and necessity of giving advice about diabetes prevention to offspring (OR = 47.55, 95% CI = 11.16 – 202.49, p < 0.001) are significantly associated with actually advising offsprings about diabetes. The only etiological factor that was not significantly associated with advising offspring was overeating (OR = 1.39, 95% CI = 0.74 – 2.61, p = 0.3008).

The model could correctly classify 81.5%, with correction prediction ratio of those giving advice of 67% and 96% of those not giving advice.
Table 5 shows significant predictors of giving advice to offspring using stepwise forward likelihood multiple logistic regression. The first step for identifying the significant predictors was entering all the independent variables to the model. In the second step, all variables with 0.10 or less p-value were entered into a stepwise forward likelihood multiple logistic regression model. After adjusting for the confounding factors, only four factors proved to be significantly predicting advising offspring about diabetes. These factors included recognizing the importance of giving the advice as well as unbalanced diet as an etiological factor of diabetes. Young age and not suffering from diabetes complications proved to be significantly associated with advising offspring after adjusting for the confounding factors.

**DISCUSSION**

The growing diabetes pandemic that is spreading all over the world necessitates more attention and rapid effective programs to control its impact. A wide spectrum of interventions to prevent diabetes or delay its onset as well as control its complications is available. The feasibility and effectiveness of these interventions varies widely. Although communicating the potential risks of diabetes and recognition of the behavioral factors that may be closely linked to the disease is the main responsibility of the primary health care staff, parents can play an active role to educate their children who are at higher risk for developing type 2 diabetes. Recent studies have illustrated the potential for intervention in persons with impaired glucose tolerance to reduce progression to type 2 diabetes. A study in the United States showed that lifestyle intervention (diet and exercise) reduced the risk of this progression by 58%. Two other large-scale studies from China and Finland demonstrated effects similar to the American study. In the Finnish study, the cumulative incidence of diabetes after four years was 11% in the intervention group and 23% in the control group. During the trial, the risk of diabetes was reduced by 58% (p < 0.001) in the intervention group, and was directly associated with changes in lifestyle.

Proper risk perception of diabetic parents and adopting a positive attitude toward prevention of diabetes among their offspring can urge them to educate their children and guide them to adopt a healthy behavior. Thus, the current study was formulated to investigate the factors that can stimulate parents to advise their offspring about diabetes prevention and the factors affecting the giving of this advice. Several studies were carried out in Kuwait to reveal knowledge of diabetic patients about etiological risk factors and management procedures to deal with the disease. One study revealed that mean score for the total knowledge test was 58.9%. Knowledge deficits were apparent in the questions related to diet and self-care.

One study carried out in Japan revealed that diabetic disease status was related to giving advice. Use of insulin or oral treatment and the presence of complications were related to giving advice. However, the results of this study revealed that patients with complications were less likely to advise their children (OR = 0.15, 95% CI = 0.08-0.28). The same trend was noticed for family history as those with positive family history were also less likely to advise their children (OR = 0.39, 95% CI = 0.19-0.79). The absence of complications might be due to adopting effective techniques and behavior that might stimulate them to advise their children to adopt these successful lifestyles. Also, a negative family history which means that the diabetic parent is the only person in the family with diabetes might make them feel that they have a greater responsibility toward advising their children.

Delaying the onset of type 2 diabetes depends essentially on implementing successful lifestyle intervention strategies. Cognitive and behavioral strategies have been used to reduce weight through dietary restriction and increased physical activity. However, to be able to implement these healthy behaviors; diabetic patients must first recognize the importance as well as the role of these factors in preventing diabetes. However, the association between risk perception and behavior has been inconsistent; while some studies revealed a positive association between risk perception and health behaviors, other studies failed to demonstrate this association. This might be attributed to the poorly specified relationship between behavior and risk perception. Also, other factors may affect relationship such as knowledge of diabetes factors, perceived personal control, or the degree to which one believes that risk is modified by one’s action, and optimistic bias, or one’s assessment of their risk compared with others like them.

One finding about risk perception revealed by this study is the very low recognition of the probability of children to develop type 2 diabetes in presence of positive family history when compared with negative history. Similar findings were revealed by a Korean study among offspring of diabetic parents where only 9.9% of the study children could correctly perceive their risk of developing diabetes.

Multiple logistic regression revealed that young age, not experiencing complication related to diabetes, and recognizing the importance of the role of healthy behavior in preventing diabetes development as well as specifically recognizing the role of unbalanced diet are significant predictors for advising children. In Japan, a similar study dealing with passing of advice to children revealed that being male, living with offspring, hospitalizations related to diabetes, suffering from complications, risk perception, and...
recognizing the role of lack of exercise as an etiological factor for diabetes proved to be significantly associated with giving advice to children in the multiple logistic regression[5]. The differences between the two studies might be attributed to the difference in culture and the high prevalence of factors such lack of activity and obesity.

Although this study dealt with a relatively large number and a high response rate, yet, due to the nature of the study, some limitations can be identified. These limitations include dealing only with a sample from one primary health care center which might undermine generalization of the results. The study is a cross-sectional one, while perception of risk would be more appropriately a longitudinal study. Thus, it is recommended that a large study sample involving diabetic patients representing the whole state of Kuwait be undertaken in order to confirm the results of this study.

CONCLUSION
The findings of the current study illustrate the need to improve the knowledge and perception of type 2 diabetic patients about the etiological factors of diabetes as well as perception of risk of development of diabetes among their offsprings. It is essential to encourage parents to advise their children to adopt healthy lifestyle behavior. In this context, a comprehensive approach that addresses behavioral, social, and physical environment interventions is expected to achieve the required outcomes. Proper risk communication from primary health care workers to parents and their children needs more attention in the primary health care units.

REFERENCES
ABSTRACT

Objectives: To present the results of our experience with stereotactic surgery, which is a safe and minimally invasive technique, in the field of neurosurgery.
Design: Prospective study
Settings: Department of Neurosurgery, Ibn Sina Hospital, Kuwait
Subjects and Methods: Forty patients underwent stereotactic surgery for diagnostic and therapeutic purposes during the five years between 2006 and 2011. There were 26 male and 14 female patients with a mean age of 47 years (range 9 – 70 yrs). Twenty seven (67.5%) patients had diagnostic brain procedures and 13 (32.5%) had diagnostic as well as therapeutic procedures. The stereotactic surgery was carried out with the help of computerized tomography (CT) - guided Leksell stereotactic frame® and Leksell SurgiPlan® software.

Intervention: Stereotactic surgery

Main Outcome Measures: Outcome of surgery and complications

Results: Stereotactic biopsies confirmed 28 (70%) patients with brain tumors; six (14%) with cerebral infections, four (10%) with multiple sclerosis and one with cerebral infarction. Stereotactic aspirations were performed in nine patients; four with cystic brain tumors and five with brain abscesses. Stereotactic insertion of Ommaya reservoir was performed in four patients with cystic brain lesions. Complication, related to the procedure was observed only in one patient and was managed conservatively. No other morbidity or mortality was noted.

Conclusions: Stereotactic surgery is a minimal invasive technique that helps the neurosurgeon in further planning of an appropriate treatment after tissue biopsy. It can also be used as primary mode of treatment in patients with brain abscesses, cysts and intracranial hematomas.

INTRODUCTION

Most neurosurgical patients can be diagnosed correctly on the basis of the natural history of their brain disorders and after clinical, laboratory and imaging findings but in some cases, diagnosis is difficult and the treatment is based on presumptive diagnosis. Stereotactic surgery is an image-guided technique which is used to detect the nature of lesion and decide about the appropriate treatment plan. This technique is used for an accurate localization of anatomical or pathological brain structures in three-dimensional (3-D) space.

Leksell stereotactic system is unique for its simplicity, accuracy and versatility [1]. It is light weight frame and all three (x, y and z) coordinates can be calculated quickly from a 2-dimensional image without a computer. Stereotactic biopsy is used as a diagnostic tool to obtain tissue samples that are suspicious for tumors, infections, infarctions or other brain pathologies like neurodegenerative disease. This is the most accurate method of taking biopsies in deep or highly functional areas of the brain and in patients with multiple brain lesions or in medically compromised patients with minimal morbidity and mortality [2-4].

Stereotactic aspiration is a valuable procedure in this field for the primary treatment of different brain tumors like gliomas (cystic part), craniopharyngiomas [5] and colloid cysts [6-7].

Stereotactic drainage is also a treatment of choice for brain abscesses. Kondziolka et al [8] treated 16 patients with deeply located brain abscesses using this

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technique for diagnosis and abscess drainage. Lunsford et al.\[9\] reported good results with overall bacteriologic identification of 97% and cure rates of 72% in patients with brain abscesses. Stereotactic aspirations of intracerebral hypertensive hemorrhages (acute or subacute) have shown encouraging results\[10\]. Catheter reservoirs may be implanted into the hematoma, followed with streptokinase or tissue plasminogen activator injections to lyse the clot\[11\].

Although it is a minimally invasive technique, yet complications have been reported. Sometimes, sample of the brain tissue taken for biopsy may be non-diagnostic and may warrant a repeat biopsy. Other risks include intracranial hemorrhage, infection or seizures.

Appuzo et al.\[12\] reported 1% morbidity (intracranial hemorrhage, infection, increased neurological deficit and seizures) and 0.2 % mortality. Lunsford et al.\[13\] reported postoperative complications in 2.9% (77) patients in a series of 2651 patients who underwent different stereotactic procedures. Out of those, intracranial hemorrhage occurred in 55 (2.07%) patients; 11 (0.41%) had local infections at pin sites; 11 (0.41%) patients had post-procedural seizures. Two (0.075%) patients died from the complications of the procedure. Although some centers are currently migrating to frameless stereotactic procedures, their complication rates are yet to be reported\[13\].

PATIENTS AND METHODS

Between 2005 and 2011, we have managed 40 patients with stereotactic surgery. The patients were selected on the basis of following diagnostic and therapeutic indications.

**Diagnostic**
1. Tumors not correlating with their natural history
2. Multiple brain lesions
3. Small and deeply located tumors
4. Patients in good clinical condition (Karnofsky score > 70)

**Therapeutic**
5. Cystic lesions that need aspiration
6. Intracranial abscesses

The mean age of the patients was 47 years (range 9 - 70 years). There were 26 male and 14 female patients. Most of the patients presented with occasional headaches followed by nausea. Five patients presented with focal seizures and 12 with neurological deficits. Twenty patients had lesions, located in the supratentorial region, 12 in the thalamic and basal ganglia area, two in the suprasellar region and seven had multiple intracranial lesions. Stereotactic surgery was performed with computed tomography (CT)/magnetic resonance imaging (MRI) - guided Leksell stereotactic system® and Leksell SurgiPlan® software v2.20. The procedure started with fixation of Leksell frame to the head after conscious sedation and local anesthesia (Fig. 1). All the patients underwent CT scan with contrast after the attachment of the fiducial box to the frame. All the brain images were exported to the computer workstation through Diicom system.

**RESULTS**

Stereotactic biopsy established brain tumors in 28 (70%) patients, brain abscesses in five (12.5%) and
neurodegenerative diseases (multiple sclerosis) in four (10%) patients. One had fungal infection (Aspergilliosis) and another had brain infarction (Stroke). The biopsy was negative in one patient and was not repeated due to refusal by the relatives (Fig. 1). Patients with stroke and multiple sclerosis were referred to neurology for their management. Patients with pyogenic brain abscesses were treated by stereotactic aspiration along with administration of adequate antibiotics (Fig. 3a & 3b). All these patients recovered and are doing well at two to five years follow-up. Patient with cerebral fungal infection was managed conservatively with antifungal drugs and recovered. Among 28 patients with brain tumors, 21 were diagnosed with gliomas of different grades according to World Health Organization (WHO) grading system; (4 patients with Grade I; 3 patients with Grade III; 14 patients with Grade IV). The other pathologies were lymphoma in two, craniopharyngioma in two, brain metastasis (from lung carcinoma) in one, malignant melanoma in one and tuberculoma in one patient (Table 1). Out of 28 patients with brain tumors, eight (28.6%) patients were managed with stereotactic therapeutic procedures. Stereotactic aspiration of the cystic part of the tumor was performed in four patients (2 patients with GBM; one with pilocytic astrocytoma and one with malignant glioma) and insertion of Ommaya reservoir was done in four patients (2 in pilocytic astrocytomas; one in GBM and one in recurrent craniopharyngioma). After the procedure, all the patients were referred for chemotherapy and radiation therapy. All the patients with GBM, lymphoma, recurrent craniopharyngioma, malignant melanoma were without mass effect

<table>
<thead>
<tr>
<th>Table 1: Results of stereotactic biopsy of 28 patients with brain tumors done at Ibn Sina Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological diagnosis</strong></td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Gliomas (N = 21 patients)</strong></td>
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<tr>
<td>Pilocytic Astrocytomas (WHO* Grade I)</td>
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<td>Anaplastic Astrocytomas (WHO Grade III)</td>
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<td>Glioblastoma Multiforme (WHO Grade IV)</td>
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<td>Anaplastic Gangliogioma</td>
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<td><strong>Others (N = 7 patients)</strong></td>
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<tr>
<td>Lymphomas</td>
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<tr>
<td>Tuberculoma</td>
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<tr>
<td>Brain Metastasis (Lung Carcinoma)</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
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</table>

* WHO- World Health Organization
and were referred for chemotherapy and radiation therapy. The patient with brain metastasis was further investigated and his origin of the primary disease was found to be in the lungs. The patient was referred to radiation oncologist for further management.

Stereotactic drainage of the intracranial abscess was performed in five patients. Pus was sent for culture sensitivity and postoperatively, patients were managed conservatively with antibiotics. Post surgical imaging showed reduction in size of the abscess cavities and clinically all the patients improved.

Post-operative complication occurred in one patient. This was asymptomatic hemorrhage after tissue biopsy which was managed conservatively. There was no other procedure-related morbidity or mortality.

**DISCUSSION**

Stereotactic surgery has been recognized since many decades after the use of freehand biopsy techniques resulted in too many postoperative complications.[14-16]

Stereotactic surgery either for diagnosis or treatment provides us precision, accuracy and safety to localize the target in the brain. Stereotactic biopsy stresses the importance of histological diagnosis with low morbidity and zero mortality. Many reports are published in the literature on the safe use of this technique and a tissue diagnosis is always required prior to treatment for most cerebral lesions. In their early experience, Lunsford et al.[17] published results of 102 patients with brain disorders who were referred to University of Pittsburgh for surgical exploration, using CT-guided stereotactic system. All the patients were referred because of critical size and location of the lesions in brain. Diagnostic stereotactic biopsy demonstrated diagnosis in 98 (96.1%) patients. Direct therapeutic intervention using this technique was possible in 26 (25.5%) patients. There was no morbidity and mortality seen in this early series. According to them, histological diagnosis must be sought in all patients with symptomatic brain lesions regardless of their size or location and “Empiric” forms of therapy are no longer justified in the age of CT scanning. Lunsford et al.[18] reported another series of 39 patients with craniopharyngiomas who underwent multimodality stereotactic techniques. Cystic craniopharyngiomas were treated successfully with stereotactic implantation of radioactive P32 in the cystic cavity of the tumor. The success rate was 96%. Kondziolka et al.[9] reported a series of 29 patients with brain abscess. Out of these, 22 (76%) patients had stereotactic abscess drainage with purulent centers and seven (24%) patients underwent lesion biopsy for diagnosis. Twelve patients with large abscess of diameter > 3 cm, underwent stereotactic insertion of drainage catheters. Long-term clinical and imaging follow-up confirmed disease resolution in 21 patients (72%) and eventual abscess resolution occurred in an additional six patients (21%), who required multiple procedures. Lakecivic et al.[19] published an article to differentiate the results of survival and outcome of patients with malignant brain gliomas who were treated by different modes. The control group of 21 patients had undergone craniotomy and surgical excision, followed by oncological protocol while the case group of 11 patients underwent stereotactic biopsy followed by oncological protocol. The majority of patients diagnosed by a stereotactic biopsy survived for more than two years. The survival and outcome for the patients in whom a stereotactic biopsy was performed were notably better compared to the patients who were diagnosed after surgical excision. Consequently, it appears that a stereotactic biopsy is a better option for primary treatment of patients with malignant brain gliomas when the survival and quality of life are concerned. Broggi et al.[20] published their experience in 35 patients who underwent stereotactic biopsy for deeply located lesions. According to them, the biopsies confirmed the diagnosis based on clinical and imaging findings in 25 patients but in 10 patients the histological diagnosis was different from the presumptive one. The treatment option was changed in these ten patients. Ostertag et al.[4] reported their experience with 302 cases of stereotactic biopsy and advocated that exploratory craniotomies, risky free-hand punctures and aspirations deep in the brain should not be done without prior diagnosis.

Our report emphasizes the importance of histological diagnosis to avoid the hazards of treatments based on clinical and radiological findings. Only one of 40 patients had complication, which shows safety profile of frame based stereotactic surgery.
CONCLUSION

Results of our study showed that stereotactic surgery is a safe and accurate technique which is introduced and applied safely in Kuwait for the management of different brain disorders.

REFERENCES

Synergy between Dendritic Cell-Based Vaccine and Anti-CD137 Monoclonal Antibody in the Treatment of Mouse Renal Cell Carcinoma

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ABSTRACT

Objective: Therapeutic efficacy of dendritic cell-based vaccine for renal cell carcinoma remains limited. In this study, we investigated whether anti-CD137 monoclonal antibody is capable of potentiating anti-tumor effect of dendritic cell-based vaccine.

Design: Experimental study

Setting: Research laboratory

Subjects: Balb/c mice (8-10 weeks old)

Interventions: A renal cell carcinoma model was established by subcutaneous injection of Renca tumor cells into Balb/c mice on day 0. After three days, tumor-bearing mice were treated with Renca tumor lysate-pulsed dendritic cells (i.e., dendritic cell-based vaccine), anti-CD137 monoclonal antibody, or combination of Renca tumor lysate-pulsed dendritic cells with anti-CD137 monoclonal antibody. Mice were killed on day 20 after tumor cell inoculation, and spleens were harvested for analysis of anti-tumor immune responses.

Main Outcome Measures: The anti-tumor immune responses were analyzed by measuring proliferation and activity of T cells, which have the ability to kill tumor cells. The anti-tumor effect was assessed by measuring tumor size.

Results: The combination therapy with Renca tumor lysate-pulsed dendritic cells and anti-CD137 antibody significantly increased T-cell proliferation and activity, and significantly inhibited tumor growth, compared with a single treatment with Renca tumor lysate-pulsed dendritic cells or anti-CD137 antibody.

Conclusion: These results suggest that combination therapy can enhance anti-tumor effect by increasing T-cell proliferation and activity.

INTRODUCTION

Human renal cell carcinoma accounts for approximately 2 - 3% of all adult cancers[1]. It has the third highest mortality rate among genitourinary malignancies, with an estimated 12,000 deaths per year[2,3]. Incidence rates for renal cell carcinoma have been increasing continuously by 2 - 3% per year[1,2]. More than 30% of renal cell carcinoma patients have metastatic disease at the time of diagnosis, thereby losing the chance of an operation[3]. In addition, 30% of patients with primary localized renal cell carcinoma will subsequently develop metastatic spread after radical nephrectomy[4]. Metastatic renal cell carcinoma is resistant to conventional therapies, such as chemotherapy and radiotherapy[5]. As a result, these patients with metastatic renal cell carcinoma have a poor prognosis with 2-year survival rate of < 20%[6].

The spontaneous regression of metastases has been reported in 1 - 6% of metastatic renal cell carcinoma patients[7]. Furthermore, many studies have revealed infiltration of renal cell carcinoma tissue with T lymphocytes and dendritic cells[8]. These findings suggest that immune system plays an important role in controlling renal cell carcinoma growth. Therefore, the present treatment strategy for renal cell carcinoma is to stimulate the patient’s immune system to increase anti-tumor immune response by using immunostimulatory cytokines, such as interferon-α and interleukin-2[9]. Clinical trials have shown that cytokine therapy with interferon-α and interleukin-2 can produce objective
responses in 10 - 15% of patients, but is associated with severe toxicity\textsuperscript{4,10}. Hence, new immunotherapeutic approaches with more effective anti-tumor activity and less toxicity are urgently required.

The recent trend in cancer immunotherapy has been directed toward dendritic cell-based vaccine. It can induce anti-tumor immune response by activation of tumor-specific T lymphocytes\textsuperscript{11}. In 14 clinical studies, 197 patients with metastatic renal cell carcinoma underwent treatment with dendritic cell-based vaccine\textsuperscript{12,13}. According to the World Health Organization criteria, clinical responses to vaccine are defined as follows\textsuperscript{13}.

Complete response means complete disappearance of tumor; partial response means ≥ 50% decrease in tumor size without the appearance of new metastases; stable disease means < 50% decrease or < 25% increase in tumor size; and progressive disease means > 25% increase in tumor size or the appearance of new metastases. Out of the 197 patients, 73 (37%) had clinical responses, eight partial responses and 61 disease stabilizations\textsuperscript{13,14}. Only mild side-effects, such as low-grade fever, fatigue, diarrhea, flu-like symptoms, and local reactions around the injection site, were observed in these patients. Though dendritic cell-based vaccine had encouraging results in the treatment of metastatic renal cell carcinoma, clinical response rate remained limited. Dendritic cell-based vaccine was administered in combination with interleukin-2 to treat patients with metastatic renal cell carcinoma in order to improve vaccine efficacy\textsuperscript{14}. However, clinical response rate was 40%, similar to single treatment with dendritic cell vaccine. Therefore, new approaches to significantly increase vaccine effect are needed.

The CD137 (4-IBB), a member of tumor necrosis factor receptor (TNFR) superfamily, is an inducible co-stimulatory molecule expressed primarily on activated T cells\textsuperscript{15}. Ligation of CD137 by anti-CD137 monoclonal antibody delivers a potent co-stimulatory signal to T cells, and enhances proliferation and activity of T cells, which have the ability to kill tumor cells\textsuperscript{16}. Previous study has demonstrated that treatment of tumor-bearing mice with anti-CD137 antibody can result in T cell-mediated tumor rejection\textsuperscript{17}. We hypothesized that anti-CD137 antibody may potentiate anti-tumor effect of dendritic cell-based vaccine. The reason is as follows. Treatment with dendritic cell-based vaccine induces up-regulation of CD137 expression on T cells by activating T cells. Subsequent administration of anti-CD137 antibody further increases T cell proliferation and activity through ligation of CD137 on T cells, thereby strengthening anti-tumor effect. To confirm this hypothesis, we investigated the combined effect of dendritic cell-based vaccine with anti-CD137 antibody in renal cell carcinoma mouse model.

**MATERIALS AND METHODS**

**Animals**

Balb/c mice, 8 - 10 weeks of age, were obtained from Shanghai Laboratory Animal Center (Shanghai City, China) and maintained under specific pathogen-free conditions. They were provided with sterilized food and water \textit{ad libitum}. All animal experiments were conducted in accordance with the US National Institutes of Health guidelines for appropriate use of experimental animals and approved by Animal Research and Care Committee at our university.

**Preparation of dendritic cell-based vaccine**

Dendritic cell-based vaccine was prepared as described by Lim \textit{et al}\textsuperscript{18}. In brief, bone marrow cells of Balb/c mice were cultured in complete medium supplemented with 10 ng/ml recombinant mouse granulocyte macrophage colony-stimulating factor (R & D Systems, Minneapolis, MN, USA) and 10 ng/ml recombinant mouse interleukin-4 (R&D Systems, Minneapolis, MN, USA). Complete medium consisted of RPMI-1640 containing 10% heated-inactivated fetal bovine serum, 2 mmol/l L-glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin (all from Life Technologies, Grand Island, NY, USA). On day two, suspended cells were removed and adherent cells were cultured in fresh complete medium containing cytokines. Half of the medium was replaced with fresh medium containing cytokines every other day. On day seven, nonadherent and loosely adherent cells (\textit{i.e.}, immature dendritic cells) were harvested. The Balb/c-derived renal cell carcinoma cell line (Renca) was obtained from American Type Culture Collection (Manassas, VA, USA) and suspended in phosphate-buffered saline. Renca tumor cell lysate was prepared by four rapid freeze-thaw cycles (liquid nitrogen, 37 °C water bath). In order to induce dendritic cell maturation, immature dendritic cells were incubated with Renca tumor cell lysate at the ratio of three tumor cells lysate to one dendritic cell in complete medium. After 8 hours, 10 ng/ml recombinant mouse tumor necrosis factor-α (R & D Systems, Minneapolis, MN, USA) and 10 ng/ml recombinant mouse interferon-γ (R & D Systems, Minneapolis, MN, USA) were added to induce dendritic cell further maturation. After incubation for 16 hours, Renca tumor lysate-pulsed dendritic cells (\textit{i.e.}, mature dendritic cells) were harvested and used as dendritic cell-based vaccine in our study. Dendritic cells were evidenced by phenotype analysis.

**Phenotype analysis of dendritic cells**

Immature and mature dendritic cells were harvested, stained with fluorescein isothiocyanate-labeled anti-CD11c (dendritic cell marker) monoclonal
antibody (BD PharMingen, San Diego, CA, USA) and phycoerythrin-labeled anti-CD83 (maturation marker of dendritic cells) monoclonal antibody (BD PharMingen, San Diego, CA, USA), and then analyzed by flow cytometry for expressions of CD11c and CD83 on the cell surface.

**Analysis of CD137 expression on T cells**

Spleens from Balb/c mice were prepared as cell suspensions. T cells were isolated from splenocytes by the use of T cell separation reagents (Miltenyi Biotec, Auburn, CA, USA). Purified T cells (1 × 10⁵ /well) were cultured alone or with Renca tumor lysate-pulsed dendritic cells (1 × 10⁴/well) in round-bottom 96-well plates, harvested at 24-hour intervals for 7 days, and stained with fluorescein isothiocyanate-labeled anti-CD3 (T-cell marker) monoclonal antibody (BD PharMingen, San Diego, CA, USA) and phycoerythrin-labeled anti-CD137 monoclonal antibody (BD PharMingen, San Diego, CA, USA). CD137 expression on T cells was analyzed by flow cytometry.

**Measurement of interferon-γ production**

Twenty days after tumor implantation, spleens from control and differently treated mice were harvested. CD4⁺ T cells were isolated from splenocytes by the use of CD4⁺ T cell separation reagents (Miltenyi Biotec, Auburn, CA, USA), and stimulated with Renca tumor lysate-pulsed dendritic cells at a ratio of 10:1 in vitro. After 24 hours, culture supernatants were collected and determined for interferon-γ content by enzyme-linked immunosorbent assay (ELISA) kit (BD PharMingen, San Diego, CA, USA).

**Statistical analysis**

The data were presented as mean ± standard deviation (SD). Two-tailed Student’s t-test was used for data analysis. A p-value of less than 0.05 was considered statistically significant. GraphPad Prism software (GraphPad Software Inc, San Diego, CA, USA) was used for all statistical analysis.

**RESULTS**

**Characteristics of dendritic cells**

As shown in Fig. 1, cultured cells highly expressed CD11c (dendritic cell marker), suggesting that these cells were dendritic cells. Renca tumor lysate-pulsed
phenotype of dendritic cells. The dendritic cells were cultured as described in the methods. Immature and mature dendritic cells were harvested, stained with fluorescein isothiocyanate-labeled anti-CD11c (dendritic cell marker) monoclonal antibody and phycoerythrin-labeled anti-CD83 (maturation marker of dendritic cells) monoclonal antibody, and then analyzed by flow cytometry. Expression rates of CD11c and CD83 in unpulsed dendritic cells (i.e., immature dendritic cells) and Renca tumor lysate-pulsed dendritic cells (i.e., mature dendritic cells) were 85.9% (i.e., 3.6% + 82.3%) and 3.6%, and 87.1% (i.e., 71.5% + 15.6%) and 71.5%, respectively. Dendritic cells (i.e., mature dendritic cells) expressed higher level of CD83 (maturation marker of dendritic cells), compared with unpulsed dendritic cells (i.e., immature dendritic cells).

Tumor lysate-pulsed dendritic cells up-regulate CD137 expression on T cells

CD137 expression on T cells was measured before and after stimulation of T cells with Renca tumor lysate-pulsed dendritic cells. As shown in Fig. 2, unstimulated T cells showed low expression of CD137. At three days after stimulation with Renca tumor lysate-pulsed dendritic cells, T cells increased the expression of CD137.

Anti-CD137 antibody potentiates the anti-tumor efficacy of tumor lysate-pulsed dendritic cells

We tested the anticancer effect of tumor lysate-pulsed dendritic cells and anti-CD137 antibody, alone or in combination, in the subcutaneous Renca tumor mouse model. As shown in Fig. 3, tumor lysate-pulsed dendritic cells or anti-CD137 antibody treatment significantly suppressed tumor growth compared with control (untreated) group (p < 0.05). However, the combination therapy with tumor lysate-pulsed dendritic cells and anti-CD137 antibody resulted in the greatest inhibition of tumor growth (p < 0.05), indicating a synergistic anticancer effect of the combined treatment.

Combination of tumor lysate-pulsed dendritic cells with anti-CD137 antibody augments T-cell proliferation

T cells isolated from splenocytes of control and differently treated mice were assayed for cell proliferation in response to Renca tumor lysate-pulsed dendritic cells. As shown in Fig. 4, mice treated with tumor lysate-pulsed dendritic cells or anti-CD137 antibody alone showed a significant increase in T-cell proliferation, compared with control group (p < 0.05). However, co-administration of tumor lysate-pulsed dendritic cells with anti-CD137 antibody resulted in stronger cell proliferation than any other groups (p < 0.05).

Combination therapy improves cytotoxic T-lymphocyte activity

CD8+ T cells isolated from splenocytes of control and differently treated mice were stimulated in vitro by co-culture with Renca tumor lysate-pulsed dendritic cells and analyzed for cytotoxic T-lymphocyte activity. The cytotoxic T-lymphocyte activity in tumor lysate-pulsed dendritic cells or anti-CD137 antibody-only-treated mice was significantly increased in comparison with control (untreated) mice (p < 0.05) (Fig. 5). The combination treatment with tumor lysate-pulsed dendritic cells and anti-CD137 antibody caused a much higher cytotoxic T-lymphocyte activity than either monotherapy (p < 0.05) (Fig. 5).
Tumor lysate-pulsed dendritic cells and anti-CD137 antibody synergistically enhance interferon-γ production

CD4+ T cells isolated from splenocytes of control and differently treated mice were assayed for interferon-γ production in response to Renca tumor lysate-pulsed dendritic cells. Interferon-γ production is shown in Fig. 6. Therapy with tumor lysate-pulsed dendritic cells or anti-CD137 antibody significantly increased interferon-γ production (p < 0.05), with the highest increase in the combination treatment (p < 0.05).
DISCUSSION

Dendritic cells, the most potent antigen-presenting cells, have the ability to process and present tumor antigen to both CD4+ and CD8+ T cells[21]. The interaction between dendritic cells and T cells induces proliferation and activation of T cells[21]. Activated CD8+ T cells become cytotoxic T lymphocyte with the ability to kill tumor cells[22]. Activated CD4+ T cells have been shown to provide help for CD8+ T cell activation by releasing cytokines, such as interferon-γ and interleukin-2[23]. Dendritic cell-based vaccines have been applied clinically for the treatment of metastatic renal cell carcinoma[12, 24]. However, a number of clinical studies have displayed limited success[12, 24]. The CD137 is expressed predominantly on activated CD4+ and CD8+ T cells[15]. Ligation of CD137 by anti-CD137 monoclonal antibody increases T-cell proliferation and activation[16], and prevents activation-induced death of T cells[25]. It has been reported that treatment with anti-CD137 antibody leads to regression of well-established tumors in animal models[17, 26]. On the basis of the reason as mentioned in the introduction, we postulated that anti-CD137 antibody may enhance the anti-tumor effect induced by dendritic cell-based vaccine. Our study showed that T cells up-regulated CD137 expression after stimulation by tumor lysate-pulsed dendritic cells (i.e., dendritic cell-based vaccine) (Fig. 2). The result provided scientific basis for subsequent application of anti-CD137 antibody. In the present study, we found that combination therapy with tumor lysate-pulsed dendritic cells and anti-CD137 antibody might further improve the anti-tumor effect.
anti-CD137 antibody significantly inhibited tumor growth, compared with a single treatment with tumor lysate-pulsed dendritic cells or anti-CD137 antibody (Fig. 3). These data suggest that anti-CD137 antibody administration improves anti-tumor efficacy of tumor lysate-pulsed dendritic cells. In addition, we have not observed apparent side effects in mice treated with tumor lysate-pulsed dendritic cells and anti-CD137 antibody. The result suggests that combination therapy is safe.

The anti-tumor immune responses can be monitored by T-cell proliferation assay, cytotoxicity test, and cytokine secretion assay[13]. In the present study, mice immunized with tumor lysate-pulsed dendritic cells plus anti-CD137 antibody showed a stronger T-cell proliferation compared with mice immunized with tumor lysate-pulsed dendritic cells or anti-CD137 antibody alone (Fig. 4). These findings indicate that combination treatment promotes T-cell proliferation. Moreover, cytotoxic T-lymphocyte activity was higher in mice receiving combination therapy than in mice treated with tumor lysate-pulsed dendritic cells or anti-CD137 antibody alone (Fig. 5), suggesting that combination therapy increases CD8+ T cell activity to kill tumor cells. In cytokine secretion assay, significantly higher interferon-γ levels were observed in mice that received combination therapy than those treated with tumor lysate-pulsed dendritic cells or anti-CD137 antibody alone (Fig. 6), implying that combination therapy enhances CD4+ T cell activity to secrete interferon-γ. The interferon-γ has been demonstrated to activate CD8+ T cells[23]. After considering all these results, we think that combination therapy may augment anti-tumor effect by enhancing T-cell proliferation and activity.

Tumor cells are known to secrete transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and interleukin-10 (IL-10)[18]. These tumor-related cytokines can suppress maturation of dendritic cells in vivo, leading to impaired antigen presentation and T-cell stimulation, and finally failure to induce a full anti-tumor immune responses[18, 27, 28]. As a result, we used in vitro cultured dendritic cells in the present study. The immature dendritic cells can be produced in vitro by differentiation of bone marrow cells by addition of granulocyte macrophage colony-stimulating factor and interleukin-4 for six days[18]. They can be further differentiated into mature dendritic cells by addition of maturation stimuli such as tumor lysate, tumor necrosis factor-α, and interferon-γ[18, 29]. In our study, cultured cells were characterized as dendritic cells based on high expression of CD11c, which is a typical dendritic cell marker (Fig. 1). In clinical trials, immature or mature dendritic cells have been used for the treatment of renal cell carcinoma[12]. Recent clinical studies have showed that the use of mature dendritic cells can generate a better anti-tumor efficacy[12]. Thus, we used mature dendritic cells (i.e., Renca tumor lysate-pulsed dendritic cells) in our experiment. The mature dendritic cells were characterized by high expression of CD83 (maturation marker of dendritic cells) (Fig. 1).

Dendritic cells pulsed with tumor antigens, such as tumor lysate, defined tumor-associated peptides, apoptotic or necrotic tumor cells, and tumor RNA or DNA, are able to induce specific T-cell responses against tumor cells[20]. The most commonly used tumor antigen in the clinical studies is tumor lysate[12]. We also used tumor lysate as tumor antigen in our study. The use of tumor lysate has unique advantages. It provides entire repertoire of tumor-associated antigens, thereby decreasing possibility of tumor escape. In addition, it also removes the requirement to identify tumor-associated antigens.

We found that CD137 expression on T cells reached a peak three days after stimulation of T cells with tumor lysate-pulsed dendritic cells (Fig. 2B). For this reason, in combination therapy group, we injected anti-CD137 antibody three days after treatment with tumor lysate-pulsed dendritic cells. Some studies have shown that anti-CD137 antibody at a dose of 100 μg is effective in treating tumors in mice, such as breast cancer, melanoma, mastocytoma and myeloma[31, 32]. Consequently, we chose this dose in renal cell carcinoma mouse model.

CONCLUSION

Our findings present the first evidence that dendritic cell-based vaccine in combination with anti-CD137 antibody can enhance anti-tumor effect in mice bearing renal cell carcinoma by increasing T-cell proliferation and activity. We propose that combination therapy may have the clinical applicability in patients with renal cell carcinoma. Additional clinical trials will be required to address this issue.

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The Effect of Gene Polymorphisms (ENOS G894T, PON1 and Catalase -262C→T) on Fertility and Sperm Parameters in Turkish Men with Clinical Varicocele: A Pilot Study

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ABSTRACT

Objective: Scrotal varicocele is found to be associated with increased spermatozoal reactive oxygen species (ROS) production and decreased seminal plasma antioxidant activity. Our objective was to search for an association between male infertility and gene polymorphisms (PON1, ENOS G894T and Catalase -262C→T).

Design: Controlled prospective study

Setting: Atatürk and Yüksek İhtisas Education and Training Hospitals, Ankara, Turkey

Subjects: Forty primary infertile men and forty healthy men were included in the study. Patients with clinical varicocele in the study group had no endocrinopathy, no surgery for varicocele / inguinal hernia, and / or no leukospermia. They were non-smokers.

Intervention: Doppler ultrasonography (USG) was performed for the patients. For genetic analysis, 5 ml of venous blood was drawn into tubes containing EDTA from each patient.

Main Outcome Measures: Gene polymorphism, progressive sperm motion and vein diameter

Results: Existence of gene polymorphisms was statistically important in patients who had clinical varicocele with affected progressive forward motion. We determined statistically significant rate of gene polymorphisms in enzymatic antioxidant defence systems in patients with clinical varicocele, with a diameter of spermatic vein above 2.2 mm and forward progressive sperm motion below 32% (p < 0.001).

Conclusions: These polymorphisms might represent risk factors for Turkish men with clinical varicocele and forward progressive sperm motion defect. This is a pilot study. We intend to continue these studies with larger sample sizes to confirm these findings.

INTRODUCTION

Varicocele is an abnormal dilatation of the spermatic vein, and it is observed in around 30 - 50% of men in infertile couples[1]. A considerable number of infertile men have no known mechanism for their infertility[2]. Several mechanisms which involve the pathophysiology of testicular dysfunction in the population with varicocele have been defined. The other pathophysiological mechanisms of varicocele are Leydig cell and germinal cell dysfunction due to small vessel occlusion, testicular hypoxia due to venous stasis, retrograde flow of adrenal and renal metabolites from the renal vein into the spermatic vein, increased scrotal and testicular temperature and decreased secretion of gonadotropins and androgens[3]. In addition to these, varicocele also reduces both the seminal and blood plasma antioxidant defenses[4]. Scrotal varicocele is found to be associated with increased spermatozoal reactive oxygen species (ROS) production and decreased seminal plasma antioxidant activity[5]. Excess ROS leads to DNA damage and oxidation of lipoprotein components at the cellular and subcellular level. Oxidative stress (OS) adversely affects sperm function by changing membrane fluidity and permeability, and...
impaired sperm functional competence\[6\]. We searched for an association between polymorphisms of different plasma enzymatic antioxidants (PON1, ENOS G894T and Catalase -262C→T gene polymorphisms) in a Turkish male population with fertility and varicocele, based on the impairment of spermatozoa functions related with increased ROS. This study also aims to examine, if there is an association between different plasma enzymatic antioxidants (PON1, ENOS G894T and Catalase -262C→T gene polymorphisms) and idiopathic male infertility.

**SUBJECTS AND METHODS**

**Population of the Study**

Forty male patients with primary infertility with a mean age of 36.8 ± 6.91 years and forty healthy men with a mean age of 41.2 ± 7.63 years were included in the study. The patients were included in the study after physical examination by an urologist. Patients, in whom left-sided grade 2 varicocele was detected, were evaluated radiologically with scrotal coloured doppler ultrasonography (USG). After evaluation with scrotal doppler\[7\], patients with clinical varicocele who had varicose vein with reflux and diameter above 2.2 mm were included in the study group. Patients were included in the study after 3 - 5 days of sexual abstinence. Two different laboratory examinations were performed, at least 15 days apart, and the sperm parameters were evaluated according to WHO guidelines\[8\]. Fertile men were included in the study as control group. The patients had sperm profiles with a count of 5 - 55 million/ml, a viscosity with a volume of 2 – 5 ml, normal pH values, and no leukospermia. The motility was classified as motile a (rapid progressive motion), motile b (slow progressive motion), motile c (non-progressive motion), motile d (non-motile sperm percentiles), motile a + b (32%; progressive sperm motion) and motile a + b + c (40%; total motion)\[9\]. The patients with clinical left-sided varicocele in study group had no endocrinopathy, no previous surgery for varicocele or inguinal hernia and no leukospermia. They were also non-smokers. The study group consisted of patients who had no child despite regular sexual intercourse for at least a year. Fertile men were included in the control group. Informed consent forms, compatible with the Helsinki declaration, were taken from the patients and the Institutional Review Board approved the study.

**Genotyping For eNOS G894T Polymorphism**

For genetic analysis, 5 ml of blood was drawn into tubes containing EDTA from each patient. DNA was extracted using a commercial kit (QIAamp DNA mini kit; Qiagen, Hilden, Germany). In this study, for the detection of G894T polymorphism on ENOS gene, we used primer pairs to amplify a part of the ENOS gene containing exon 7, by polymerase chain reaction (PCR) with the following flanking intronic primers: sense 5’-CATGAGGGCTCAGCCCCCCAGAAC-3’ and antisense 5’-AGTCAATCCCTTTTGCTCAC-3’, followed by Mbo I restriction endonuclease digestion for 16h at 37°C and resolution by electrophoresis on 3% agarose gel. The resulting 206 bp PCR product was cleaved into two smaller fragments of 119 and 87 bp in the presence of a T nucleotide at 894 (corresponding to Asp 298) but not in its absence. Digested fragments were visualized after ethidium bromide staining under UV light.

**Genotyping for Catalase -262C→T polymorphism**

Genotyping for the CAT -262C→T polymorphism was conducted according to the method described by Forsberg \textit{et al} with modifications\[11\]. PCR amplification of the associated region of the CAT gene promoter site was performed using the primers 5’-AGAGCCTCGCCGCCGGACCG-3’ (antisense) and 5’-TAAGAGCTGAAGAGCATAGCT -3’ (sense) with a touch-down program designed as follows: 94°C for 30 s, 68 °C for 45 s, 72 °C for one min, -0.5 °C/cycle, 19 times, then 94°C for 30 s, 58 °C for 45 s, 72°C for one min, 25 times. The final elongation step was 10 min at 72 °C. Each reaction mixture (25 ml) contained approximately 50 ng of DNA template, five units of Taq DNA polymerase, 1 mM of each primer, 200 mM dNTPs, 20 mM Tris–HCl (pH 8.4), 50 mM KCl and 1.5 mM MgCl2. For restriction digestion with Smal, 15 ml were withdrawn from the amplification mixture and incubated with five units of the enzyme in the presence
of the accompanying buffer (50 mM potassium acetate, 20 mM Tris–acetate, 10 mM magnesium acetate, 1 mM dithiothreitol, pH 7.9), in a final volume of 25 ml, at room temperature for 4 h. The polymorphism was visualized by separating the DNA contained in 10 ml of the SmaI digest, in a 2% agarose gel, with ethidium bromide. The - 262T allele produced an undigested product of 185 bp, as opposed to a 155 bp product of SmaI digestion yielded by the - 262C allele.

Statistical Analysis

Statistical analyses were performed using the Statistical Packages for the Social Sciences 11.5 for Windows (SPSS software package, version 11.5). Kolmogov Smirnov and Shapiro-Wilk normalization tests were performed initially on the associated variables. A decision was made to perform parametric tests according to the histograms. Accordingly, Student t-test was used to search for differences between two groups in terms of variables. The results of the analysis is summarized in tables including p-values for mean ± standard deviation and median(minimum - maximum). Differences in the distribution of genotypes between cases and controls were tested using the Chi-square statistic and Fisher’s exact test. The analyses are shown on the bias tables including percentiles. A p-value of < 0.05 was considered statistically significant.

RESULTS

The study included 40 infertile patients with a mean age of 36.8 ± 6.91 years and 40 fertile males with a mean age of 41.2 ± 7.63 years. There was statistically significant difference among the forward progressive sperm motility, total sperm motility, age and diameters

| Table 1: Distribution as per age, sperm motility and varicose vein diameter in study and control groups |
|---|---|---|---|---|
| Demographic features | Patient (n = 40) | Control (n = 40) |
| | M ± SD | Median (Min-Max) | M ± SD | Median (Min-Max) | p-value |
| Age | 36.8 ± 6.91 | 36 (22 - 49) | 41.2 ± 7.63 | 42 (28 - 56) | 0.006** |
| motile a | 16.3 ± 7.99 | 16 (2 - 35) | 34.3 ± 16.58 | 31.5 (11 - 70) | <0.001** |
| motile b | 25.6 ± 6.21 | 26 (10 - 36) | 19.5 ± 11.45 | 13.5 (5 - 44) | 0.004** |
| motile a + b | 41.9 ± 10.87 | 42.5 (13 - 67) | 53.5 ± 13.59 | 50 (30 - 85) | <0.001** |
| motile c | 17.1 ± 9.2 | 15.5 (0 - 38) | 14.9 ± 6.3 | 15 (5 - 30) | 0.216 |
| motile d | 41.4 ± 12.48 | 38 (18 - 78) | 31.4 ± 11.53 | 30 (3 - 50) | <0.001** |
| Diameter of spermatic vein (mm) | 2.8 ± 0.39 | 2.9 (2.2 - 3.6) | 2.1 ± 0.6 | 2 (1.20 - 3.5) | <0.001** |

**p < 0.05 ; Student t-test
motile a: rapid progressive motion, motile b: slow progressive motion, motile c: non-progressive motion, motile d: non-motile sperm percentiles, motile a + b: progressive sperm motion

| Table 2: Demographic distribution of PON1, ENOS G894T and Catalase -262C→T gene polymorphisms |
|---|---|---|---|---|---|
| Groups | Normal | Heterozygote | Homozygote | Normal | Heterozygote | Homozygote |
| PON1 | 24 | 13 | 3 | 29 | 9 | 2 |
| ENOS G894T | 23 | 13 | 4 | 25 | 12 | 3 |
| Catalase-262C→T | 21 | 16 | 3 | 24 | 14 | 2 |

| Table 3: Distribution of varicocele in fertile and infertile men who were detected with PON1, ENOS G894T and Catalase -262C→T gene polymorphisms |
|---|---|---|---|---|
| Groups | Patients n | PON1 polymorphism n (%) | ENOS G894T polymorphism n (%) | Catalase polymorphism n (%) |
| Fertile men | 40 | 15 (37.5) | 11 (27.5) | 16 (40) |
| With varicocele | 12 | 12 (100) | 10 (83.3) | 10 (83.3) |
| Without varicocele | 28 | 3 (10.7) | 1 (3.6) | 6 (21.4) |
| Infertile men | 40 | 17 (42.5) | 16 (40) | 19 (47.5) |
| With varicocele | 40 | 17 (42.5) | 16 (40) | 19 (47.5) |
| Without varicocele | 0 | 0 | 0 | 0 |
To accomplish this, seminal plasma possesses an array of enzymatic and non-enzymatic defense mechanisms. Increased ROS generation was reported in 40% of the general infertile population, compared to 80% in the infertile varicocele population\cite{21-25}. Despite these results in the literature, in our study, we determined that antioxidant gene polymorphisms are associated with varicoceal vein diameter and forward progressive sperm motion rather than fertility (Table 4 and 5). A relationship has also been detected between oxidative stress and impaired sperm function rather than fertility (Table 5). A significant difference was found in terms of the gene polymorphisms (p-value was 0.920, 0.901 and 0.641 respectively) (Table 5). But, when progressive sperm motion with a motility above 32% and below 32% were compared in all of the patients, there was no statistically significant difference in terms of gene polymorphisms (p-value was 0.001, 0.001 and 0.020 respectively) (Table 5). Spermatic vein diameters of all of the patients were classified and evaluated. According to this evaluation, when spermatic vein diameters above 2.20 mm and below 2.20 mm were compared, there was a statistically significant difference in terms of the gene polymorphisms (p-value was 0.001, 0.001 and 0.003, respectively) (Table 5).

**Discussion**

Oxidative stress results from an imbalance between production and removal of ROS, leading to both a steady state concentration of reactive intermediates higher than normal and to increased cellular damage. Several studies have shown that there is a correlation between oxidative stress and impaired sperm function\cite{12-15}. Although ROS play important roles in the promotion of spermatogenesis, hyperactivation, and fusion\cite{16-19}, they must be controlled to avoid harmful effects\cite{20}. To accomplish this control, seminal plasma possesses an array of enzymatic and non-enzymatic defense mechanisms. Increased ROS generation was reported in 40% of the general infertile population, compared to 80% in the infertile varicocele population\cite{21-23}. Despite these results in the literature, in our study, we determined that antioxidant gene polymorphisms are associated with varicoceal vein diameter and forward progressive sperm motion rather than fertility (Table 4 and 5). A relationship has also been detected between oxidative stress and impaired sperm function rather than fertility (Table 5 and 6). A significant difference was found in terms of the gene polymorphisms (PON1, ENOS G894T and Catalase -262C → T gene polymorphisms) between the infertile and fertile groups (p > 0.05, p-value was 0.648, 0.237 and 0.499 respectively) (Table 4). Similarly, total sperm motion in all the patients between above 40% and below 40% were compared and no statistically significant difference was found in terms of gene polymorphisms (p-value was 0.920, 0.901 and 0.641 respectively) (Table 5). But, when progressive sperm motion with a motility above 32% and below 32% were compared in all of the patients, there was a statistically significant difference in terms of gene polymorphisms (p-value was 0.001, 0.001 and 0.020 respectively) (Table 5). Spermatic vein diameters of all of the patients were classified and evaluated. According to this evaluation, when spermatic vein diameters above 2.20 mm and below 2.20 mm were compared, there was a statistically significant difference in terms of the gene polymorphisms (p-value was 0.001, 0.001 and 0.003, respectively) (Table 5).

**Table 4: Distribution of PON1, ENOS G894T and Catalase -262C → T gene polymorphisms in fertile and infertile groups**

<table>
<thead>
<tr>
<th>Polymorphism and group</th>
<th>Normal n (%)</th>
<th>Polymorphism n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PON1 Polymorphism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertile</td>
<td>23 (28.8)</td>
<td>17 (21.2)</td>
<td>0.648 *</td>
</tr>
<tr>
<td>Fertile</td>
<td>25 (31.2)</td>
<td>15 (18.8)</td>
<td></td>
</tr>
<tr>
<td>ENOS G894T Polymorphism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertile</td>
<td>24 (30)</td>
<td>16 (20)</td>
<td>0.237 *</td>
</tr>
<tr>
<td>Fertile</td>
<td>29 (36.2)</td>
<td>11 (13.8)</td>
<td></td>
</tr>
<tr>
<td>CATALASE -262C→T Polymorphism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertile</td>
<td>21 (26.2)</td>
<td>19 (23.8)</td>
<td>0.499 *</td>
</tr>
<tr>
<td>Fertile</td>
<td>24 (30)</td>
<td>16 (20)</td>
<td></td>
</tr>
</tbody>
</table>

*p > 0.05

A significant difference in terms of gene polymorphism (PON1, ENOS G894T and Catalase -262C → T gene polymorphisms) between the infertile and fertile groups (p > 0.05, p-value was 0.648, 0.237 and 0.499 respectively) (Table 4). Similarly, total sperm motion in all the patients between above 40% and below 40% were compared and no statistically significant difference was found in terms of gene polymorphisms (p-value was 0.920, 0.901 and 0.641 respectively) (Table 5). But, when progressive sperm motion with a motility above 32% and below 32% were compared in all of the patients, there was a statistically significant difference in terms of the three gene polymorphisms (p-value was 0.001, 0.001 and 0.020 respectively) (Table 5). Spermatic vein diameters of all of the patients were classified and evaluated. According to this evaluation, when spermatic vein diameters above 2.20 mm and below 2.20 mm were compared, there was a statistically significant difference in terms of the gene polymorphisms (p-value was 0.001, 0.001 and 0.003, respectively) (Table 5).
that the outcome of varicocelectomy may be influenced on one or more of these genetic polymorphisms and susceptibility to varicocele-induced ROS may depend with a varicocele
different groups. One study shows that there is a good defenses depletion, average values are plotted for the stress the relationship between local and systemic plasma antioxidant defenses. In order to further Varicocele reduces both the seminal and blood plasma antioxidant potential (TRAP) in the seminal plasma. For example, it has been reported deplete the defenses present in the testes and in below 32% (Table 5). Increased ROS production can radicals in systematic circulation cause negative
effects on sperm function. This implies that significant antioxidant consumption at the testis level can be related to the increased ROS production[21]. The results discussed above suggest that antioxidant defenses could be depleted both locally and systemically in varicocele patients. In particular, it was considered important to establish if oxidative stress indicators are modified and non-enzymatic antioxidants are depleted in seminal and blood plasma of varicocele patients[22]. In our study, we used peripheral blood both in the study group (infertile patients) and the control group (fertile group), because using the specimen from the varicose vein of the control group was an ethical concern. We determined statistically significant rate of gene polymorphism in enzymatic antioxidant defence systems in patients with clinical varicocele, with a diameter of spermatic vein above 2.2 mm and forward progressive sperm motion below 32%. But, we could not determine any significant difference in terms of gene polymorphisms in our infertile study group compared to fertile control group. There was also no statistically significant difference in patients with total sperm motion (below and above 40%). This is a controlled prospective study and it is also the first study which searches the association between infertility and gene polymorphism of enzymatic antioxidant defense system. Although our patient and control group is small, this is the first pilot study which includes patients with fertility and infertility, their sperm features (progressive and total sperm motion) and spermatic vein diameter (with and without varicocele) in literature. We want to continue the study with larger groups in future. Perhaps then, we will also find a relationship between infertility and gene polymorphism as the number of the patients increase.

In our study, there was no statistically significant difference for gene polymorphisms between study and control group (Table 4), but it was significant in patients with varicocele who had a vein diameter of above 2.2 mm and forward progressive sperm motion below 32% (Table 5). Increased ROS production can deplete the defenses present in the testes and in seminal plasma. For example, it has been reported that total reactive antioxidant potential (TRAP) in the internal spermatic vein (measured during surgery) is significantly lower than in a peripheral vein[32]. Varicocele reduces both the seminal and blood plasma antioxidant defenses. In order to further stress the relationship between local and systemic defenses depletion, average values are plotted for the different groups. One study shows that there is a good correlation between both sets of values. This is the first instance in which it is established that a systemic decrease in antioxidant defenses is present in those with a varicocele[33]. It is difficult to determine if the systemic decrease is reflected in the seminal levels or in systemic circulation[33,34]. Increased reactive oxygen radicals in systematic circulation cause negative effects on sperm function. This implies that significant

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10. Adkins S, Gan KN, Mody M, La Du BN. Molecular basis for the polymorphic forms of human serum paraoxonase/arylesterase glutamine or arginine at position 191, for the respective A or B allozymes. Am J Hum Genet 1993; 52:598-608.
Ward Mechanical Ventilation (WMV) Audit

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ABSTRACT

Objective: To look at the characteristics and mortality of mechanically ventilated patients on a general medical ward. The purpose of this audit is to evaluate this practice and also help clarify the need for “do not resuscitate” orders in Kuwait.

Design: Prospective, observational audit

Setting: Mubarak Al-Kabeer Hospital, Ministry of Health, Kuwait

Subjects: Mechanically ventilated patients on medical wards in Mubarak Al-Kabeer Hospital over a six-month period

Intervention: Mechanical ventilation

Main Outcome Measures: Primary outcome was death and secondary outcome was extubation

Results: Eighty-one patients met the inclusion criteria. Most patients had over three medical problems with a high number of patients having brain dysfunction, cancer and end-stage diseases. The mortality rate was 95%.

Conclusion: There is great need to further look into this practice which appears to be highly fatal. There is evidence for the need to introduce a “do not resuscitate” policy in Kuwait, which is an ethical necessity in the practice of medicine.

INTRODUCTION

Ever since the creation of the first positive pressure mechanical ventilator in the 19th century there has been a constant demand for it in hospitals around the world. The number of patients requiring such devices has also grown exponentially since that time. The outcome of patients on mechanical ventilation even in specialized centers, like the Intensive Care Unit (ICU) has been inconsistent due to a variety of causes[1].

Due to limited resources and the increasing demand for ICU beds with no “do not resuscitate (DNR)” policy, for the past 10 years in Kuwait, we have selectively placed some patients on mechanical ventilators in the general medical wards. Most of these patients are usually those on medical grounds “should not have been resuscitated or intubated” due to predicted poor prognosis. The aim of this audit was to look at the mortality of these patients who are mechanically ventilated in the medical wards in Mubarak Al-Kabeer Hospital, Kuwait (MKH).

MKH is a secondary referral hospital servicing approximately one third of the population of Kuwait (1 million inhabitants). It has a total of 450 beds of which 186 are allocated to adult medical patients. To the best of our knowledge, there are very few countries in the world that do not have a DNR policy and selectively place poor prognosis patients on invasive mechanical ventilation in the general medical ward. This is the first time in Kuwait that the mortality and characteristics of such patients has been reviewed systematically.

SUBJECTS AND METHODS

We collected data from the general medical wards in MKH over a six-month period starting from 1st May to 31st October, 2010. The need for written consent and ethical approval was waived by the local hospital administration due to the observational nature of the study. Mechanical ventilation (MV) was either through a tracheostomy or an endotracheal tube.

We included all patients that were placed on mechanical ventilation in the medical wards that survived at least two hours from onset of MV. Since all patients unselectively receive CPR and are intubated during the process, we chose two hours as the minimal survival time post MV. This is to ensure that we are measuring the mortality of patients on MV in the ward rather than the mortality of cardiac arrest patients in the hospital, who are usually intubated during resuscitation.

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The following exclusion criteria were used:
1. Patient on home mechanical ventilator admitted to hospital
2. Patients on MV in the ward prior to 1st May 2010
3. Patients transferred to ICU or CCU (coronary care unit) within 48 hours

The decision to transfer a patient to the ICU or keep him in the ward was made by the ICU doctors on call for that evening, and was based on the patient's previous medical history and the perceived benefit from MV, resuscitation or further ICU management.

By visiting the wards every 48 hours and reviewing the patient's charts, we collected data about the age, reason for MV and admission, number of days on MV and number of days to onset of MV, past medical history, and location of patients. The reason for admission was recorded as per the admission sheet. The reason for MV was recorded as the reason written at the time of intubation. If the reason for MV was changed to a more specific one during follow-up, the reason for MV was changed accordingly. The primary outcome was death. The secondary outcome was extubation, which was defined as being disconnected from mechanical ventilation for a two-week period. If the patient was reconnected to a ventilator during the course of the same admission, the period of mechanical ventilation was considered as one prolonged period. Unfortunately the final cause of death was not recorded due to great uncertainty in the cause of death in many of these patients as well as lack of post-mortem examination. Therefore, this data was not collected. The investigators had no input regarding any aspect of management of the patients.

RESULTS

Over the six-month period, 81 patients were placed on MV in the ward that met the inclusion criteria. Complete data were collected for all patients. The background medical history was grouped into related diseases for ease of collection and to compare patient’s characteristics.

Out of the 81 patients that were reviewed, only four had met the survival criteria achieving an overall survival of 5% and a mortality of 95% for patients on MV in the medical ward. Two of the survivors died during the course of the same admission. Twenty-five patients survived less than 48 hours (31% of patients), and 56 survived over 48 hours (69%).

The patients were almost equally divided between the medical wards. The ratio of male to female patients was 1:1 (40 patients). The average age of patients was 70.9 years with over 80% of patients being over 60 years (age range 15 – 92 years). The mean number of medical co-morbidities between male and female patients was four (mode 5, median 4). 61% of patients had four or more medical conditions (Fig. 1). All the survivors had three or less medical conditions. The commonest diseases were hypertension (68%) and diabetes (60%), both present in over 60% of patients. Chronic kidney disease (CKD), ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), stroke, and cancer were also found to be present in many of the patients (Fig. 2). The commonest reason for MV was cardiac arrest followed by decreased level of consciousness and then desaturation (Table 1).

![Fig. 1: Percentage of patients and associated number of medical conditions. This bar chart shows the percentage of patients and their associated number of diseases. Most patients had four or more diseases.](image)

Table 1: Indication for mechanical ventilation

<table>
<thead>
<tr>
<th>Indication for MV</th>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>24</td>
<td>29.6</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>19</td>
<td>23.5</td>
</tr>
<tr>
<td>Desaturation</td>
<td>14</td>
<td>17.3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>10.0</td>
</tr>
<tr>
<td>Septic shock</td>
<td>6</td>
<td>7.4</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>3</td>
<td>3.7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Fit</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The mean length of MV was 20 days and the mean time to onset of MV from admission was 18 days. There were 61 (75%) patients in cubicles (a four-bed room with no door and glass windows on either side that lets the nurses see the patient from the corridor) and 30 (25%) patients in private rooms.

Cost analysis for the 81 patients for one year was estimated at over a quarter of a million Kuwaiti
dinars / year. Average cost of running a mechanical ventilation bed on the general medical floor was calculated to be approximately 85 KD / day which is only 5 KD over the average cost of normal general medical bed. Also included into the calculation was the average cost of expected laboratory and imaging investigations over that period. This is considered to be a large underestimate, given the fact that cost of manpower, medication and the cost of redirection and utilization of other resources for other patients that need medical beds was not taken into account in this estimation.

**DISCUSSION**

There is very little literature that evaluates the mortality of patients on mechanical ventilation outside specialized units like the ICU and CCU. This is mainly due to the rarity of this clinical scenario in the world and the general consensus that mechanically ventilated patients need a higher degree of specialized care.

The mortality rate obtained in this audit was staggering. At first glance, it seems that mechanically ventilating a patient on the ward is almost a sure death sentence for the patient, especially when compared to the mortality of medical patients that received mechanical ventilation in the ICU (30%, obtained form the ICU, MKH mortality census for May to October of the same year). Looking at the number of the medical conditions the ventilated patients in the ward had, it was found that over 84% of them had three or more medical conditions with a high percentage having brain dysfunction (dementia, mental retardation or stroke), cancer and end-stage diseases. These figures raise many questions and concerns. Why is the mortality rate of these patients so high? Could it be due to suboptimal quality of care received by these patients, our very aggressive resuscitation efforts, lack of a DNR policy or any selection bias by ICU not admitting patients they thought will not survive.

Through literature search, we found two articles that examined at similar problems[2,3]. In both studies, the authors compared the mortality rate of patients on invasive MV in the ICU and in the general medical ward. They showed significant difference in mortality / survival of ICU to non-ICU ventilated patients in favor of ventilation in the ICU.

We compared the care that our patients received to the care received in the study by Lieberman *et al*[2]. The patients in the general medical ward in MKH are generally examined three times per day. Only one time a day are they seen by the ICU personnel, who are trained to deal with mechanically ventilated patients and can adjust the ventilator to meet the patient’s needs. The rest of the visits, if any, are done by medical personnel who have limited experience in dealing with mechanical ventilators. With regard to nursing care, the nurse assigned to each patient is looking after 3 - 4 other patients at the same time. They have minimal expertise in dealing with mechanically ventilated patients. The patients were also placed in different rooms including private rooms that are isolated from the nurse’s station. Lieberman and colleagues[2] reported a mortality of 68% in patients who were ventilated in the ward. Their patients were seen five to six times per day including a visit at night by personnel who were skilled in managing ventilator patients and the patients were cared for in one room with a nurse skilled in their management. Therefore, it seems that care might have contributed to our higher mortality outcome and although our audit was observational and not designed specifically to detect difference in the outcome based on care, it seems unlikely that this difference in mortality can be explained by quality of care alone especially when looking at Lieberman[2], and Hersch[3] patient exclusion criteria.

In contrast to our audit, both studies of Lieberman[2], and Hersch[3] excluded DNR patients and those who are unlikely to survive over six months. On the other hand, our study sample was almost entirely made up of patients who on medical grounds, as judged by ICU doctors, should not have been resuscitated. Examples are stroke patients, patients with metastatic cancers, end-stage heart and lung diseases, which contributed to our much higher mortality rate. Currently in Kuwait, we have no DNR orders and when these patients deteriorate, they are resuscitated for purely medico-legal or religious purposes. This we deem as a highly unethical practice.

One could also argue that there is obvious selection bias of leaving patients that were perceived “will do worst” to the ward, therefore increasing the mortality rate in the ward, which is true especially because

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**Fig. 2:** Prevalence of medical conditions excluding HTN and DM. This bar chart shows the prevalence of each disease among the study population.
the method of selection was not standardized in the hospital and was left to the discretion of the ICU doctor. The counter argument to that is, selection was based on medical judgment of futility and not only on resource allocation, and therefore, ICU doctors were correct 95% of the time in selecting patients that were judged not to benefit from initial resuscitation and transfer to the ICU.

It is likely that both suboptimal care and aggressive resuscitation contributed to the high mortality rate obtained in this audit. The results of this audit cannot with certainty determine the exact cause of this high mortality, because our data was very heterogeneous and will not allow firm conclusions to be made. However, the data obtained in this audit is a very strong proof that we are not benefiting these patients by resuscitating them and leaving them on the ward. On the contrary, we are simply prolonging the inevitable and causing the patient a great deal of harm through the process of ventilation. Also, it results with a negative psychological impact on the family by allowing them to see their relatives in this situation while they are being falsely reassured that their relative will become better. There are also obvious massive economic implications associated with this practice.

Through the decades, physicians have come to recognize their limitations. They look at the quality of life of patients that have end-stage disease rather than simply ensuring that patients have a heart beat and a recordable blood pressure. Around the world, the laws have adopted these changes, but unfortunately in Kuwait, we are still lagging behind in this very crucial matter due to medical, social and especially religious misconceptions. Religion has been a powerful driving force influencing enactment of many polices in Kuwait. Although it is not in our ability to make recommendations about religious aspects of ‘end of life’ policies, it would make sense that the role of religion is to empower doctors to make a decision for or against DNR and we have found that, contrary to popular societal beliefs, Islam does indeed support the practice of DNR[4]. Patients family and doctors are paying the price, not only through spending our limited resources, but also by patient's losing faith in local medical practice. This loss in faith has resulted in large number of people looking for medical care outside Kuwait.

CONCLUSION

It is clear from this audit that ventilating a patient out of the ICU in our hospital is fatal. Although the exact reasons for this high mortality rate cannot be determined from our data, there is overwhelming evidence that we need to update our laws regarding DNR (medical, legal, and religious cooperation). Lastly, we need to further study the characteristics of these patients who end up ventilated on the general medical ward in order to make the proper recommendations on how to improve their survival.

REFERENCES

Unusual Presentation of Duplex Collecting System: A Case Report

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ABSTRACT

Duplex collecting systems (also known as duplicated collecting systems) can be defined as renal units containing two pyelo-caliceal systems that are associated with a single ureter or double ureters. The two ureters empty separately into the bladder or fuse to form a single ureteral orifice. We came across a case in which the diagnosis was in dilemma until actual surgery when it was finally diagnosed as a case of duplex collecting system.

KEY WORDS: duplicated collecting system, retrograde pyelogram

INTRODUCTION

Complete duplication of ureters occurs in 0.2% of live births; the chance of occurrence is 12% in first-degree relatives of persons with this condition. The prevalence of partial duplication found on urograms is 0.6%.[1] We encountered such a case that was initially diagnosed as infection of the upper urinary tract. However, subsequent investigation diagnosed it as a case of complex renal cyst. Finally, intra-operatively the case could be correctly diagnosed as a case of duplex collecting system.

CASE HISTORY

A 40-year-old patient presented to our out-patient department with complaints of dull aching pain occurring in the right flank region since the last six months. There was no history of hematuria. On examination the right kidney was palpable. An ultrasound examination of the patient revealed a single, irregular shaped cyst of size 104.2 x 66.1 mm with echogenic fluid in the lumen, in upper cortex of the right kidney. Intravenous urography showed the upper and middle calyx of the right kidney to be displaced in an arc-like fashion, suggestive of a cyst / mass lesion of the right kidney (Fig. 1). Keeping a provisional diagnosis of renal cyst in mind the patient was advised a contrast enhanced CT scan of the abdomen and pelvis which showed a thick walled, lobulated cystic lesion with thin peripheral calcification and few internal septa, measuring 82.5 x 64.77 x 100 mm arising from the anterior aspect of the right kidney (Fig. 2). The wall of the cyst and the internal septa were seen to enhance post-contrast. With the diagnosis of complex renal cyst (Bosnaick’s type 3) the patient was posted for partial / radical nephrectomy. A retrograde pyelogram done during the operation showed upper calyx of the right kidney to be arc-like, besides a faintly opacified grossly dilated pelvi-calyceal system inferior to the arched upper calyx (Fig. 3). It was at this time that the possibility of a duplex renal system occurred to us. On exploration the patient was found to have a duplicated pelvi-calyceal system with duplex upper ureter (Fig. 4). The lower system had a very short ureter along with obstruction of the pelvi-ureteric junction. The lower pelvi-calyceal system was grossly dilated. However, the upper system was not dilated. The narrowed pelvi-ureteric junction and the short lower ureter were excised and the pelvis of the lower system was anastomosed in an end to side fashion to the ureter of the upper system. Postoperative recovery was uneventful and the patient was found to be progressing well during follow-up.

Differential diagnoses considered in this case were:
- Complex renal cyst (Bosnaick’s type 3)
- Infected cyst (abscess or antibioma)
- Duplex kidney with non-functioning lower pole

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DISCUSSION

Duplicated collecting systems (also known as duplex collecting systems) can be defined as renal units containing two pyelo-caliceal systems that are associated with a single ureter or double ureters. The prevalence of partial duplication found is 0.6%\[2\]. When a single ureteral bud bifurcates before the ampulla bifurcates, a duplex kidney with a bifid renal pelvis or bifid ureter results\[1\].

Fig. 1: Intravenous urography showing the upper and middle calyx of the right kidney displaced in an arc-like fashion, suggestive of a cyst / mass lesion

Fig. 2: NCCT scan showing a thick walled, lobulated cystic lesion with thin peripheral calcification and few internal septa in right kidney

Fig. 3: Retrograde pyelogram showing upper calyx of the right kidney to be arc-like. This is besides a faintly opacified grossly dilated pelvi-calyceal system inferior to the arched upper calyx.

Fig. 4: Intra-operative image showing the lower system having a very short ureter along with obstruction of the pelvi-ureteric junction
Most patients are asymptomatic, with genitourinary tract abnormalities being detected incidentally on imaging studies performed for other reasons. Urinary tract infection and parenchymal scarring is increased in patients with a duplex collecting system; patients can present with pyrexia, pain and dysuria. Ureteropelvic junction obstruction is more common when a duplex kidney exists. Giant hydronephrosis in a duplex kidney can manifest as an extremely large abdominal and retroperitoneal mass; in rare cases, it can cause hypertension.

During ultrasonography, the duplex kidney appears as two central echo complexes with intervening renal parenchyma. Hydronephrosis at one pole is suggestive of a duplex kidney. Although hydronephrosis can occur at either pole, it is more common in the upper one. The ultrasonographic appearance of a duplex kidney is specific but not sensitive. Differentiating an atrophied lower pole moiety of a duplex kidney (nubbin) from other renal masses is difficult.

With excretory urography, duplex kidney is usually longer than the non-duplex kidney. Calyces are asymmetric. Ectopic, upper pole ureteric insertion can produce a non-opacified segment. This mass effect results in the “drooping lily” sign with the depression of the lower pole pelvi-calyceal system. If the lower pole of the duplex kidney is functioning poorly or not at all, the lower pole collecting system may not opacify, and no discernible parenchyma will surround it (Nubbin sign). The appearance of the kidney may consequently resemble that of a non-duplex kidney with a lower polar mass or renal infarct.

In computed tomography, the intervening renal parenchyma in a duplex kidney lacks a collecting system and major vessels. It is described as having a “faceless kidney” appearance, the collecting system in the nubbin or the mass effect of tissue at the pole. Additional relevant findings include focal infarcts, cortical scars and atrophic scarred kidney. CT scan is superior to ultrasonography and excretory urography in diagnosing the lower pole nubbin. In addition, the modality is helpful when function is poor or absent.

CONCLUSION
Careful history, examination and investigation may not rule out congenital abnormality of the kidneys like duplex collecting system. It may require a high index of suspicion as well as some invasive investigation to reach a final diagnosis. However, intra-operative findings can still surprise us with an entirely different diagnosis.

REFERENCES
Case Report

Double Appendix: Report of a Case

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ABSTRACT

A 30-year-old female presented to the surgery outpatient department with complaint of pain in right iliac fossa of one day duration. The pain was associated with nausea and vomiting. On examination, there was localized tenderness and rigidity in the right iliac fossa with positive rebound tenderness. Multiple pigmentation of skin in the abdomen, accessory nipple and scoliosis were also noted. Laboratory investigation revealed neutrophilic leukocytosis. Ultrasound abdomen showed an appendix measuring 4 cm in length and a fibroid uterus. Diagnostic laparoscopy revealed an inflamed appendix with a small blind structure in continuity with the cecum. Operative diagnosis of double appendix was made. Microscopic examination confirmed double appendix with features of appendicitis and periappendicitis in the bigger appendix. We report this case because of its rarity. The surgical resident should be aware of this rare congenital anomaly to avoid missing the other appendix in appendectomy procedures and avoid its medico-legal consequences.

KEY WORDS: appendicitis, congenital anomaly, double appendix

INTRODUCTION

Despite the notorious range of variation in character and position natural to the human vermiform appendix, the extremes of variation (absence or duplication) affect this organ so very rarely that they are worth mentioning and recording. Duplication of vermiform appendix is rare with reported incidence of 0.004%[1] and may be associated with other congenital duplications or other anomalies[2]. Doubled appendix is usually asymptomatic. When symptomatic, they are usually the result of obstruction and inflammation. Majority of the cases are diagnosed at surgery or on postmortem examination. Some of them can be picked up preoperatively on barium enema. The clinical presentation can vary according to the location of the appendixes[3]. Here we report a case of double appendix because of its extreme rarity and discuss its etiology and different types of anatomic presentation.

CASE REPORT

A 30-year-old female patient presented with right lower abdominal pain of one day duration with associated nausea and vomiting. She gave no history of change in bowel habits, urinary symptoms, menstrual disturbance or similar previous attacks. On examination she was afebrile. There was localized tenderness and rigidity with positive rebound tenderness in right iliac fossa. Multiple pigmentation of skin especially in the abdomen, accessory nipple (polythelia) and scoliosis were noted. No mass could be felt. Her pelvic examination did not reveal any positive findings. Laboratory investigations revealed a total white blood count of 24.8 x 10⁹ cells per liter with neutrophilia (72%). Other laboratory investigations including blood urea, creatinine and liver function test were unremarkable. Ultrasound abdomen showed an appendix measuring 4 cm in length and a fibroid uterus with minimal localized collection of fluid, in the right iliac fossa.

With a presumptive diagnosis of acute appendicitis, diagnostic laparoscopy was performed on the day of admission with insufflation of CO₂ gas and insertion of three trocars, two 10 mm ports and one 5 mm port. There was minimal fluid in the pelvis with an inflamed appendix, which could be easily identified. No evidence of perforation or mass formation was noted. However, another blind structure was seen in continuity with the cecum and was incidentally discovered during dissection of mesoappendix (Fig. 1). An operative diagnosis of double appendix was made. The operation was terminated after retrieval of the appendixes with endopouch and exploration of rest...
of small and large bowels, which ruled out any other associated congenital anomaly. Her postoperative course was uneventful and she was discharged on postoperative day five.

Gross pathological examination of the specimen showed duplex vermiform appendix (Fig. 2). The bigger appendix measured 5.1 cm and the small one measured 1.5 in length. Both the appendices were attached to mesoappendix in close proximity. The specimen displayed focal congestion in the serosal aspect of the bigger appendix. Microscopic examination revealed two lumina of appendices having two separate muscle coats and lymphoid follicles in the mucosa (Fig. 3). The bigger and longer appendix revealed mixed acute and chronic inflammatory infiltrate in the mucosa as well as in the muscle coat showing features of acute appendicitis with periappendicitis. The small one showed regular morphology without any inflammation. Thus the operative diagnosis of double appendix was microscopically confirmed with one appendix showing features of acute appendicitis.

**DISCUSSION**

Duplication of the vermiform appendix, originally described in 1930, is rare with a reported incidence of 0.004%[1]. The etiology of double appendix is unknown, but the most rational explanation was offered by Kelly and Hurdon who examined 54 human embryos to explain the origin and development of the appendix[4]. They described a minute budding “transient appendix” on the tip of the cecum in a 6-week-old embryo[4]. This small “transient appendix” usually atrophied or disappeared in the 8-week-old embryo[6]. Hence “transient appendix” is a definite potential for the embryological origin for the development of a supernumerary appendix and the most plausible explanation of the appendix duplex. Cave[5] classified three types of appendicular duplication as:

- **Type A**: Single cecum with one appendix exhibiting partial duplication
- **Type B**: Single cecum with two obviously separate appendices (complete duplicity)
- **Type C**: Duplication of cecum with each cecum bearing its proper appendix

The simplest illustrations of the first type are those curious specimens of ‘double-barrelled’ appendix wherein the single organ presents two distinct lumina throughout either length or throughout only a part thereof[9]. The second type was first recorded by Paterson and Emrys-Robert (1906) wherein a full-term fetus, the subject of ectopia viscerum, spina bifida and other congenital anomalies showed a small ‘sacculated and curved appendix’ lying on each side of the ileo-cecal junction[9]. Type C was first reported by Greig (1934) in which the whole bowel duplicates distal to the site of Meckel’s diverticulum; two separate ceca were present, each bearing its proper vermiform appendix[9].
Wallbridge modified Cave's original classification of duplicated vermiform appendix into three types as follows:

A: Partial duplication of the appendix on a single cecum

B: Single cecum with two completely separate appendices

B1: “Bird-like appendix” called so because of its resemblance to the normal arrangement in birds, where there are two appendices symmetrically placed on either side of the ileo-cecal valve

B2: One appendix arises from the usual site on the cecum, with another rudimentary appendix arising from the cecum along the line of the tenia at varying distance from the first

C: Two ceca, each bearing its own appendix

Though majority of the cases are diagnosed at surgery or on postmortem examination, some of the cases can be picked up preoperatively on barium enema. Peddu et al reported an incidental finding of Type B1 double appendix by barium enema in a 73-year-old man who was investigated for the rectal bleeding. In such cases the patient may be informed about the abnormality; however the role of conventional / laparoscopic appendectomy for the removal of the asymptomatic double appendix has not been well-defined. Although preoperative diagnosis could be made with the aid of radiological studies such as a barium enema, in cases associated with duplication of colon, the majority of cases have been diagnosed at surgery or upon pathological examination.

The present case represents type B2 of appendicular duplication, thought to represent the persistence of the “transient appendix”. Duplication of the vermiform appendix must be distinguished from a solitary diverticulum of the cecum. True double appendices have lymphoid tissue and muscular walls, but a cecal diverticulum does not contain lymphoid tissue and is merely an out-pouching of mucosa and submucosa through a muscular defect. In the current case, there were two separate appendices which were proved microscopically.

Some cases of double appendix are associated with intestinal, genitor-urinary or vertebral malformation. We should be aware of these possible malformations and the patient should be explored for the same at time of operation. The risk of associated malformation seems to be greater in young children, especially those with type B1 and C malformations. In our present case, double appendix was incidentally found while performing laparoscopic appendectomy and we did not find any other gastrointestinal congenital anomalies like intestinal duplications that were commonly associated with double appendix. But she had other anomalies like scoliosis and skin lesions which were recorded for further notification with double appendix in the future. Kothari et al reported duplex appendix in association with imperforate anus.

In patients with double appendix, when only a single appendix is found to be inflamed on exploration or laparoscopy, both the appendices should be removed so as to avoid diagnostic confusion that may arise on removal of a single appendix. To the best of our knowledge, surgical management for the double appendix is same as the conventional / laparoscopic appendectomy. No literature describes any unique technique for double appendix differently. However, one should explore for the possible associated malformation. In the current case, only the bigger and longer appendix was inflamed, however we removed both the appendices including the smaller non-inflamed one.

**CONCLUSION**

Double appendix is extremely rare. Surgical residents should be aware of the possibility of duplication of appendix to avoid missing double appendix and its medico-legal consequences.

**REFERENCES**

Case Report

Oncocytic and Clear Cell Areas in a Solid Pseudopapillary Tumor of the Pancreas: A Case Report

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ABSTRACT

Solid pseudopapillary tumor (SPT) of pancreas is a rare, distinct, low-grade malignant neoplasm. Variable areas like clear cell foci can exist in this tumor, which can easily mislead the pathologist. Diagnosis of the same is important to distinguish from other clear cell lesions in the pancreas. Oncocytoid differentiation is rarer still and can raise doubts about the diagnosis, especially on trucut biopsies. Herein, we discuss a case of SPT of the pancreas exhibiting variable cellular morphology, of which very few cases have been reported in world literature.

KEY WORDS: oncocyty, pancreas, solid pseudopapillary tumor

INTRODUCTION

Solid pseudopapillary tumor (SPT) is an uncommon, low-grade malignant neoplasm accounting for 1% of all exocrine pancreatic tumors. Exact histogenesis of this tumor remains uncertain. As the various names for the tumor suggest, it is a solid and cystic pancreatic neoplasm with characteristic pseudopapillae and sheets of intermediate and small sized polygonal cells with minimal morphological deviation. Herein, we report a case of oncocytic variant of this tumor on account of its rarity and the few cases reported till date.

CASE HISTORY

A 29-year-old lady presented to the surgical outpatient department, with a history of swelling in the upper abdomen of one month duration, which was not associated with pain, vomiting or abdominal distention. Patient had a past history of exploratory laparotomy 10 years ago, for palliative gastrojejunostomy and enterostomy in view of biopsy reported as suspected neuroendocrine tumor of pancreas, which, however, was not removed. On examination, a firm to hard mass of 10 x 7 cm, moving with respiration was palpated in the left hypochondrial region. All routine laboratory investigations were within normal range except an ESR of 40. Ultrasound abdomen was normal and upper GI endoscopy revealed extraluminal compression on stomach. A CT-scan revealed a cystic neoplasm arising from the head of pancreas and a clinical diagnosis of cystic neoplasm of mucinous origin of pancreas was made, in view of which the patient underwent Whipple’s pancreatectomy. Post-operative period was uneventful and the patient was discharged on the tenth post-operative day. The patient had no fresh complaints on follow-up after two months. However, she presented with amenorrhea after four months, post-operatively. On ultrasonography, polycystic ovaries were detected and she was advised for weight reduction. The patient was lost to follow-up after that.

Pathological findings

Gross: The tumor was well-demarcated, nodular and unencapsulated, weighing 911 grams and measuring 16 x 11 x 10 cm. Cut section showed a multiloculated cystic tumor with variegated appearance comprising grey-white, friable irregular solid areas, yellow areas and hemorrhagic foci and peripheral rim of pancreatic tissue.

Microscopy: Sections showed a well demarcated but unencapsulated tumor composed of sheets and trabeculae of loosely cohesive polygonal cells with central ovoid nuclei, few with eccentrically placed nuclei and finely stippled or granular chromatin. Focal clear cell areas (Fig. 1) were identified with abundant cytoplasmic, PAS and mucicarmine negative vacuoles and rare mitotic figures, separated by bands of hyalinised fibrous tissue with myxoid changes. Areas showing solid nests of polygonal cells with abundant eosinophilic granular cytoplasm and central vesicular nucleus with prominent nucleolus were

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seen (Fig. 2). Extensive cystic degeneration with classical pseudopapillae were seen, which helped clinch the diagnosis (Fig. 3). Immunohistochemistry (IHC) performed revealed tumor cells to be positive for vimentin, and negative for endocrine markers (synaptophysin, chromogranin) and the epithelial marker, cytokeratin. Further immunohistochemical markers were later done, including CD117, CD10 and cyclin D1, all of which were positive, thus confirming our diagnosis (Fig. 4).

**DISCUSSION**

The first cases of SPT of the pancreas were described by Frantz[2]. Various synonyms include solid and papillary neoplasm, solid and papillary epithelial neoplasm, papillary-cystic carcinoma, solid and cystic acinar cell tumor of the pancreas relating to gross features and most obvious histological pattern. WHO, in 1996, proposed the name ‘solid-pseudopapillary neoplasm to encompass the two most conspicuous histological features[3]. They account for < 1% of all pancreatic neoplasms[4]. It is most common in women (82%) about 30 years of age but, occasionally, the tumor occurs in older women, men or children[5].

Although the pathogenesis is so far unknown, studies have thrown new insights regarding the same, the most acceptable being of pancreatic duct origin due to the related strong expression of galectin-3 by the neoplastic cells[6].

SPT on fine needle aspiration (FNA) and trucut biopsy samples can often mimic neuroendocrine...
tumors\cite{7}, especially if the classical areas have not been sampled, as may have been the case in this patient, who was earlier misdiagnosed.

Microscopically, classical areas are characterized by pseudopapillae and solid sheets of medium to small sized polygonal cells with vesicular nucleus and rare mitotic figures. This case was distinguished by the presence of focal areas with large polygonal cells with abundant eosinophilic granular cytoplasm and few with prominent nucleoli, along with areas showing multiple cytoplasmic vacuoles of varying sizes in many neoplastic cells. The vacuoles did not contain glycogen or mucin. Clear cells with cytoplasmic vacuoles are seen as a focal change in the classical form of SPT. They are formed by dilatation of the smooth endoplasmic reticulum and mitochondria\cite{1}. Another source of clear cells is foamy macrophages. The differential diagnosis included clear cell endocrine pancreatic neoplasms with small lipid droplets and chromogranin positive neurosecretory granules\cite{7}. Clear cell variant of ductal carcinoma of pancreas is distinguished by the presence of malignant cells with stromal desmoplasia, cytologic atypia, increased mitotic activity and areas of mucin-producing ductal carcinoma. Although serous cystadenoma is composed of clear cells, they contain glycogen and line small or large cystic spaces. Metastatic renal cell carcinoma should be considered in older individuals with cells showing lipid.

Oncocytic areas in SPT have been recently described. Oncocytic changes may mean a favorable prognosis in neoplasms. It is seen in pancreatic neoplasms, and has been reported in acinar cell carcinoma, pancreatoblastoma, and intraductal oncocytic papillary neoplasm of the pancreas\cite{8}. Oncocytic acinar cell carcinomas are usually solid, do not have a papillary and/or glandular component and are clinically aggressive\cite{8}. Intraductal oncocytic papillary neoplasm of the pancreas is composed of cystically dilated ducts with long, thick papillae with fibrovascular cores, lined by cells with eosinophilic granular cytoplasm, and single eccentric nuclei\cite{9}. Other unusual cell types described in SPT include pleomorphic spindle cells and cells with melanocytic differentiation\cite{1}.

IHC shows strong vimentin and CD10 positivity of SPT tumor cells, negativity for chromogranin, and weak or focal positivity for epithelial markers. Of late, SPT has been found to be positive for CD117 and cyclin D1\cite{9}. The clinical features, gross characteristics and immunoprofile of all the variants are similar to those of the classical SPT.

CONCLUSION
This is an interesting case of SPT of the pancreas with oncocytoic and clear cell areas posing diagnostic difficulty, especially on trucut biopsies. Clinicopathological correlation, microscopic pattern, extensive search for classical, non-oncocytic areas of the tumor with immunohistochemical stains help to arrive at an accurate diagnosis in this scenario.

REFERENCES
Celiac Disease as Uncommon Cause of Death in Type 1 Diabetes Mellitus: A Case Study

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ABSTRACT

Celiac disease (CD) is one of the most common immune mediated diseases. This disease is triggered by ingestion of wheat gluten and related other cereal proteins, particularly those in rye and barley. The prevalence of CD in type 1 diabetes in children is 1:6 to 1:103 and in adults 1:16 to 1:76. In spite of that, there is no current clinical evidence supporting routine screening of adult type 1 diabetic patients for CD. Most patients who have diabetes and CD have non-classic forms of CD, with various presentations such as short stature, sideropenic anemia, or hypertransaminasemia; in many cases, patients are totally symptom free. CD elevates the mortality risks of a wide array of diseases in CD patients. This case had an atypical presentation of CD, and died unexpectedly because of the disease. We report this case to emphasize on the value of high index of suspicion of CD in type 1 diabetes mellitus.

KEY WORDS: diet, gluten free, immune-mediated diseases, tissue, transglutaminase

INTRODUCTION

Celiac disease (CD) is one of the most common immune-mediated diseases[1]. Atypical asymptomatic form and absent gastrointestinal manifestations, are common, and a case may be discovered on duodenal biopsy for any other reason or immunology screening[2]. Studies in the United States and Europe show the prevalence of the disease approaching 1%[3,4]. Based on small bowel biopsy diagnosis, the prevalence of CD in type 1 diabetes in children is 1:6 to 1:103 and in adults 1:16 to 1:76[5]. CD is most often present before the onset of diabetes. Most patients who have both diabetes and CD have non-classic forms of CD, with various presentations such as short stature, sideropenic anemia, or hypertransaminasemia; in many cases, patients are totally symptom free[6]. In spite of that, there is no current clinical evidence supporting routine screening of an adult type 1 diabetic patient for CD[7].

CASE HISTORY

A twenty-two-year old Kuwaiti single female presented to us in the outpatient department with abdominal pain, bilateral lower limb edema and skin pigmentation of two months duration. She was known case of type 1 diabetes mellitus for 13 years on intensive insulin regimen, but non-compliant to her medication and with poor glycemic control. She had irregular menstruation and good scholastic performance. Her body weight was 42 kg, height was 158 cm and body mass index was 16.8 kg/m². On clinical examination, she was conscious, alert and oriented. Her BP was 110/70 mmHg, pulse rate was 75 bpm, temperature was 36.8 ºC and respiratory rate was 22/min. General examination revealed bilateral lower limb pitting edema with brownish, patchy and scaly pigmentation on the extremities but without pruritus. There was neither lymphadenopathy nor thyroid enlargement. Examination of the chest, heart, abdomen and CNS was unremarkable. Routine urine examination was unremarkable. Liver function tests showed an elevation of ALT (85 IU/l, normal up to 45 IU/l), AST (58 IU/l, normal up to 40 IU/l) and ALP (181 IU/l, normal up to 132 IU/l), with decreased plasma albumin to (18 g/l, normal 35 - 50 g/l). Total bilirubin was 11 μmol/l (normal upto 17 μmol/l) and direct bilirubin was 3 μmol/l (normal upto 5 μmol/l). INR was elevated to 2.3. 24-hour urinary protein was normal (160 mg/day). Complete blood picture showed a hemoglobin level of 123 g/l(normal female range 135 - 150 g/l), WBC count was 7400/mm³ (normal range 4000 – 11,000/mm³) and platelets were 230,000/mm³ (normal range 150,000 – 450,000/mm³). Abdomen and pelvic ultrasonography was unremarkable, Investigations for hepatitis A, B

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and C, antinuclear antibodies and anti-double strand antibodies were negative. α-1 antitrypsin and serum ceruloplasmin were within normal limits. Serum protein electrophoresis was normal. Further enquiry into patient’s history, revealed that the patient had frequent attacks of diarrhea over the previous three months.

The common association of CD with type 1 diabetes mellitus attracted our attention to the possibility of this disorder as a cause of the presenting picture of this patient. Anti-gliadin antibodies were evaluated together with anti-endomysial antibodies and tissue transglutaminase antibodies (tTGA). Anti-gliadin antibodies were elevated (IgA 62 u/l, normal < 5 u/l) IgG was 69 u/l (normal < 7 u/l), anti-endomysial antibodies were positive and tTGA were elevated (IgA was > 120 u/l, normal < 7 u/l). These findings were highly suggestive of CD. We proceeded for upper gastrointestinal endoscopy with duodenal biopsy for histopathology which showed nearly complete villous atrophy with intraepithelial lymphocytic infiltration.

The patient was diagnosed to have CD with elevated liver enzymes as a result. Further investigations showed decreased level of vitamin D (41.45 nmol/l, normal 50 - 80 nmol/l) and serum iron (3 μmol/l, normal 6 - 7 μmol/l). A dietitian and gastroenterologist were consulted and gluten free diet (GFD) was started for the patient with multivitamin supplementation including vitamin D, K, folic acid, and iron.

Four weeks later, although liver enzymes became normal, we were informed by the mother that her daughter was poorly compliant for GFD.

Five weeks after diagnosis, the patient was admitted to the hospital because of urinary tract infection, diarrhea and increasing lower limb edema. Clinical examination was unremarkable except for bilateral lower limb pitting edema and brownish patchy skin pigmentation on the extremities. Plasma albumin was as low as 15g/dl. Random blood sugar was 12.7 mmol/l with no acetone in urine and blood pH was 7.39. CBC showed Hb of 12.1g/dl WBCs 15,000/mm³ (85% were polymorphs) and platelets were 235,000/mm³. Urine culture and sensitivity were sent. Empirical antibiotic ciprofloxacin 500 mg BD was started and this choice was confirmed by the result of urine culture and sensitivity test. IV albumin 20 g twice daily was started with intensive insulin regimen.

The patient became distressed after six days of admission with a temperature of 38.1 ºC and hypoxia. X-Ray chest showed bilateral bronchopneumonia. Patient was shifted to the ICU and ventilated as her respiratory rate had reached 35/min. Antibiotics were modified to Tazocin 4.5 g/6 hourly and IV clarithromycin 500 mg BD. Tracheal aspirate was sent for culture and sensitivity test along with blood culture and sensitivity. The patient did not respond well to antibiotics, and deteriorated within two days and died. Result of tracheal aspirate and blood culture showed <em>Klebsiella pneumoniae</em>.

**DISCUSSION**

CD is triggered by ingestion of wheat gluten and related other cereal proteins, particularly those in rye and barley. These molecules induce an inflammatory response in the small intestine, resulting in villous atrophy, crypt hyperplasia and lymphocytic infiltration[1]. CD is sometimes divided into clinical subtypes. The terms classic apply to cases which meet the classic features of CD, which include chronic diarrhea, abdominal distension and pain, weakness and sometimes malabsorption. In contrast in atypical asymptomatic form, no gastrointestinal manifestations are present, but features such as anemia, osteoporosis, short stature, infertility and neurological problems are common, and a case may be discovered on duodenal biopsy for any other reason or immunology screening. Nevertheless, the disease remains widely under-recognized[2].

Studies in the United States and Europe show the prevalence of the disease approaching 1%[3,4]. Based on small bowel biopsy diagnosis, the prevalence of CD in type 1 diabetes in children is 1:6 to 1:103 and in adults is 1:16 to 1:103[5]. CD is most often present before the onset of diabetes[6]. The association between the development of both diseases may be explained by the inheritance of common major histocompatibility complex immunogenotypes that influence the presentation of auto antigens to CD4+ T-Cells[7].

In adults with CD, hypertransaminasemia is frequent and normalizes with gluten free diet. If not, liver biopsy should be done to rule out autoimmune hepatitis and primary biliary cirrhosis[8]. Isolated elevation of ALP (alkaline phosphatase) is less common and may reflect presence of secondary hyperparathyroidism (bone-specific form). Hypoalbuminemia and prolonged prothrombin time may indicate severe form of malabsorption[9].

The American Gastroenterological Association (AGA) Institute recommended that testing for CD should be considered in symptomatic patients who are at particular risk. These include those with unexplained iron deficiency anemia, premature osteoporosis, Down syndrome, unexplained hypertransaminasemia, autoimmune hepatitis and primary biliary cirrhosis.

The diagnostic tests for CD widely used now include IgA antiendomysial antibodies and IgA tTGA (sensitivity - 90% and specificity - 95%), but distal duodenal biopsy remains the gold standard diagnostic method (showing total or partial villous atrophy, crypt lengthening and increased lymphocytes in lamina propria and intraepithelial region). Biopsy is indicated even if serology is negative and CD is still
highly suspected. Compliance with GFD is likely to be protective against development of non-Hodgkin lymphoma and dermatitis herpeticformis in CD. It can improve nutritional status, body mass index, increase insulin requirement in type 1 diabetes, but no convincing change in diabetes control[10].

CD patients have overall, two-fold increased mortality risk compared with the general population. CD elevates the mortality risks of a wide array of diseases in CD patients, including non-Hodgkin lymphoma (SMR 11.4), small intestinal cancer (SMR 17.3), autoimmune diseases as rheumatoid arthritis (SMR 7.3) and diffuse disease of connective tissue (SMR 17.0), allergic disorders such as bronchial asthma (SMR 2.8), inflammatory bowel disease including ulcerative colitis and Crohn’s disease (SMR 70.9), diabetes mellitus (SMR 3.0), disorders of immune-deficiency (SMR 20.9), tuberculosis (SMR 5.9), pneumonia (SMR 2.9) and nephritis (SMR 5.4)[11].

CONCLUSION

It is important to have a high index of suspicion for CD in adult patients with type 1 diabetes mellitus, in view of the common association between these two diseases and the elevated mortality risks for a wide array of diseases in CD patients.

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Squamous Cell Carcinoma of the Penis: Magnetic Resonance Imaging Findings

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ABSTRACT
Most primary penile malignancies are squamous cell carcinoma (SCC) and occur most often during the 6th and 7th decades of life. Uncircumcised men are more often affected, probably because of the chronic irritative effect of smegma. An association between human papilloma viruses 16 and 18 and SCC of the penis has also been reported. We describe a case of a 43-year-old uncircumcised Asian male patient who presented with an ulcerating penile mass. MRI images were helpful in making a preoperative diagnosis of penile cancer. MR imaging can play an important role in the evaluation of a penile mass.

KEY WORDS: penile mass, penile SCC, MRI of penis

INTRODUCTION
Squamous cell carcinoma (SCC) of the penis usually begins on the glans as a focal epithelial thickening with or without ulceration[1]. The lesions are generally not painful, and affected patients often delay seeking medical attention[2]. After penectomy with 2 cm margins, patients with tumors that have not invaded the corpora cavernosa have a greater than 95% 3-year survival rate[3]. Survival decreases markedly with cavernosal invasion or with spread to regional lymph nodes[4]. Although not often performed in the acute setting, MR imaging can play an important role in the evaluation of penile mass[5]. Ultrasound (US) can help detect solid penile mass in the majority of patients[6].

CASE HISTORY
An Indian uncircumcised male patient aged 43 years presented with a painless penile mass of six-month duration. The clinical examination revealed a solid mass lesion underneath the foreskin and the patient was referred to our department for an MRI. MRI revealed a solid isointense to low signal intensity mass lesion both on T1-weighted (Fig. 1) and T2-weighted (Fig. 2) images, mainly located at the left lateral aspect of the glans of the penis extending to its dorsal aspect with a definite invasion of the hypointense adjacent tunica albuginea (Fig. 3). However, the urethra was not compromised (Fig. 3). After Gd-chelate agent injection, homogenous enhancement pattern was elicited with multiple signal void foci that were confirmed to be hypervascular on color Doppler study (Fig. 3 and Fig. 4). The clinical examination revealed a solid mass lesion underneath the foreskin (Fig. 5) with concealed external meatus and with discharge from cutaneous fistula from the foreskin.

Diagnosis and Treatment: Circumcision with excisional biopsy was done and histopathological examination confirmed penile SCC. So the patient underwent partial penectomy with 2 cm safety margin. The patient was planned for bilateral ilio-inguinal lymph node dissection.

DISCUSSION
Carcinoma of the urethra and penis is extremely rare, accounting for less than 1% of genitourinary cancers in males[7]. Histological examination reveals SCC in more than 95% of cases of penile carcinoma[8]. At MR imaging, SCC is usually hypointense relative to the corpora on both T1- (Fig. 1) and T2- (Fig. 2) weighted images. At contrast-enhanced imaging, these lesions do increase in signal intensity but less so than the normal corporal bodies. Although neither MR nor other imaging is generally needed for diagnosis (the tumor is usually visible at physical examination), MR imaging may be performed for staging purposes. In the commonly used Jackson staging system, stage I lesions are confined to the glans or prepuce, stage II lesions

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Fig. 1: Coronal T1WI: Hypointense mass is seen relative to corpora

Fig. 2: Axial T2WI: Hyperintense pattern of the mass, compared to the corpora

Fig. 3: Post-contrast axial WI: Homogenously enhanced mass

Fig. 4: Post-contrast coronal T1WI: Multiple signal void foci represent hypervascularity

Fig. 5: Exploration of the mass before operation

Regardless of the organ of origin, MRI aids in the delineation of the extent of tumor dissemination, enabling detection of invasion into the corpora cavernosa or tunica albuginea. As mentioned previously, surgical treatment of carcinoma of the penis consists of either partial or total penectomy. Follow-up physical examination to look for local recurrence is limited in allowing the detection of pelvic lymphadenopathy and distant metastases. Both computed tomography (CT) and MR imaging depict pelvic lymphadenopathy, but MR imaging is superior for evaluation of the primary lesion.

CONCLUSION

Regardless of the organ of origin, MRI aids in the delineation of the extent of tumor dissemination, enabling detection of invasion into the corpora cavernosa or tunica albuginea. As mentioned previously, surgical treatment of carcinoma of the penis consists of either partial or total penectomy. Follow-up physical examination to look for local recurrence is limited in allowing the detection of pelvic lymphadenopathy and distant metastases.
deep recurrence. Therefore, cross-sectional imaging is often performed. In addition to identification of sites of tumor recurrence, MR imaging can be helpful in the identification of normal post-surgical findings. Complications of surgery of the lower urinary tract can also be shown clearly with MR imaging.

REFERENCES

Case Report

Unstable Carpometacarpal Dislocation of Ulnar Four Fingers – An Easily Overlooked Injury

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ABSTRACT

Multiple carpometacarpal (CMC) joint dislocations are rare. These clinical entities require significant amount of force to produce dislocation at this inherently stable joint level. We present a case of unstable dorsal dislocation of ulnar four carpometacarpal joints without associated fractures which was fixed with multiple K-wires with good functional outcome. Although carpometacarpal dislocations are uncommon entities, the case is reported here not just by virtue of its rarity but also because of a tendency for such injuries to be overlooked by surgeons with resultant delay in diagnosis and treatment.

KEY-WORDS: internal fixation, k-wire

INTRODUCTION

Carpometacarpal (CMC) dislocations other than thumb are uncommon injuries accounting for less than 1% of hand injuries. It is rare for multiple CMC dislocations to occur without associated fractures[1,2]. Disability is significantly severe in untreated cases and initially neglected cases. The dislocation of multiple joints at CMC junction is not an anticipated diagnosis in cases of polytrauma with hand swelling. The injury is often missed or overlooked owing to many factors, both on the surgeon’s side and patient’s side[3].

CASE HISTORY

A 26-year-old male presented to the emergency department after riding his motorbike into a roadside vehicle with gross swelling on the dorsum of the right hand and inability to move the wrist. The wrist movements were grossly restricted but finger movements were elicitable with pain. Distal hand perfusion was adequate.

After adequate first aid measures, an X-ray of the hand in antero-posterior and oblique plane was ordered. Hand radiographs primarily revealed no bony injury as screened by emergency medical officer against awaited metacarpal fracture. A dorsal splint was applied taking cognizance of severe hand contusion. Screening of radiographs by consultants gave a clue to missed diagnosis of CMC dislocation. There was overlapping of joint surface of metacarpal bases over carpals. The lateral view hand radiograph promptly clarified diagnosis of CMC dislocation of ulnar four fingers. Lateral radiograph revealed a significant dorsal offset of metacarpal complex over carpals. There was no associated fracture of adjacent CMC entities (Fig. 1A, B)

An unsuccessful closed reduction with slab application was attempted with linear traction along line of fingers. The reduction could only be maintained with multiple trans-CMC Kirschner wires (K-wires) (Fig. 1C). Postoperatively, wrist was splinted on dorsal side for six weeks; K-wires were removed at the end of six weeks. Reduction was satisfactorily sustained after slab removal as confirmed by check radiographs. Full range of motion of hand was regained with support of active hand-specific physiotherapy in the early convalescent period showing excellent functional result (Fig. 2A, B).

DISCUSSION

Less commonly encountered injury of CMC dislocation gains importance in emergency scenarios by virtue of it getting overlooked and a resultant delayed diagnosis. The delayed diagnosis and consequent delayed treatment of this joint dislocation has implications in functional outcome of wrist[4].

Many factors play a role in such uninvited overlook. Occurrence in settings of polytrauma, primary management by junior ranks, customary less
revealing antero-posterior and oblique radiographs of hand, gross swelling of hand are incriminating factors. Literature also suggests repeated mistakes with this diagnosis even by experts[3].

Multiple CMC dislocations are often a high energy trauma often occurring in motorcyclists and boxers. Deduced pathway of injury appears to be forceful impact on metacarpal bases with a closed fist[5]. The patient will often have a diffuse swelling of dorsum of hand and distal forearm. It may be fluctuant depicting a hematoma collection. The characteristic hump of dislocation at root of hand is often masked by swelling of hand and forearm.

Routinely ordered X-rays in antero-posterior and oblique plane suggest the diagnosis. Lateral projection radiograph will confirm the multiple CMC dislocations in suspicious cases[6]. Often dislocation is dorsal. There can be associated fracture of adjacent carpal or metacarpal bones. The clues for such an obscure diagnosis are loss of parallelism between joint spaces at base of metacarpals and carpals. There will be an overlap of joint surfaces of base of metacarpals over carpus. There can be appreciable offset of fifth metacarpal base as in our case[3,7]. A lateral radiograph will affirm the misalignments of metacarpals over carpus.

Fig. 1: (A) Initial X-rays showing dorsal dislocation of ulnar four metacarpal bases with overlapping of joint surfaces; (B) Lateral X-ray showing dorsal offset of metacarpal complex; (C) postoperative radiograph showing satisfactory reduction and stabilization of joint with multiple Kirschner wires

Fig. 2: (A) Radiograph at four weeks post injury after removal of K-wire showing satisfactory healing and congruent reduction of joint surfaces; (B) Post-rehabilitation photographs showing gradual improvement in hand function from four weeks to eight weeks
Dislocation at CMC level essentially needs emergent reduction as soon as it is diagnosed. Failure to do so may result in impaired functional ability of hand, impaired grip, loss of transverse and longitudinal arches of hand and stiffness of hand. Danger of ulnar nerve injury in proximity of 5th CMC joint and reflex sympathetic dystrophy will always be there.[3,8].

Closed reduction is successful in fresh dislocations less than 10 days old. It can be maintained in plaster cast in majority cases. Intraoperatively ascertained unstable dislocations can be supplemented with trans-CMC K-wires along with external immobilisation. Late presentations and irreducible dislocations will require open relocation.[1,7,9]. Removal of external splint and K-wires can be done as early as six weeks. An early physiotherapy will hasten rehabilitation of hand. Good functional results can be expected in properly treated cases with anatomical reduction.

CONCLUSION

Diagnosis of CMC dislocation requires a high index of suspicion, careful examination and good radiography. Otherwise, the outcome will be inferior. The treatment will require a relocation of joint structures on emergency basis and its maintenance to ensure a favourable outcome.

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Prostatic Adenocarcinoma and Chronic Lymphocytic Leukemia: A Case Report

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Kuwait Medical Journal 2012; 44 (4): 344 - 346

ABSTRACT

We report a rare case of a collision tumor. Our patient was found to have prostatic adenocarcinoma colliding with chronic lymphocytic leukemia, with no previous risk factors or even a clinical suspicion. We review the literature for similar cases and make an attempt to address the possible shared risk factors.

KEYWORDS: collision tumors, multiple primaries,

INTRODUCTION

Synchronous involvement of the same tissue by two different tumors is rare, but has been well-reported[1]. Many examples of collision tumors having either prostatic adenocarcinoma or chronic lymphocytic leukemia were described, but only very rarely showed both neoplasms colliding together. Being a curious phenomenon which causes confusion in the diagnosis and treatment for physicians, with an ominous effect on the patient, we report this case in order to look for possible common risk factors and a proposed way of treatment.

CASE REPORT

A 76-year-old man, presented to the Jordan University Hospital in December, 2008 complaining of fatigue and weight loss of two months duration. He was a known case of diabetes mellitus. Physical examination demonstrated hepatosplenomegaly, but no enlarged lymph nodes. No urological findings were evident in history or physical examination. The initial workup showed abnormal complete blood count numbers. Hemoglobin concentration was 8.5 g/dl and the packed cell volume (PCV) was 25%. The white blood count was 22,000, out of which 77% were lymphocytes, while neutrophils formed 21% of blood cells. Platelet count was normal. The peripheral blood film showed abnormal complete blood count numbers. The peripheral blood film showed diffuse lymphocytosis. The lymphocytes were small and mature with numerous smudge cells and minimal atypia. Astonishingly, a bone marrow trephine biopsy demonstrated the same neoplastic lymphocytes intermingling with aggregates of large epithelioid cells (Fig. 1). Immunohistochemical study revealed the latter to be of prostatic origin (Fig. 2). Flow cytometry confirmed the diagnosis of chronic lymphocytic leukemia (CLL) (Fig. 3).

The patient was retrospectively investigated for prostatic carcinoma. Serum total prostate specific antigen (PSA) was highly elevated (100), and pelvic magnetic resonance image (MRI) scan detected a prostatic mass and liver metastasis.

DISCUSSION

A collision tumor is defined as the co-existence of two adjacent but histologically different malignant neoplasms occurring in the same organ without histological admixture or an intermediate cell population zone[1]. It is termed collision tumor when the components are present in the originating organ and collision metastasis when they collide in a distant site discontinuous from the original organ. When both tumors fuse and intermingle to the extent that it is difficult to distinguish between them, the process then is called a composite tumor[1,2]. Another similar phenomenon is the hybrid tumor, which is composed of two different tumor entities, each of which conforms with an exactly defined tumor category and has an identical origin within the same topographical area[3]. This is different from multiphasic tumor which corresponds to one tumor entity with different morphological patterns. Discordant tumors are two
different types of tumors occurring far from each other\textsuperscript{[4]}\textsuperscript{[i]}. Examples are illustrated in Table 1.

Inherited cancer syndromes are examples of conditions where patients develop multiple different tumors and might have collision or composite phenomena. However, in sporadic cases, the tumors are unpredictable and might be causatively unrelated. Being an interesting phenomenon, with a confusing
impact on the diagnosis and modality of treatment, dozens of cases of collision tumors have been reported. Besides, an attempt to discover a relationship between the originating tumors is usually made.

Our case does not fall under any definition, as it includes one primary and one metastatic tumor. However, as there is no strict definition for this situation in the literature, we prefer to consider it as collision tumor, and to restrict “collision metastasis” to cases when both tumors collide outside their primaries. Prostatic carcinoma occurring together with CLL was reported in the literature, but with different clinical scenarios. None of the previously reported cases showed a collision metastasis between prostate carcinoma and CLL. We are unaware of a similar reported case where collision metastasis was the first hint for the presence of two hidden neoplasms.

It was demonstrated that patients with CLL are susceptible to develop other primary malignancies. In the large study carried out by Hisada et al., 2% of patients with CLL developed prostate carcinoma, with a relative risk of 1.01. The study did not specify the relationship between the two neoplasms or the common risk factors between them. However, the relative increased incidence of both neoplasms in older ages, with the relative indolent course of CLL, may suggest this occurrence. The immune derangement status, believed to occur in indolent course of CLL, may suggest this occurrence.

CONCLUSION
We conclude that a collision tumor of both CLL and prostate carcinoma exists, although rare. Physicians should be aware of the possible second malignancy in patients with CLL, and should not stop at peripheral blood smear findings alone.

Table 1: The differences between collision tumor and other similar phenomena

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Example</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collision tumor</td>
<td>Endometrial carcinoma and adjacent endocervical carcinoma</td>
<td>Two tumors with different cell origin arise proximal to each other</td>
</tr>
<tr>
<td>Collision metastasis</td>
<td>Axillary lymph node showing breast and ovarian carcinomas</td>
<td>The two tumors meet outside their primary organs</td>
</tr>
<tr>
<td>Composite tumor</td>
<td>A lymph node containing classic Hodgkin’s lymphoma and T-cell lymphoma</td>
<td>Two different tumors fuse and intermingle between each other</td>
</tr>
<tr>
<td>Hybrid tumor</td>
<td>Concomitant basal cell adenoma and canalicular adenoma of the parotid</td>
<td>Two tumor entities share a similar cellular origin</td>
</tr>
<tr>
<td>Multiphasic tumor</td>
<td>Wilms’ tumor</td>
<td>A single tumor entity with different morphologic patterns</td>
</tr>
</tbody>
</table>

ACKNOWLEDGMENT
Conflict of interest: none

REFERENCES
To date, little evidence is available about the association between peptic ulcer disease and commercially available cyclooxygenase-2 inhibitors (COX-2 inhibitors) in Taiwan. Therefore, we conducted this population-based cohort study from the National Health Insurance (NHI) program in Taiwan to directly compare the effects of individual COX-2 inhibitors on the risk of peptic ulcer disease. The details of insurance program can be found in previous studies[1-4]. This study consisted of 1388 patients aged 20 years or older who had ever used COX-2 inhibitors (770 men and 618 women, mean age 51.4 years, standard deviation 18.5 years), and 5403 subjects who never used COX-2 inhibitors (3080 men and 2323 women, mean age 50.6 years, standard deviation 18.2 years), frequency matched with sex, age, and index year for comparison, from 2000 to 2006. The incidence of peptic ulcer disease (based on International Classification of Diseases 9th Revision - Clinical Modification, ICD-9 531, 532, 533, and 534) at the end of 2009 was determined. An index date for patients with peptic ulcer disease was defined as their date of diagnosis. Subjects diagnosed with peptic ulcer disease before the index date were excluded from the study. The subjects, who had ever used combination of COX-2 inhibitors, or ever used aspirin, or other non-steroidal anti-inflammatory drugs (NSAIDs), were excluded from this study. Other co-morbidities before the index date were defined as follows: Helicobacter pylori infection (ICD-9 041.86), tobacco use (ICD-9 305.1), and alcoholism (ICD-9 303, 305.00, 305.01, 305.02, 305.03 and V11.3, and A-code A215). The potentially related medications included were as follows: proton pump inhibitor, histamine-2 receptor antagonist, clopidogrel, ticlopidine, systemic corticosteroid, warfarin, and heparin.

We found that the incidence of peptic ulcer disease was 3.26-fold higher in the COX-2 inhibitors group, compared with the non-COX-2 inhibitors group (19.28 per 1000 person-years Vs 5.91 per 1000 person-years, 95% confidence interval - CI = 2.63 - 4.04). After controlling for variables that were significantly related to COX-2 inhibitors found in the Chi-square test, the multivariable Cox proportional hazard regression showed use of COX-2 inhibitors was substantially associated with increased risk of peptic ulcer disease (hazard ratio - HR = 3.23, 95% CI = 2.59 - 4.04). In sub-analysis, individual COX-2 inhibitors, including celecoxib (HR = 3.29, 95%CI = 2.00 - 5.39), meloxicam (HR = 3.19, 95%CI = 2.33 - 4.36), nabumetone (HR = 3.19, 95% CI = 2.39 - 4.25), and nimesulide (HR = 2.21, 95% CI = 1.08-4.52), would substantially increase the risk of peptic ulcer disease, respectively.

Previous studies have reported that COX-2 inhibitors can reduce the risk of upper gastrointestinal ulcers, compared with non-selective NSAIDs[5, 6]. In Rostom et al’s systematic review[7], COX-2 inhibitors correlate with lower risk of upper gastrointestinal ulcers (relative risk, 0.26 - 0.39), compared with non-selective NSAIDs. An observational study by Hsiang et al in Taiwan[8], the annual incidence of
upper gastrointestinal ulcers in patients using COX-2 inhibitors was 4.6%. In this present study, the overall risk of peptic ulcer disease was 3.23-fold higher in patients using COX-2 inhibitors, compared with non-use of COX-2 inhibitors. In sub-analysis, patients who used celecoxib, meloxicam, or nabumetone for less than three months were at higher risk of peptic ulcer disease. As reported in the literature, celecoxib is more selective and safe than the other non-specific NSAIDs.[5] However, this present study showed that use of celecoxib had the highest risk of peptic ulcer disease. Because this is an observational study, we do not have a plausible explanation for this phenomenon.

It is widely established that COX-2 inhibitors are only relatively rather than absolutely safe. These findings further alert clinicians about the risk of peptic ulcer disease when prescribing COX-2 inhibitors.

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**Authorship:** The first two authors contributed equally to this study.

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

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2012, 44 (4): 349 - 352

Risk Factors for Multiple Sclerosis in Kuwait: A Population-Based Case-Control Study

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Neuroepidemiology 2013; 40:30-35 (DOI: 10.1159/000341240)

Multiple sclerosis (MS) is a chronic and progressively disabling inflammatory autoimmune disorder of the central nervous system. MS has a multifactorial etiology and is triggered by environmental factors in individuals with complex genetic risk profiles. The epidemiology of MS changes with the spatial and temporal distribution of these genetic and nongenetic risk factors. This population-based matched case-control study aimed to determine the risk factors for MS in Kuwait. From May 2 to 9, 2010, we enrolled 101 confirmed MS cases using the list frame maintained by the Multiple Sclerosis Association of Kuwait. For each case, two population controls individually matched for age (± 2 years), gender and nationality were selected. Data on demographic, socioeconomic variables, potential genetic and environmental factors were collected using a structured questionnaire. For a case, the questions were directed to the period that preceded the recognition of the disease, while for each of the two matched controls, a date of ‘pseudodiagnosis’ of MS was established, i.e. the date on which the control subject was of the same age as his/her matched case was at MS diagnosis and accordingly questions were directed to the preceding period. The multivariable conditional logistic regression model showed that compared with controls, the cases were significantly more likely to have a family history of MS [matched odds ratio (OR)\textsubscript{adj} = 6.7; 95% confidence interval (95% CI): 2.5 - 18.0; p < 0.001] or have suffered from a head trauma in the past before MS diagnosis (matched OR\textsubscript{adj} = 2.6; 95% CI: 1.2 - 5.5; p = 0.014). Furthermore, compared with controls, cases were significantly more likely to have stayed in Kuwait during the Iraqi invasion of 1990 (matched OR\textsubscript{adj} = 1.8; 95% CI: 1.1 - 3.5; p = 0.022). This study showed that a family history of MS, a history of head injury, and presence in Kuwait at the time of the Iraqi invasion of 1990 were associated with a significantly increased MS risk. Future retrospective cohort studies by using existing biological and epidemiological databases may provide a clue to MS etiology.

Rhizoremediation of Oil-Contaminated Sites: A Perspective on the Gulf War Environmental Catastrophe on the State of Kuwait

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The Gulf War brought about to the State of Kuwait some of the worst environmental pollution as a result of oil spill. Since 1995, research programs have been initiated to avoid further damage to the Kuwaiti desert and marine environment and to restore and rehabilitate the polluted land, water, and air ecosystems. During the following 15 years, different bioremediation methods both on laboratory and small field scales were tested and evaluated. The findings of these studies were implemented to establish a bio-park in which ornamental shrubs and trees were grown in bioremediated soil. This review will focus on Kuwait’s experience in rhizoremediation and its positive impacts on oil-contaminated sites.
Some Epidemiological Measures of Cancer in Kuwait: National Cancer Registry Data from 2000 -2009

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Introduction: Cancer is the second cause of death in Kuwaiti people after cardiovascular diseases. This study is the first in the country to describe epidemiological measures related to cancer in this population.

Methods: Data obtained from the Kuwait cancer registry included all Kuwaiti patients between years 2000 - 2009. Analyses were conducted using age-specific rates, the age-standardization-direct method, 95% confidence intervals (95% CI), cumulative risk by the age of 74 years, limited-duration prevalence, mortality and forecasting to year 2029.

Results: It was noted that the commonest cancer sites were colorectal with an age standardized incidence rate (ASIR) of 16.1/100,000 in males and breast (49.4/100,000) in the female population. The trend of cancer incidence (1974 - 2009) showed no statistically significant change. First causes of death due to cancer were female breast 8(6.4 - 9.6)/100,000 and lung (males) 8.1/100,000 (6.6 - 10.0). The risk of developing cancer by the age of 74 was 13.4% (1/8) and 14.3% (1/7) in males and females respectively, and the risk of dying from cancer in the same age group was 1/17 and 1/23. By the end of 2009, prevalent cases represented 0.52% of the Kuwaiti population. In the year 2029, the total number of cancer cases is expected to reach 1200 cases compared to 889 cases in 2009.

Conclusions and recommendations: The most common cancers in Kuwait (breast, colorectal and lung) are largely preventable. Prompt and effective interventional prevention programs that vigorously involve diet, anti-smoking and physical activity for both sexes are urgently required.

Clinical Audits in a Postgraduate General Practice Training Program: An Evaluation of 8 Years’ Experience

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Background: Clinical audit can be of valuable assistance to any program which aims to improve the quality of health care and its delivery. Yet without a coherent strategy aimed at evaluating audits’ effectiveness, valuable opportunities will be overlooked. Clinical audit projects are required as a part of the formative assessment of trainees in the Family Medicine Residency Program (FMRP) in Kuwait. This study was undertaken to draw a picture of trainees’ understanding of the audit project with attention to the knowledge of audit theory and its educational significance and scrutinize the difficulties confronted during the experience.

Methodology/Principal Findings: The materials included the records of 133 audits carried out by trainees and 165 post course questionnaires carried out between 2004 and 2011. They were reviewed and analyzed. The majority of audit projects were performed on diabetic (44.4%) and hypertensive (38.3%) care. Regarding audits done on diabetic care, they were carried out to assess doctors’ awareness about screening for smoking status (8.6%), microalbuminuria (19.3%), hemoglobin A1c (15.5%), retinopathy (10.3%), dyslipidemia (15.8%), peripheral neuropathy (8.8%), and other problems (21.7%). As for audits concerning hypertensive care, they were carried out to assess doctors’ awareness about screening for smoking status (38.0%), obesity (26.0%), dyslipidemia (12.0%), microalbuminuria (10.0%) and other problems (14.0%). More than half the participants (68.48%) who attended the audit course stated that they
Hospitalization Patterns and Outcomes of Infants with Influenza A(H1N1) in Kuwait

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Introduction: Infants represent an important risk group for influenza associated hospitalizations and mortality. This study evaluated the clinical presentations, hospitalization course and outcome of infants hospitalized with the pandemic influenza A H1N1 [Influenza A(H1N1)pdm09] in relation to their previous health status.

Methodology: We conducted a retrospective chart review of hospitalized infants with laboratory-confirmed Influenza A(H1N1)pdm09 infection in two hospitals in Kuwait. Demographic characteristics, pre-existing high-risk medical conditions, clinical presentations, complications and mortality were analyzed. Previously healthy infants’ data were compared with infants with pre-existing high-risk medical conditions for severity of the illness and outcome.

Results: We identified 62 infants comprising 32% of all admissions with Influenza A(H1N1)pdm09. The median age ± SD was 7 ± 4 months. Nineteen (31%) had pre-existing high-risk medical conditions. Complications were documented in 53% of previously healthy infants compared to 47% in high-risk infants. Mean duration of hospitalization was 4.9 days in healthy infants and 6.7 for infants with high-risk medical conditions. Bacterial pneumonia complicated 7% of previously healthy infants compared to 26% with high-risk conditions (P = 0.03). Four infants (6.5%) required admission to the intensive care unit (ICU), of whom three had high risk medical condition.

Conclusion: The majority of hospitalized infants with Influenza A(H1N1)pdm09 were previously healthy. Prolonged hospitalization, ICU admission and mortality were more observed in infants with high-risk medical conditions. According to the latest Advisory Committee on Immunization Practices (ACIP) recommendations, annual influenza vaccination is recommended for any child six months of age and older, particularly those with risk factors.

Pre-hypertension and Hypertension in College Students in Kuwait: A Neglected Issue

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J Family Community Med 2012; 19:105-112

Objective: To determine the proportion of pre-hypertension and hypertension in college students in Kuwait and their related risk factors.
Materials and Methods: A total of 803, randomly selected students aged 17 to 23 years (346 male, 457 female) from different colleges in Kuwait, were included in the study between 2009 and 2010. Systolic and diastolic blood pressure measurements were taken by trained personnel. Pre-hypertension was defined as systolic pressure between 120 and 139 mm Hg or diastolic pressure between 80 and 89 mm Hg. Risk factor measurements that were determined, included smoking, body mass index (BMI), and family history of hypertension. Blood samples were collected and impaired glucose tolerance (IGT) and lipid profile levels were determined.

Results: There were no hypotensive students. Normotensives constituted 53.5% (n=430), pre-hypertensives formed 39.5% (n = 317), and hypertensive students comprised of 7% (n = 56). The overall proportions of hypertension and pre-hypertension were higher among male students (85.7 and 64.4%) than female students (14.3 and 35.6%), respectively. Hypertensive and pre-hypertensive students versus normotensive students had significantly higher levels of BMI-based obesity, smoking, glycated hemoglobin (HbA1c), and IGT. Also, hypertensive and pre-hypertensive, compared to normotensive students, had significantly higher proportions (21.4, 18.3, and 4.0%, respectively) of risky high-density lipoprotein (HDL) level (< 1 mg / dL), cholesterol (7.1, 3.8, and 1.4%, respectively), and triglycerides (TG) (17.9, 9.1, and 7.9%, respectively) where p was< 0.001, 0.016, and 0.051, respectively.

Conclusion: Hypertensive and pre-hypertensive students showed elevated levels of lipids and BMI-based obesity more than normotensive students. TG, HDL, HbA1c, and cholesterol appeared to influence pre-hypertension.

Closed Reduction and Percutaneous Cannulated Screws Fixation of Displaced Intra-Articular Calcaneus Fractures

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Foot Ankle Surg 2012; 18:164-179

Background: Displaced intra-articular calcaneal fractures remain a therapeutic challenge due to fracture complexity and different treatment options. One of the adverse effects of operative treatment is secondary damage to soft tissues. To avoid soft tissue complications, several less invasive procedures have been introduced. The most frequently used minimally invasive technique is closed reduction of fracture and percutaneous cannulated screws fixation.

Method: This study evaluates the medium-term outcome of a new technique of percutaneous treatment in 60 cases operated in Al-Razi orthopedic hospital in Kuwait in the period from 2007 to 2009. The described technique applies the principle of closed manipulation with new reduction method using a medial subperiosteal tunnel to manipulate the fragments. The technique involves new method of distribution of screws required to fix the fracture.

Results: According to the American Orthopedic Foot and Ankle Society Hind foot Score, 38.3% of all cases (22 cases) had excellent results, 41% good (25 cases), fair results in 15% (9 cases), and poor results in 5% (4 cases). The overall satisfactory results (excellent and good) were 79.3%.

Conclusion: The technique is suitable for most types of intra-articular fractures especially in patients with compromised soft tissues in which open reduction and internal fixation is contraindicated.
Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

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Internal Medicine for Primary Care: Gastro/Endo/Neuro
Dec 28 - 30, 2012
United States / New York
Contact: Medical Education Resources
Tel: 303-798-9682; Fax: 303-798-5731
Email: info@mer.org

Primary Care Guide to Emergencies
Dec 28 - 29, 2012
United Kingdom / London
Contact: Anthone Nancy, Medical-Credits by MedCW
Tel: 011-32-1-643-8402
Email: nancy.anthone@medical-credits.com

Medical CBT: Ten-Minute Techniques For Real Doctors (Cognitive Behavior Therapy)
Jan 3 - 5, 2013
British Columbia / Whistler
Contact: Greg Dubord, MD, CME Director, CBT
Canada
Tel: 877-466-8228
Email: registrar@cbt.ca

Breast Imaging From A - Z
Jan 4 - 6, 2013
United States / California / Pebble Beach
Contact: Wendy Ryals, Office Manager, IICME
Tel: 205-467-0290; Fax: 205-467-0195
Email: wryals@iicme.net

13th Annual Multi-Specialty Conference on Medical Negligence & Risk Management
Jan 5 - 8, 2013
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Tel: 800-688-2475; Fax: 617-638-4905

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Drug Development, Pharmacokinetics and Imaging
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Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

8th Medical Dermatology Conference
Jan 10, 2013
United Kingdom / London
Contact: Chris Garrett, British Association of Dermatologists
Email: conference@bad.org.uk

Pathogenic Processes in Asthma And COPD
Jan 10 - 15, 2013
New Mexico / Santa Fe
Contact: Keystone Symposia on Molecular and Cellular Biology
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525
Email: info@keystonesymposia.org

6th Imaging & Physiology Summit / 7th Chronic Total Occlusion Live 2013
Jan 11 - 12, 2013
South Korea / Seoul
Contact: Secretariat, CardioVascular Research Foundation (CVRF)
Fax: 011-82-2-475-6898
Email: cvrf@summitMD.com
FRCS (Tr and Orth) Viva Course for Orthopaedic Surgeons
Jan 11 - 12, 2013
United Kingdom
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6th International Hokkaido Trauma Conference
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Japan / Rusutsu
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Fax: 011-61-3-9342-8623

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Fax: 847-330-1090
Email: moshi@aad.org

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2nd ESCMID Conference on Invasive Fungal Infections
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Tel: 011-39-41-526-2530; Fax: 011-39-41-527-1129

Advanced Cognitive Therapy Studies - An Introduction to Service Development
Jan 16 - Mar 20, 2013
United Kingdom / Oxford
Contact: Department for Continuing Education, University of Oxford
Tel: 011-44-18-6527-0360
Email: oxtc@oxfordhealth.nhs.uk

2013 ICJR 5th Annual Winter Hip & Knee Course
Jan 17 - 20, 2013
United States / Colorado / Vail
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Tel: 760-942-7859; Fax: 760-942-1140
Email: info@icjr.net

2013 National Conference of Urological Society Of India
Jan 17 - 20, 2013
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Contact: Dr. Jaydeep Date, Organising Secretary, Lokmanya Hospital
Email: usicon2013@gmail.com

5th Breast Gynecological International Cancer Conference
Jan 17 - 18, 2013
Egypt / Cairo
Contact: Prof. Hesham El Ghazaly, Professor of Clinical Oncology, Head of Oncology Department [GOTHI], BGICS President, BGICS
Tel: 011-20-100-130-0236
Email: bgicc2010@gmail.com

Controversies and Updates in Vascular Surgery (CACVS) 2013
Jan 17 - 19, 2013
France / Paris
Contact: Michèle Caboste, divine [id]
Fax: 011-33-4-9157-1961
Email: mcaboste@divine-id.com

Current Topics in Anesthesia
Jan 17 - 20, 2013
United States / Florida / Duck Key
Contact: Northwest Anesthesia Seminars, Conference / Meetings, Northwest Anesthesia Seminars, Inc.
Tel: 800-222-6927; Fax: 509-547-1265
Email: info@nwas.com
Forthcoming Conferences and Meetings December 2012

Advances in Thyroid Cancer Diagnosis and Therapy  
Jan 18 - 19, 2013  
United States / Arizona / Phoenix  
Contact: Beverly Hastings, American Association of Clinical Endocrinologists  
Tel: 904-404-4162  
Email: bhastings@aace.com

Controversies & Updates in Venous Disease  
Jan 18 - 19, 2013  
France / Paris  
Contact: Michèle Caboste, divine [ID]  
Fax: 011-33-4-9157-1961  
Email: mcaboste@divine-id.com

Essential Obstetric Ultrasound Course  
Jan 18, 2013  
United Kingdom / London  
Contact: Royal College of Obstetricians and Gynaecologists  
Email: events@rcog.org.uk

Cardiology, Endocrinology + Infectious Diseases: South East Asia CME Cruise  
Jan 20 - Feb 3, 2013  
Singapore / Singapore  
Contact: Sea Courses Cruises  
Tel: 888-647-7327; Fax: 888-547-7337  
Email: cruises@seacourses.com

Malaria  
Jan 20 - 25, 2013  
United States / Louisiana / New Orleans  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525  
Email: info@keystonesymposia.org

22nd Annual Musculoskeletal MR Course  
Jan 21 - 25, 2013  
United States / Florida / Palm Beach  
Contact: Wendy Ryals, Office Manager, IICME  
Tel: 205-467-0290 ext. 1; Fax: 205-467-0195  
Email: wryals@iicme.net

Delayed Effects of Disease & Treatment on Individuals Who Have Had Head & Neck Cancer  
Jan 21, 2013  
United Kingdom / London  
Contact: Royal Marsden  
Tel: 011-44-20-7808-2921  
Email: conferencecentre@rmh.nhs.uk

MRI of the Joints  
Jan 21 - 25, 2013  
Slovenia / Ljubljana  
Contact: Jana Schiro  
Tel: 011-386-1-522-8530; Fax: 011-386-1-522-2497  
Email: emricourse.lj@gmail.com

4th Advanced Course on Knee Surgery  
Jan 22 - 27, 2013  
France / Val D’isère  
Contact: Advanced Course on Knee Surgery  
Tel: 011-33-4-7906-2123; Fax: 011-33-4-7906-1904  
Email: knee2012@valdisere-congres.com

Operative Skills in Urology: Modules 1 And 2  
Jan 22 - 23, 2013  
United Kingdom / London  
Contact: Royal College of Surgeons of England  
Tel: 011-44-20-7869-6300  
Email: education@rcseng.ac.uk

Advanced Cardiovascular Intervention  
Jan 23 - 25, 2013  
United Kingdom / London  
Contact: Millbrook Medical Conferences  
Tel: 011-44-14-5555-2559; Fax: 011-44-14-5555-7377  
Email: ACI2013@millbrookconferences.co.uk

Case Studies in Structural Heart Disease And Intervention  
Jan 24 - 27, 2013  
United States / Florida / Miami Beach  
Contact: Sheila Fick, Meeting Specialist, Mayo Clinic  
Tel: 507-284-0536; Fax: 507-266-7403  
Email: fick.sheila@mayo.edu

20th International Symposium on Pancreatic and Biliary Endoscopy  
Jan 25 - 27, 2013  
United States / California / Los Angeles  
Contact: Lalita Gupta, Continuing Medical Education, Cedars - Sinai Medical Center  
Tel: 310-423-5548; Fax: 310-423-8596  
Email: cme@cshs.org

Cardio/Pulmonary Medicine for Primary Care  
Jan 25 - 27, 2013  
United States / Nevada / Las Vegas  
Contact: Medical Education Resources  
Tel: 303-798-9682; Fax: 303-798-5731  
Email: info@mer.org

Fetal/Neonatal Imaging  
Jan 25 - 27, 2013  
United States / Florida / Orlando  
Contact: Society for Pediatric Radiology  
Tel: 703-648-0680 ext. 4691; Fax: 703-648-1863  
Email: sprmeetings@acr.org

Advanced Suturing and Wound Repair  
Jan 26 - 27, 2013  
United States / Texas / San Antonio  
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute  
Tel: 800-674-2631; Fax: 512-329-0442  
Email: julie@npinstitute.com
Melanoma 2013: 23rd Annual Cutaneous Malignancy Update  
Jan 26 - 27, 2013  
United States / California / San Diego  
Contact: Scripps Health  
Tel: 858-652-5400; Fax: 858-652-5565  
Email: med.edu@scrippshealth.org

Society of Thoracic Surgeons 49th Annual Meeting  
Jan 26 - 30, 2013  
United States / California / Los Angeles  
Contact: Society of Thoracic Surgeons  
Tel: 312-202-5800; Fax: 312-202-5801

14th International Colorectal Forum  
Jan 27 - 29, 2013  
Switzerland / Verbier  
Contact: M & S Event Services  
Tel: 011-41-27-771-8585; Fax: 011-41-27-771-8586  
Email: icf@ms-event.ch

Cancer Immunology and Immunotherapy  
Jan 27 - Feb 1, 2013  
British Columbia / Vancouver  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525  
Email: info@keyestonesymposia.org

Arrhythmias and the Heart: A Cardiology Update  
Jan 28 - Feb 1, 2013  
Hawaii / Maui  
Contact: Mayo Clinic in Rochester  
Tel: 507-284-2509  
Fax: 507-284-0532

Geriatrics: A Primary Care Approach to the Aging Population  
Jan 28 - Feb 1, 2013  
United States / Florida / Sarasota  
Contact: Trish or Tara, American Medical Seminars, Inc.  
Tel: 866-267-4263 or 941-388-1766; Fax: 941-365-7073  
Email: tkeeton@ams4cme.com

32nd Annual Advanced Nephrology: Nephrology for the Consultant  
Jan 31 - Feb, 2013  
United States / California / San Diego  
Contact: Bermellyn Imamura, Continuing Medical Education, UC San Diego  
Tel: 619-543-7602  
Email: ocme@ucsd.edu

School Mental Health: Treating Students K - 12  
Feb 1 - 2, 2013  
United States / Massachusetts / Boston  
Contact: Continuing Medical Education, Harvard Medical School  
Tel: 617-384-8600; Fax: 617-384-8686  
Email: hms-cme@hms.harvard.edu

3rd World Congress of Regional Anaesthesia and Pain Therapy  
Feb 3 - 7, 2013  
Australia / Sydney  
Contact: Secretariat, SAPMEA  
Tel: 011-61-8-8274-6048; Fax: 011-61-8-8274-6000  
Email: wcrap@sapmea.asn.au

Mitochondria, Metabolism & Myocardial Function – Basic Advances to Translational Studies  
Feb 3 - 8, 2013  
United States / Colorado / Keystone  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525  
Email: info@keyestonesymposia.org

New Frontiers in Neurodegenerative Disease Research  
Feb 3 - 8, 2013  
New Mexico / Santa Fe  
Contact: Keystone Symposia on Molecular and Cellular Biology  
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525  
Email: info@keyestonesymposia.org

Head and Neck Imaging  
Feb 4 - 8, 2013  
Austria / Vienna  
Contact: Ines Fischer  
Fax: 011-43-1-40400-4898  
Email: ines.fischer@meduniwien.ac.at

24th International Congress on Anti-Cancer Treatment: ICACT 2012  
Feb 5 - 7, 2013  
France / Paris  
Contact: Valérie Caillon, International Medical Events (IME)  
Tel: 011-33-1-4743-5084; Fax: 011-33-1-4743-2226  
Email: valerie.caillon@im-events.com

2nd World Congress of Cutaneous Lymphomas (Wccl)  
Feb 6 - 9, 2013  
Germany / Berlin  
Contact: Legal Organizer (PCO), MCI Deutschland GmbH  
Tel: 011-49-30-204-590; Fax: 011-49-30-204-5950  
Email: lymphomas2013@mci-group.com
Forthcoming Conferences and Meetings December 2012

Infant, Child, and Adolescent Medicine
Feb 6 - 9, 2013
United States / Florida / Orlando
Contact: American Academy of Family Physicians
Tel: 800-274-2237 or 913-906-6000; Fax: 913-906-6075

Operative Skills in Neonatal and Paediatric Surgery
Feb 6 - 7, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

AAOS Total Ankle Arthroplasty
Feb 7 - 9, 2013
United States / Illinois / Rosemont
Contact: Customer Service Department, American Association of Orthopaedic Surgeons
Tel: 800-626-6726 (US and Canada) or 847-823-7186
Email: custserv@aaos.org

Emirates Surgical Pathology Conference 2013
Feb 7 - 9, 2013
United Arab Emirates / Abu Dhabi
Contact: Sujatha Krishensen, Project Co-ordinator, Meeting Minds: Experts
Tel: 011-97-14-427-0492; Fax: 011-97-14-427-0493
Email: pco@espc2013.com

Meniscus 2nd International Meeting
Feb 7 - 9, 2013
France / Versailles Orthopedics
Contact: Viviane Barbarisi, MCO Congres
Fax: 011-33-4-9509-3801
Email: viviane.barbarisi@mcocongres.com

BRONCOCON 2013: 18th Annual Conference of Indian Association for Bronchology
Feb 8 - 10, 2013
India / Vadodara
Contact: Dr. Anand K. Patel, Conference Secretariat, Global Meridian Hospital
Tel: 011-91-98-7977-1079
Email: dranandkpatel@gmail.com

Toronto Cataract Course 2013
Feb 9, 2013
Canada / Ontario / Toronto
Contact: Continuing Education and Professional Development, University of Toronto
Tel: 416-978-2719
Email: info-opt1301@cepdtoronto.ca

Cardiology Update 2013
Feb 10 - 15, 2013
Switzerland / Davos
Contact: Zurich Heart House
Tel: 011-41-44-250-4080; Fax: 011-41-44-250-4090
Email: contact@zhh.ch

33rd Annual Meeting of The Society of Maternal-Fetal Medicine (SMFM): The Pregnancy Meeting
Feb 11 - 16, 2013
United States / California / San Francisco
Contact: SMFM
Tel: 202-863-2476; Fax: 202-554-1132

Transcranial Doppler Course
Feb 13 - 15, 2013
United States / California / Los Angeles
Contact: Karen Einstein, Office of Continuing Medical Education, UC Los Angeles
Tel: 310-206-0626

36th Annual Advanced Ultrasound Seminar: Ob/Gyn
Feb 14 - 16, 2013
United States / Florida / Lake Buena Vista
Contact: American Institute of Ultrasound in Medicine
Tel: 800-638-5352 or 301-498-4100
Fax: 301-498-4450
Email: ddelanko@aium.org

Sclerotherapy
Feb 15 - 16, 2013
United States / Tennessee / Nashville
Contact: Julie Woods, Registration and Product Coordinator, National Procedures Institute
Tel: 800-674-2631; Fax: 512-329-0442
Email: julie@npinstitute.com

2nd American Society For Nutrition Middle East Congress 2012 (ASNME 2013)
Feb 20 - 22, 2013
United Arab Emirates / Dubai
Contact: Pure Spot Congress and Event Organizers
Tel: 011-20-2-267-2144
Email: Info@EGYPURE.org

Asian Pacific Society of Cardiology 2013
Feb 21 - 24, 2013
Thailand / Pataya
Contact: Pattama Thuanchai, Project Manager, Kenes Asia
Tel: 011-66-02-748-7881; Fax: 011-66-02-748-7880
Email: apscoffice2013@apsc2013.org
8th International Breast Cancer Congress  
Feb 22 - 24  
Iran / Tehran  
Tel: 011-98-21-2274-8001 ext. 2; Fax: 011-98-21-2274-8001 ext. 2  
Email: drakbari.drakbari@gmail.com

Obstetric Ultrasound: Setting the Standard for 2013  
Feb 22 - 24, 2013  
Canada / Ontario / Toronto  
Contact: Elizabeth Gan, CME Administrative Course Director, University of Toronto  
Tel: 416-586-4800 ext. 2489; Fax: 416-586-5958  
Email: egan@mts.mtsinai.on.ca

23rd Annual Neuroscience Conference: Brain Plasticity & Neurorehabilitation  
Mar 4 - 6, 2013  
Canada / Ontario / Toronto  
Contact: Paula Ferreira, Baycrest  
Tel: 416-785-2500 ext. 2363  
Email: P.Ferreira@baycrest.org

11th International Congress on Alzheimer’s And Parkinson’s Disease  
Mar 6 - 10  
Italy / Florence  
Contact: Kenes International, Media and Advertising, Kenes International  
Tel: 011-41-22-908-0488  
Fax: 011-41-22-908-9140  
Email: adpd@kenes.com

3rd Emirates Haematology Conference  
Mar 7 - 9, 2013  
United Arab Emirates / Dubai  
Contact: Bahaa Eldin Okasha, Project Manager, Meeting Minds: Experts  
Tel: 011-971-4427-0492  
Email: pco@ehc2013.com

6th Dubai Anaesthesia 2013  
Mar 7 - 9, 2013  
United Arab Emirates / Dubai  
Contact: Hana Holy, Project Manager, INDEX Conferences and Exhibitions Est  
Tel: 011-971-4-362-4717 ext. 120; Fax: 011-971-4-362-4718  
Email: hana.holy@index.ae

6th International Conference on Ocular Infections (ICOI)  
Mar 7 - 10, 2013  
United States / California / Santa Monica  
Contact: Shirley Dinenson, Conference secretariat, Paragon Conventions  
Tel: 011-41-22-533-0948; Fax: 011-41-22-580-2953  
Email: sdinenson@paragon-conventions.com

International Conference on Cerebral Palsy & Developmental Medicine  
Mar 8 - 10, 2013  
India / Lucknow  
Contact: R. P. Shah Memorial Trust for Children with Disabilities  
Tel: 011-91-930-554-2233

Vascular Ultrasound Course  
Mar 12 - 13, 2013  
United Kingdom / Birmingham  
Contact: Secretariat, Wessex Scientific  
Fax: 011-44-13-8435-0132  
Email: info@wessexscientific.com

7th International Dip Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy  
Mar 14 - 16, 2013  
Italy / Florence  
Contact: Kenes International, Kenes International  
Tel: 011-41-22-908-0488; Fax: 011-41-22-906-9140  
Email: dip@kenes.com

Essentials of Bronchoscopy  
Mar 14 - 15, 2013  
United States / Illinois / Northbrook  
Contact: American College of Chest Physicians  
Tel: 847-498-1400; Fax: 847-498-5460

Neurology/Psychiatry for Primary Care Physicians  
Mar 15 - 17, 2013  
United States / Nevada / Las Vegas  
Contact: Medical Education Resources  
Tel: 303-798-9682; Fax: 303-798-5731  
Email: info@mer.org

Oncology  
Mar 15, 2013  
United Kingdom / Edinburgh  
Contact: Eileen Strawn, Symposium Co-ordinator, Royal College of Physicians of Edinburgh  
Tel: 011-44-13-1247-3619; Fax: 011-44-13-1220-4393  
Email: e.strawn@rcpe.ac.uk

Endobronchial Ultrasound  
Mar 16 - 17, 2013  
United States / Illinois / Northbrook  
Contact: American College of Chest Physicians  
Tel: 847-498-1400; Fax: 847-498-5460

Interdisciplinary Prostate Cancer Congress  
Mar 16, 2013  
United States / New York / New York  
Contact: Physicians’ Education Resource  
Tel: 609-451-0258; Fax: 609-257-0705  
Email: info@gotoper.com
Forthcoming Conferences and Meetings December 2012

2013 Neonatal Ultrasound Course. Why, How and When an Ultrasound Image?
Mar 18 - 21, 2013
Italy / Florence
Contact: Organizing Secretariat, AIM Group International
Tel: 011-39-55-23-388 ext.1; Fax: 011-39-55-248-0246
Email: ultrasound2013@aimgroup.eu

Epidemiology & Prevention | Nutrition, Physical Activity & Metabolism 2013 Scientific Sessions
Mar 19 - 22, 2013
United States / Louisiana / New Orleans
Contact: American Heart Association
Tel: 888-242-2453 or 214-570-5935
Email: scientificconferences@heart.org

Specialty Skills in Coloproctology Stage 1 (ST3-5)
Mar 19 - 20, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk
Website: http://www.rcseng.ac.uk/courses/course-search/colorectal-surgery-stage-i

11th European Meeting on Hiv & Hepatitis: Treatment Strategies & Antiviral Drug Resistance
Mar 20 - 22, 2013
Italy / Rome
Contact: Wilco Keulen, Virology Education B.V.
Tel: 011-31-30-230-7140; Fax: 011-31-30-230-7148
Email: wilco.keulen@vironet.com

CIT 2013: China Interventional Therapeutics
Mar 20 - 23
China / Beijing
Contact: Lifeng Dai, International Registration, Chinese Medical Association
Tel: 011-86-10-8515-8473
Email: lfdai@citmd.com

Monitoring of Airway Diseases
Mar 21 - 23, 2013
Belgium / Liege
Contact: European Respiratory Society
Fax: 011-41-21-213-0100
Email: school@ersnet.org

Specialty Skills in Coloproctology Stage 2 (ST6-8)
Mar 21 - 22, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

21st National Association for Study of the Liver
Mar 22 - 24, 2013
India / Hyderabad
Contact: Ritu Saigal, APM, Kenes India
Tel: 011-91-11-4519-9100; Fax: 011-91-11-2551-3052
Email: inasl2013@gmail.com

Adult Infectious Diseases: Evidence Based Primary Prevention and Treatment
Mar 25 - 27, 2013
United States / California / Anaheim
Contact: Orly Light, Director of MCE Conferences, MCE Conferences
Tel: 888-533-9031; Fax: 858-777-5588
Email: info@mceconferences.com

Thyroid and Parathyroid Masterclass
Mar 25, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

17th Pan Arab Conference on Diabetes
Mar 26 - 29, 2013
Egypt / Cairo
Contact: Conference Secretariat, Pure Spot Congress and Event Organizers
Tel: 011-20-2-2672-1944; Fax: 011-20-2-2671-8421
Email: pure@onlinediabetes.net

Head and Neck Surgical Anatomy: ‘Hands On’ Cadaver Workshop
Mar 26, 2013
United Kingdom / York
Contact: Hull York Medical School
Email: postgraduate@hyms.ac.uk

7th Middle East Cardiovascular Conference: MECC 2013
Mar 30 - Apr 2, 2013
Turkey / Istanbul
Website: http://www.mecc.ir/

Nuclear Receptors & Friends: Roles in Energy Homeostasis & Metabolic Dysfunction
Apr 3 - 8, 2013
Austria / Alpbach
Contact: Keystone Symposia on Molecular and Cellular Biology
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525
Email: info@keystonesymposia.org

Specialty Skills in Oncoplastic and Breast Reconstruction Surgery Level I
Apr 3 - 4, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk
Controversies in Rheumatology & Autoimmunity 2013
Apr 4 - 6, 2013
Hungary / Budapest
Contact: Ronit Eisenbach, APM, Kenes International
Tel: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: cora@kenes.com

Society for Emergency Medicine In Singapore Annual Scientific Meeting 2013
Apr 6 - 7, 2013
Singapore / Singapore
Contact: SEMS ASM 2013, Society for Emergency Medicine in Singapore
Email: semsasm2013@gmail.com

Intermediate Skills In Laparoscopic Surgery
Apr 9 - 10, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

7th World Congress on Controversies in Neurology (CONY)
Apr 11 - 14, 2013
Turkey / Istanbul
Contact: Congress Secretariat, ComtecMED
Tel: 011-972-3-566-6166; Fax: 011-972-3-566-6177
Email: cony@comtecmed.com

Advances in Diabetes and Insulin Therapy - Adit 2013
Apr 11 - 14, 2013
Bulgaria / Sofia
Contact: Rok Bolcina, Registration and Housing Manager, POTNIK d.o.o.
Email: info@adit-conf.org

22nd Biennial Congress of the South African Arthroplasty Society
Apr 17 - 20, 2013
South Africa / Winterton
Contact: Congress Secretariat, ICE Solution
Tel: 011-27-11-911-1921; Fax: 011-27-11-911-1939
Email: tracey@icesolution.co.za

Annual Paediatric Update Conference 2013: Operative Skills in Neurosurgery
Apr 17 - 19, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2013 World Congress on Osteoarthritis
Apr 18 - 21, 2013
United States / Pennsylvania / Philadelphia
Contact: Annemarie Kehler, Meeting & Registration Coordinator, Osteoarthritis Research Society International
Tel: 856-642-4429; Fax: 856-439-0525
Email: akehler@oarsi.org

5th Pan Arab Congress of Sexual Health
Apr 18 - 20, 2013
United Arab Emirates / Dubai
Contact: Adel Zakaria, Congress Organizer, Charisma Travel
Tel: 011-21-2-2216-3858; Fax: 011-20-2-2418-4645
Email: mohamedtarekan@gmail.com

Comprehensive Colposcopy
Apr 18 - 21, 2013
United States / Georgia / Atlanta
Contact: American Society for Colposcopy and Cervical Pathology
Tel: 301-733-3640; Fax: 301-733-5775

Update in General Surgery 2013
Apr 18 - 20, 2013
Ontario / Toronto
Contact: Continuing Education and Professional Development, University of Toronto
Tel: 416-978-2719
Email: info-sur1304@cepdtoronto.ca

Emergency Radiology in Burgundy
Apr 20 - 26, 2013
France / Beaune
Contact: Joanne Porter, Joint Department of Medical Imaging, University of Toronto
Tel: 416-340-4800 ext. 8921; Fax: 416-340-3900
Email: joanne.porter@uhn.ca

International Society for Neurochemistry / American Society for Neurochemistry 2013 Meeting
Apr 20 - 24, 2013
Mexico / Cancun
Contact: Sheilah Jewart, ISN-ASN Cancun 2013
Email: SJewart@isn-asncancun2013.org

Musculoskeletal Ultrasound Course for Rheumatologists - Fundamentals
Apr 20 - 21, 2013
United States / Illinois / Chicago
Contact: American College of Rheumatology
Tel: 800-636-4766 (US & Canada) or 415-979-2265; Fax: 415-293-5231
Email: ACRProfMtgS@cmrus.com
<table>
<thead>
<tr>
<th>Conference Name</th>
<th>Date</th>
<th>Location</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrology 2013</td>
<td>Apr 21 - 26, 2013</td>
<td>United States / Massachusetts / Boston</td>
<td>Contact: Harvard Medical School, Department of Continuing Education, Agri Meetings; Tel: 617-384-8600; Email: <a href="mailto:hms-cme@hms.harvard.edu">hms-cme@hms.harvard.edu</a></td>
</tr>
<tr>
<td>14th International Workshop on Clinical Pharmacology of HIV Therapy</td>
<td>Apr 22 - 24, 2013</td>
<td>United Kingdom / Liverpool</td>
<td>Contact: Wilco Keulen, Virology Education B.V; Tel: 011-31-30-230-7140; Fax: 011-31-30-230-7148; Email: <a href="mailto:wilco.keulen@vironet.com">wilco.keulen@vironet.com</a></td>
</tr>
<tr>
<td>1st International Pediatric Psycho-Oncology Workshop</td>
<td>Apr 22 - 25, 2013</td>
<td>Egypt / Cairo</td>
<td>Contact: Dr. Mohammad ElShami, Director of the psychiatric department, Children Cancer Hospital, Egypt 57357; Tel: 011-20-2-2535-1500; Email: <a href="mailto:mohammad.elshami@57357.com">mohammad.elshami@57357.com</a></td>
</tr>
<tr>
<td>Hot Topics In Anesthesia + ACLS + NRP + PALS</td>
<td>Apr 22 - 25, 2013</td>
<td>United States / Nevada / Las Vegas</td>
<td>Contact: Northwest Anesthesia Seminars, Inc.; Tel: 509-547-7065; Fax: 509-547-1265; Email: <a href="mailto:info@nwas.com">info@nwas.com</a></td>
</tr>
<tr>
<td>Malaria Vaccines for the World</td>
<td>Apr 22 - 24, 2013</td>
<td>Switzerland / Lausann</td>
<td>Contact: John Herriot, Meetings Management; Tel: 011-44-1483-427-440; Fax: 011-44-1483-428-516; Email: <a href="mailto:jherriot@meetingsmgmt.u-net.com">jherriot@meetingsmgmt.u-net.com</a></td>
</tr>
<tr>
<td>Angioplasty Summit TCTAP 2013</td>
<td>Apr 23 - 26, 2013</td>
<td>South Korea / Seoul</td>
<td>Contact: Harim Jin, Summit MD; Email: <a href="mailto:cvrf@summitmd.com">cvrf@summitmd.com</a></td>
</tr>
<tr>
<td>34th Annual Advances in Infectious Diseases: New Directions for Primary Care</td>
<td>Apr 24 - 26, 2013</td>
<td>United States / California / San Francisco</td>
<td>Contact: Office of Continuing Medical Education, UCSF CME Registration Office; Tel: 415-476-5808; Fax: 415-502-1795; Email: <a href="mailto:info@ocme.ucsf.edu">info@ocme.ucsf.edu</a></td>
</tr>
<tr>
<td>International Society for Heart &amp; Lung Transplantation (ISHLT) 33rd Annual Meeting &amp; Scientific Sessions</td>
<td>Apr 24 - 27, 2013</td>
<td>Canada, Quebec / Montreal</td>
<td>Contact: ISHLT; Tel: 972-490-9495; Fax: 972-490-9499; Email: <a href="mailto:meetings@ishlt.org">meetings@ishlt.org</a></td>
</tr>
<tr>
<td>8th International Congress on Vascular Access</td>
<td>Apr 25 - 27, 2013</td>
<td>Czech Republic / Prague</td>
<td>Contact: Congress Secretariat, GUARANT International; Tel: 011-420-284-001-444; Fax: 011-420-284-001-448</td>
</tr>
<tr>
<td>Bit’s 4th Annual World DNA and Genome Day (WDD-2013)</td>
<td>Apr 25 - 27, 2013</td>
<td>China / Nanjing</td>
<td>Contact: Jessica Tong, WDD-2013, BIT Congress, Inc.; Tel: 011-86-411-8479-9609 ext. 801; Fax: 011-86-411-8479-9629; Email: <a href="mailto:Jessica@dnaday.com">Jessica@dnaday.com</a></td>
</tr>
<tr>
<td>Geriatric Medicine</td>
<td>Apr 25 - 27, 2013</td>
<td>New Mexico / Albuquerque</td>
<td>Contact: American Academy of Family Physicians; Tel: 800-274-2237 or 913-906-6000; Fax: 913-906-6075</td>
</tr>
<tr>
<td>43rd Annual Aesthetic Plastic Surgery Symposium 2013</td>
<td>Apr 26 - 27</td>
<td>Canada, Ontario / Toronto</td>
<td>Contact: Continuing Education and Professional Development, University of Toronto; Tel: 416-978-2719; Email: <a href="mailto:info.cepd@utoronto.ca">info.cepd@utoronto.ca</a></td>
</tr>
<tr>
<td>23rd European Congress of Clinical Microbiology And Infectious Diseases</td>
<td>Apr 27 - 30, 2013</td>
<td>Germany / Berlin</td>
<td>Contact: Congrex Switzerland Ltd.; Tel: 011-41-61-686-7777; Fax: 011-41-61-686-7788; Email: <a href="mailto:basel@congrex.com">basel@congrex.com</a></td>
</tr>
<tr>
<td>5th International Conference: Advances in Orthopaedic Osseointegration</td>
<td>May 1 - 31, 2013</td>
<td>Sweden / Gothenburg Orthopedics</td>
<td>Contact: Office of Continuing Medical Education, UCSF CME Registration Office; Tel: 415-476-5808; Fax: 415-502-1795; Email: <a href="mailto:info@ocme.ucsf.edu">info@ocme.ucsf.edu</a></td>
</tr>
</tbody>
</table>
1. DIABETES

What is diabetes?
Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body’s systems, especially the nerves and blood vessels.

KEY FACTS
• 346 million people worldwide have diabetes.
• In 2004, an estimated 3.4 million people died from consequences of high blood sugar.
• More than 80% of diabetes deaths occur in low- and middle-income countries.
• WHO projects that diabetes deaths will double between 2005 and 2030.
• Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type 2 diabetes.

Type 1 diabetes
Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. The cause of type 1 diabetes is not known and it is not preventable with current knowledge.

Symptoms include excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes and fatigue. These symptoms may occur suddenly.

Type 2 diabetes
Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) results from the body’s ineffective use of insulin. Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity.

Symptoms may be similar to those of Type 1 diabetes, but are often less marked. As a result, the disease may be diagnosed several years after onset, once complications have already arisen.

Until recently, this type of diabetes was seen only in adults, but it is now also occurring in children.

Gestational diabetes
Gestational diabetes is hyperglycaemia with onset or first recognition during pregnancy.

Symptoms of gestational diabetes are similar to Type 2 diabetes. Gestational diabetes is most often diagnosed through prenatal screening, rather than reported symptoms.

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG)
Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable.

What are common consequences of diabetes?
Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves.
• Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke).
• Combined with reduced blood flow, neuropathy in the feet increases the chance of foot ulcers and eventual limb amputation.

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/
• Diabetic retinopathy is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment.

• Diabetes is among the leading causes of kidney failure. 10-20% of people with diabetes die of kidney failure.

• Diabetic neuropathy is damage to the nerves as a result of diabetes, and affects up to 50% of people with diabetes. Although many different problems can occur as a result of diabetic neuropathy, common symptoms are tingling, pain, numbness, or weakness in the feet and hands.

• The overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes.

What is the economic impact of diabetes?
Diabetes and its complications have a significant economic impact on individuals, families, health systems and countries.

How can the burden of diabetes be reduced?
Prevention
Simple lifestyle measures have been shown to be effective in preventing or delaying the onset of type 2 diabetes. To help prevent type 2 diabetes and its complications, people should:
• achieve and maintain healthy body weight;
• be physically active – at least 30 minutes of regular, moderate-intensity activity on most days. More activity is required for weight control;
• eat a healthy diet of between three and five servings of fruit and vegetables a day and reduce sugar and saturated fats intake;
• avoid tobacco use – smoking increases the risk of cardiovascular diseases.

Diagnosis and treatment
Early diagnosis can be accomplished through relatively inexpensive blood testing.

Treatment of diabetes involves lowering blood glucose and the levels of other known risk factors that damage blood vessels. Tobacco use cessation is also important to avoid complications.

Interventions that are both cost saving and feasible in developing countries include:
• moderate blood glucose control. People with type 1 diabetes require insulin; people with type 2 diabetes can be treated with oral medication, but may also require insulin;
• blood pressure control
• foot care

Other cost saving interventions include:
• screening and treatment for retinopathy (which causes blindness)
• blood lipid control (to regulate cholesterol levels)
• screening for early signs of diabetes-related kidney disease.

These measures should be supported by a healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use.

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

2. EPILEPSY

What is epilepsy?
Epilepsy is a chronic disorder of the brain that affects people in every country of the world. It is characterized by recurrent seizures. Seizures are brief episodes of involuntary shaking which may involve a part of the body (partial) or the entire body (generalized) and sometimes accompanied by loss of consciousness and control of bowel or bladder function. The episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks, to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day.

One seizure does not signal epilepsy (up to 10% of people worldwide have one seizure during their lifetimes). Epilepsy is defined by two or more unprovoked seizures. Epilepsy is one of the world’s oldest recognized conditions. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. Some of the stigma continues today in many countries and can impact the quality of life for people with the disorder and their families.

KEY FACTS
• Epilepsy is a chronic noncommunicable disorder of the brain that affects people of all ages
• Around 50 million people worldwide have epilepsy
• Nearly 80% of the people with epilepsy are found in developing regions.
• Epilepsy responds to treatment about 70% of the time, yet about three fourths of affected people in developing countries do not get the treatment they need.
• People with epilepsy and their families can suffer from stigma and discrimination in many parts of the world
Signs and symptoms

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms can occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood or mental function.

People with seizures tend to have more physical problems (such as fractures and bruising), as well as higher rates of other diseases or psychosocial issues and conditions like anxiety and depression.

Rates of disease

The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or the need for treatment) at a given time is between 4 - 10 per 1000 people. However, some studies in developing countries suggest that the proportion is between 6 - 10 per 1000. Around 50 million people in the world have epilepsy.

In developed countries, annual new cases are between 40 to 70 per 100,000 people in the general population. In developing countries, this figure is often close to twice as high due to the higher risk of experiencing conditions that can lead to permanent brain damage. Close to 80% of epilepsy cases worldwide are found in developing regions. The risk of premature death in people with epilepsy is two to three times higher than it is for the general population.

Causes

The most common type – for six out of ten people with the disorder – is called idiopathic epilepsy and has no identifiable cause. In many cases, there is an underlying genetic basis.

Epilepsy with a known cause is called secondary epilepsy, or symptomatic epilepsy. The causes of secondary (or symptomatic) epilepsy could be:

- brain damage from prenatal or perinatal injuries (a loss of oxygen or trauma during birth, low birth weight)
- congenital abnormalities or genetic conditions with associated brain malformations
- a severe blow to the head
- a stroke that starves the brain of oxygen
- an infection of the brain such as meningitis, encephalitis, neurocysticercosis
- certain genetic syndromes
- a brain tumor

Treatment

Recent studies in both developed and developing countries have shown that up to 70% of newly diagnosed children and adults with epilepsy can be successfully treated (i.e. their seizures completely controlled) with anti-epileptic drugs (AEDs). After two to five years of successful treatment, drugs can be withdrawn in about 70% of children and 60% of adults without relapses.

- In developing countries, three fourths of people with epilepsy may not receive the treatment they need.
- About 9 out of 10 people with epilepsy in Africa go untreated.
- In many low- and middle-income countries, there is low availability and AEDs are not affordable and this may act as a barrier to accessing treatment. A recent study found the average availability of generic antiepileptic medicines in the public sector to be less than 50%.
- Surgical therapy might be beneficial to patients who respond poorly to drug treatments.

Prevention

Idiopathic epilepsy is not preventable. However, preventive measures can be applied to the known causes of secondary epilepsy.

- Preventing head injury is the most effective way to prevent post-traumatic epilepsy.
- Adequate perinatal care can reduce new cases of epilepsy caused by birth injury.
- The use of drugs and other methods to lower the body temperature of a feverish child can reduce the chance of subsequent convulsions.
- Central nervous system infections are common causes of epilepsy in tropical areas, where many developing countries are concentrated. Elimination of parasites in these environments and education on how to avoid infections would be effective ways to reduce epilepsy worldwide, for example due to neurocysticercosis.

Social and economic impacts

Epilepsy accounts for 0.5% of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in states of less than full health. Epilepsy has significant economic implications in terms of health-care needs, premature death and lost work productivity. An Indian study calculated that the total cost per epilepsy case was US$ 344 per year (or 88% of the average income per capita). The total cost for an estimated five million cases in India was equivalent to 0.5% of gross national product.

Although the social effects vary from country to country, the discrimination and social stigma that surround epilepsy worldwide are often more difficult to overcome than the seizures themselves. People with epilepsy can be targets of prejudice. The stigma of the disorder can discourage people from seeking treatment for symptoms and becoming identified with the disorder.
Human rights
People with epilepsy experience reduced access to health and life insurance, a withholding of the opportunity to obtain a driving license, and barriers to enter particular occupations, among other limitations. In many countries, legislation reflects centuries of misunderstanding about epilepsy. For example:
- In both China and India, epilepsy is commonly viewed as a reason for prohibiting or annulling marriages.
- In the United Kingdom, a law forbidding people with epilepsy to marry was repealed only in 1970.
- In the United States, until the 1970s, it was legal to deny people with seizures access to restaurants, theatres, recreational centres and other public buildings.

Legislation based on internationally accepted human rights standards can prevent discrimination and rights violations, improve access to health care services and raise quality of life.

3. MATERNAL MORTALITY

Maternal mortality is unacceptably high. About 800 women die from pregnancy- or childbirth-related complications around the world every day. In 2010, 287,000 women died during and following pregnancy and childbirth. Almost all of these deaths occurred in low-resource settings, and most could have been prevented.

KEY FACTS
- Every day, approximately 800 women die from preventable causes related to pregnancy and childbirth.
- 99% of all maternal deaths occur in developing countries.
- Maternal mortality is higher in women living in rural areas and among poorer communities.
- Young adolescents face a higher risk of complications and death as a result of pregnancy than older women.
- Skilled care before, during and after childbirth can save the lives of women and newborn babies.
- Between 1990 and 2010, maternal mortality worldwide dropped by almost 50%.

Progress towards achieving the fifth Millennium Development Goal
Improving maternal health is one of the eight Millennium Development Goals (MDGs) adopted by the international community in 2000. Under MDG5, countries committed to reducing maternal mortality by three quarters between 1990 and 2015. Since 1990, maternal deaths worldwide have dropped by 47%.

In sub-Saharan Africa, a number of countries have halved their levels of maternal mortality since 1990. In other regions, including Asia and North Africa, even greater headway has been made. However, between 1990 and 2010, the global maternal mortality ratio (i.e. the number of maternal deaths per 100,000 live births) declined by only 3.1% per year. This is far from the annual decline of 5.5% required to achieve MDG5.

Where do maternal deaths occur?
The high number of maternal deaths in some areas of the world reflects inequities in access to health services, and highlights the gap between rich and poor. Almost all maternal deaths (99%) occur in developing countries. More than half of these deaths occur in sub-Saharan Africa and almost one third occur in South Asia.

The maternal mortality ratio in developing countries is 240 per 100,000 births versus 16 per 100,000 in developed countries. There are large disparities between countries, with few countries having extremely high maternal mortality ratios of 1000 or more per 100,000 live births. There are also large disparities within countries, between people with high and low income and between people living in rural and urban areas.

The risk of maternal mortality is highest for adolescent girls under 15 years old. Complications in pregnancy and childbirth are the leading cause of death among adolescent girls in most developing countries.

Women in developing countries have on average many more pregnancies than women in developed countries, and their lifetime risk of death due to pregnancy is higher. A woman’s lifetime risk of maternal death – the probability that a 15 year old woman will eventually die from a maternal cause – is one in 3800 in developed countries, versus one in 150 in developing countries.

Why do women die?
Women die as a result of complications during and following pregnancy and childbirth. Most of these complications develop during pregnancy. Other complications may exist before pregnancy but are worsened during pregnancy. The major complications that account for 80% of all maternal deaths are:
- severe bleeding (mostly bleeding after childbirth)
- infections (usually after childbirth)
- high blood pressure during pregnancy (pre-eclampsia and eclampsia)
- unsafe abortion.

The remainder are caused by or associated with diseases such as malaria, and AIDS during pregnancy. Maternal health and newborn health are closely
How can women’s lives be saved?

Most maternal deaths are avoidable, as the healthcare solutions to prevent or manage complications are well known. All women need access to antenatal care in pregnancy, skilled care during childbirth, and care and support in the weeks after childbirth. It is particularly important that all births are attended by skilled health professionals, as timely management and treatment can make the difference between life and death.

Severe bleeding after birth can kill a healthy woman within two hours if she is unattended. Injecting oxytocin immediately after childbirth effectively reduces the risk of bleeding.

Infection after childbirth can be eliminated, if good hygiene is practiced, and if, early signs of infection are recognized and treated in a timely manner.

Pre-eclampsia should be detected and appropriately managed before the onset of convulsions ( eclampsia) and other life-threatening complications. Administering drugs such as magnesium sulfate for pre-eclampsia can lower a woman’s risk of developing eclampsia.

To avoid maternal deaths, it is also vital to prevent unwanted and too-early pregnancies. All women, including adolescents, need access to family planning, safe abortion services to the full extent of the law, and quality post-abortion care.

Why do women not get the care they need?

Poor women in remote areas are the least likely to receive adequate health care. While levels of antenatal care have increased in many parts of the world during the past decade, only 46% of women in low-income countries benefit from skilled care during childbirth. This means that millions of births are not assisted by a midwife, a doctor or a trained nurse. In high-income countries, virtually all women have at least four antenatal care visits, are attended by a skilled health worker during childbirth and receive postpartum care. In low-income countries, just over a third of all pregnant women have the recommended four antenatal care visits.

Other factors that prevent women from receiving or seeking care during pregnancy and childbirth are:
- poverty
- distance
- lack of information
- inadequate services
- cultural practices.

To improve maternal health, barriers that limit access to quality maternal health services must be identified and addressed at all levels of the health system.

4. DIARRHEAL DISEASE

Definition

Diarrhea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Frequent passing of formed stools is not Diarrhea, nor is the passing of loose, “pasty” stools by breastfed babies. Diarrhea is usually a symptom of an infection in the intestinal tract, which can be caused by a variety of bacterial, viral and parasitic organisms. Infection is spread through contaminated food or drinking-water, or from person-to-person as a result of poor hygiene. Diarrheal disease is treatable with a solution of clean water, sugar and salt, and with zinc tablets.

Diarrheal disease is the second leading cause of death in children under five years old, and is responsible for killing 1.5 million children every year. Diarrhea can last several days, and can leave the body without the water and salts that are necessary for survival. Most people who die from Diarrhea actually die from severe dehydration and fluid loss. Children who are malnourished or have impaired immunity are most at risk of life-threatening diarrhea.

KEY FACTS

- Diarrheal disease is the second leading cause of death in children under five years old. It is both preventable and treatable.
- Diarrheal disease kills 1.5 million children every year.
- Globally, there are about two billion cases of Diarrheal disease every year.
- Diarrheal disease mainly affects children under two years old.
- Diarrhea is a leading cause of malnutrition in children under five years old.

There are three clinical types of Diarrhea:
- acute watery Diarrhea – lasts several hours or days, and includes cholera;
- acute bloody Diarrhea – also called dysentery; and
- persistent Diarrhea – lasts 14 days or longer.

Scope of Diarrheal disease

Every year, there are about two billion cases of Diarrheal disease worldwide. Diarrheal disease is a leading cause of child mortality and morbidity in the world, and mostly results from contaminated food and water sources. Worldwide, around 1 billion people lack access to improved water and 2.5 billion have no...
access to basic sanitation. Diarrhea due to infection is widespread throughout developing countries.

In 2004, Diarrheal disease was the third leading cause of death in low-income countries, causing 6.9% of deaths overall. In children under five years old, Diarrheal disease is the second leading cause of death – second only to pneumonia. Out of the 1.5 million children killed by Diarrheal disease in 2004, 80% were under two years old.

In developing countries, children under three years old experience on average three episodes of Diarrhea every year. Each episode deprives the child of the nutrition necessary for growth. As a result, Diarrhea is a major cause of malnutrition, and malnourished children are more likely to fall ill from Diarrhea.

Dehydration

The most severe threat posed by Diarrhea is dehydration. During a Diarrheal episode, water and electrolytes (sodium, chloride, potassium and bicarbonate) are lost through liquid stools, vomit, sweat, urine and breathing. Dehydration occurs when these losses are not replaced.

The degree of dehydration is rated on a scale of three.
• Early dehydration – no signs or symptoms.
• Moderate dehydration:
  - thirst
  - restless or irritable behaviour
  - decreased skin elasticity
  - sunken eyes
• Severe dehydration:
  - symptoms become more severe
  - shock, with diminished consciousness, lack of urine output, cool, moist extremities, a rapid and feeble pulse, low or undetectable blood pressure, and pale skin.

Death can follow severe dehydration if body fluids and electrolytes are not replenished, either through the use of oral rehydration salts (ORS) solution, or through an intravenous drip.

Causes

Infection: Diarrhea is a symptom of infections caused by a host of bacterial, viral and parasitic organisms, most of which are spread by faeces-contaminated water. Infection is more common when there is a shortage of clean water for drinking, cooking and cleaning. Rotavirus and Escherichia coli are the two most common causes of Diarrhea in developing countries.

Malnutrition: Children who die from Diarrhea often suffer from underlying malnutrition, which makes them more vulnerable to Diarrhea. Each Diarrheal episode, in turn, makes their malnutrition even worse. Diarrhea is a leading cause of malnutrition in children under five years old.

Source: Water contaminated with human faeces, for example, from sewage, septic tanks and latrines, is of particular concern. Animal faeces also contain microorganisms that can cause Diarrhea.

Other causes: Diarrheal disease can also spread from person-to-person, aggravated by poor personal hygiene. Food is another major cause of Diarrhea when it is prepared or stored in unhygienic conditions. Water can contaminate food during irrigation. Fish and seafood from polluted water may also contribute to the disease.

Prevention and treatment

Key measures to prevent Diarrhea include:
• access to safe drinking-water
• improved sanitation
• exclusive breastfeeding for the first six months of life
• good personal and food hygiene
• health education about how infections spread, and
• rotavirus vaccination.

Key measures to treat Diarrhea include the following.
• Rehydration: Rehydration with intravenous fluids in case of severe dehydration or shock and/or oral rehydration salts (ORS) solution for moderate or no dehydration. ORS is a mixture of clean water, salt and sugar, which can be prepared safely at home. It costs a few cents per treatment. ORS is absorbed in the small intestine and replaces the water and electrolytes lost in the faeces.
• Zinc supplements: Zinc supplements reduce the duration of a Diarrhea episode by 25% and are associated with a 30% reduction in stool volume.
• Nutrient-rich foods: The vicious circle of malnutrition and Diarrhea can be broken by continuing to give nutrient-rich foods – including breast milk – during an episode, and by giving a nutritious diet – including exclusive breastfeeding for the first six months of life – to children when they are well.
• Consulting a health worker, if there are signs of dehydration.
<table>
<thead>
<tr>
<th>Title</th>
<th>Volume</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Case of Adult Botulism following Ingestion of Contaminated Egyptian Salted Fish (“Faseikh”).</td>
<td>44 (1)</td>
<td>63 - 65</td>
</tr>
<tr>
<td>A Comparison of Outcome of Open Transvesical Prostatectomy with or Without Bladder Neck Repair.</td>
<td>44 (3)</td>
<td>211 - 214</td>
</tr>
<tr>
<td>Acromioclavicular Joint Cyst-Pseudotumour of Shoulder.</td>
<td>44 (3)</td>
<td>227 - 230</td>
</tr>
<tr>
<td>Anterior Lateral Thigh Flap Salvage Reconstruction of Composite Defects after Recurrent Head and Neck Cancer: A Case Report.</td>
<td>44 (3)</td>
<td>231 - 234</td>
</tr>
<tr>
<td>A Randomized Trial of Epidural Volume Extension by Sequential Combined Spinal Epidural Anaesthesia by Three Technique.</td>
<td>44 (1)</td>
<td>30 - 34</td>
</tr>
<tr>
<td>A Solitary Hamartomatous Polyp of the Ileum Causing Adult Intussusception: A Case Report.</td>
<td>44 (3)</td>
<td>235 - 238</td>
</tr>
<tr>
<td>Asthma During Pregnancy: An Immunologic Perspective.</td>
<td>44 (4)</td>
<td>277 - 286</td>
</tr>
<tr>
<td>A Young Male with Behcet’s Disease and Right Ventricular Thrombi.</td>
<td>44(1)</td>
<td>66 - 68</td>
</tr>
<tr>
<td>Bariatric Surgery and Hypoglycemia.</td>
<td>44(4)</td>
<td>274 - 276</td>
</tr>
<tr>
<td>Bilateral Diffuse Mucinous Cystic Adenocarcinoma of the Lungs Complicated by Recurrent Pneumothorax in a Pregnant Woman.</td>
<td>44 (1)</td>
<td>56 - 59</td>
</tr>
<tr>
<td>Bilateral Massive Angiomyolipomatosis Associated with Tuberous Sclerosis.</td>
<td>44 (2)</td>
<td>149 - 153</td>
</tr>
<tr>
<td>Can Science Teach a Thing or Two to Nature?.</td>
<td>44 (2)</td>
<td>90 - 91</td>
</tr>
<tr>
<td>Celiac Disease as Uncommon Cause of Death in Type 1 Diabetes Mellitus, a Case Study.</td>
<td>44(4)</td>
<td>335 - 337</td>
</tr>
<tr>
<td>Clinical and Bacteriologic Correlates of the PapG Alleles among Uropathogenic Escherichia Coli Strains Isolated from Cases of Adult Urinary Tract Infection.</td>
<td>44(1)</td>
<td>26 - 29</td>
</tr>
<tr>
<td>Closed Reduction and Percutaneous Fixation of Lisfranc Joints Fracture Dislocation.</td>
<td>44 (3)</td>
<td>200 - 210</td>
</tr>
<tr>
<td>Comparison of Changes in Body Image of Patients with Renal Calculi Treated by Pyelolithotomy or Percutaneous Lithotripsy.</td>
<td>44 (2)</td>
<td>113 - 117</td>
</tr>
<tr>
<td>Dengue Fever among Travelers.</td>
<td>44 (2)</td>
<td>146 - 148</td>
</tr>
<tr>
<td>Determining the Effect of Sufentanil on Propofol Injection Pain.</td>
<td>44 (2)</td>
<td>121 - 124</td>
</tr>
<tr>
<td>Diagnostic Computerized Tomography Sign in Peterson’s Space Hernia after Laparoscopic Roux-en-Y Gastric Bypass.</td>
<td>44 (1)</td>
<td>69 - 70</td>
</tr>
<tr>
<td>Donohue Syndrome: A case report.</td>
<td>44 (3)</td>
<td>224 - 226</td>
</tr>
<tr>
<td>Double Appendix: Report of a Case.</td>
<td>44 (4)</td>
<td>329-331</td>
</tr>
<tr>
<td>Effect of Granulocyte Colony-Stimulating Factor on Liver Injury Induced by CCl4: A Correlation between Biochemical Parameters and Histopathology Results.</td>
<td>44 (1)</td>
<td>46 - 49</td>
</tr>
<tr>
<td>Evaluation of Lamivudine Effect on Prevention of Hepatocellular Carcinoma Recurrence.</td>
<td>44 (2)</td>
<td>154</td>
</tr>
<tr>
<td>Evaluating the Association Between Premenstrual Syndrome and Hematologic Parameters During the Early Follicular and Late Luteal Phases.</td>
<td>44 (2)</td>
<td>125 - 132</td>
</tr>
<tr>
<td>Gaucher Disease Co-existing with Wilson Disease: A Case Report.</td>
<td>44 (2)</td>
<td>139 - 140</td>
</tr>
<tr>
<td>Giant Retroperitoneal Leiomyoma: A Rare Presentation.</td>
<td>44 (3)</td>
<td>239 - 243</td>
</tr>
<tr>
<td>Good for Old As Well As Young; Oral Rehydration Therapy (ORT).</td>
<td>44 (1)</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Hypertension and Hypoglycemia in a Child with Hepatoblastoma: A Case Report.</td>
<td>44 (2)</td>
<td>133 - 134</td>
</tr>
<tr>
<td>Impact of the Discovery of Human Zinc Deficiency.</td>
<td>44 (3)</td>
<td>180 - 182</td>
</tr>
<tr>
<td>Incomplete Small Bowel Obstruction Caused by Idiopathic Diaphragm Disease of the Proximal Ileum.</td>
<td>44 (2)</td>
<td>143 - 145</td>
</tr>
<tr>
<td>Individual Cyclooxygenase-2 Inhibitors on the Risk of Peptic Ulcer Disease: A Population-Based Cohort in Taiwan.</td>
<td>44(4)</td>
<td>347 - 348</td>
</tr>
</tbody>
</table>
Individual Statins on the Risk of Colorectal Cancer: A Population-Based Observation In Taiwan. 44 (3) 255 - 256

Intravenous Labetalol versus Oral Nifedipine in the Treatment of Severe Hypertension in Pregnancy. 44 (4) 287 - 290

Is Medical Education Really Stressful? A Prospective Study in Selcuk University, Turkey. 44 (2) 104 - 112

More Expensive Surfaces are Not Always Better. 44 (1) 40 - 45

Mucinous Cystadenoma in a Horse Shoe Kidney. Report of a Case with Review of Literature. 44 (1) 60 - 62

Neonatal Cardiac Tamponade, What is the Cause?. 44 (2) 141 - 142

New Approaches in the Diagnosis and Treatment of Susceptible, Multidrug-Resistant and Extensively Drug Resistant Tuberculosis. 44 (1) 3 - 19

Nosocomial Bacteria on Doctors Mobile Phones. 44 (2) 101 - 103

Obstetric Outcome of Teenage Pregnancies: A 5-Year Experience in a University Hospital. 44 (3) 195 - 199

Oncocytic and Clear Cell Areas in a Solid Pseudopapillary Tumor of the Pancreas: A Case Report. 44(4) 332 - 334

Pedicled Seromuscular Flap for Inforcement of High Risk Intestinal Anastomoses. 44 (3) 190 - 194

Percutaneous Fixation of Recent Scaphoid Fracture. 44 (3) 219 - 223

Persistent Junctional Reciprocating Tachycardia (PJRT). 44 (1) 53 - 55

Prostatic Adenocarcinoma and Chronic Lymphocytic Leukemia: a Case Report. 44(4) 344 - 346

Proximal Tibial Osteotomy in Medial Compartment Osteoarthritis: How High is High?. 44 (2) 92 - 100

Scaphoid Dislocation, either Isolated or Associated with Axial Carpal Dissociation: Three Cases Report. 44 (3) 244 - 250

Spinal Cord Demyelination in Biotinidase Deficiency; A Case Report. 44 (2) 135 - 138

Spontaneous Hemorrhage in an Adrenal Pheochromocytoma. 44 (3) 251 - 254

Squamous Cell Carcinoma of the Penis: Magnetic Resonance Imaging Findings. 44 (4) 338 - 340

Stereotactic Surgery: Diagnostic and Therapeutic Role in the Management of Brain Disorders and Our Experience at Ibn Sina Hospital. 44(4) 303 - 307

Subarachnoid Hemorrhage as a Rare Presentation of Cerebral Venous Sinus Thrombosis. 44 (1) 50 - 52

Synergy Between Dendritic Cell-Based Vaccine and Anti-CD137 Monoclonal Antibody in the Treatment of Mouse Renal Cell Carcinoma. 44(4) 308 - 315

The Effect of Gene Polymorphisms (ENOS G894T, PON1 and Catalase -262C→T) on fertility and Sperm Parameters in Turkish Men with Clinical Varicocele: A Pilot Study. 44(4) 316 - 321

The Impact of Metabolic Risk Management on Recurrence of Urinary Stones. 44 (3) 215 - 218

The Microbiology of Vaginal Discharge and the Prevalence of Bacterial Vaginosis in a Cohort of Non-pregnant women in Kuwait. 44 (1) 20 - 25

The Prevalence and Route of Delivery of Prolonged Pregnancies. 44 (2) 118 - 120

Total Hip Replacement after Hip Fracture. Primary or Secondary Surgery? A Comparison of Clinical and Radiological Results. 44 (1) 35 - 39

Total Hip Replacement in Nigeria: A Preliminary Report. 44(4) 291 - 296

Towards Prevention of Diabetes in Offsprings of Type 2 Diabetic Patients. 44(4) 297 - 302

Unstable Carpometacarpal Dislocation of Ulnar Four Fingers – An Easily Overlooked Injury. 44 (4) 341 - 343

Unusual Presentation of Duplex Collecting System: a Case Report. 44(4) 326 - 328

Vitamin A and Zinc Alter the Immune Function in Tuberculosis. 44 (3) 183 - 189

Ward Mechanical Ventilation (WMV) Audit. 44 (4) 322 - 325
### Yearly Author Index

**Kuwait Medical Journal (KMJ) 2012; Volume 44**


<table>
<thead>
<tr>
<th>Author Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abassi R</td>
<td>46</td>
</tr>
<tr>
<td>Abbas A</td>
<td>190</td>
</tr>
<tr>
<td>Abdelgaid SM</td>
<td>200, 219</td>
</tr>
<tr>
<td>Abdel-Malak F</td>
<td>200</td>
</tr>
<tr>
<td>Abdul-Azeem ME</td>
<td>244</td>
</tr>
<tr>
<td>Abdulla AA</td>
<td>297</td>
</tr>
<tr>
<td>Abdulsalam SM</td>
<td>146</td>
</tr>
<tr>
<td>Acarturk O</td>
<td>125</td>
</tr>
<tr>
<td>A glamis E</td>
<td>113, 316</td>
</tr>
<tr>
<td>Ahmad I</td>
<td>183</td>
</tr>
<tr>
<td>Ahmad S</td>
<td>3</td>
</tr>
<tr>
<td>Ahrar B</td>
<td>274</td>
</tr>
<tr>
<td>Akin Y</td>
<td>215</td>
</tr>
<tr>
<td>Amaechi KU</td>
<td>291</td>
</tr>
<tr>
<td>Alabed A</td>
<td>135</td>
</tr>
<tr>
<td>Aldily TN</td>
<td>344</td>
</tr>
<tr>
<td>Al-Adwani M</td>
<td>338</td>
</tr>
<tr>
<td>Al-Ali M</td>
<td>322</td>
</tr>
<tr>
<td>Al Awadi Y</td>
<td>303</td>
</tr>
<tr>
<td>Al-Duajj S</td>
<td>50</td>
</tr>
<tr>
<td>Aleinati T</td>
<td>66</td>
</tr>
<tr>
<td>Al-Fahdli M</td>
<td>50</td>
</tr>
<tr>
<td>Al-Hamdan R</td>
<td>53</td>
</tr>
<tr>
<td>Al Harbi O</td>
<td>235</td>
</tr>
<tr>
<td>Ali F</td>
<td>149</td>
</tr>
<tr>
<td>Ali QE</td>
<td>30</td>
</tr>
<tr>
<td>Ali W</td>
<td>183</td>
</tr>
<tr>
<td>Al-Jama FE</td>
<td>195</td>
</tr>
<tr>
<td>Almasi V</td>
<td>211</td>
</tr>
<tr>
<td>Al-Merri K</td>
<td>66</td>
</tr>
<tr>
<td>Almutairi H</td>
<td>338</td>
</tr>
<tr>
<td>Al Mutairi M</td>
<td>66</td>
</tr>
<tr>
<td>Al Nassr M</td>
<td>63</td>
</tr>
<tr>
<td>AlOasimi S</td>
<td>235</td>
</tr>
<tr>
<td>AlRashidi FM</td>
<td>56</td>
</tr>
<tr>
<td>Al-Shammar M</td>
<td>101</td>
</tr>
<tr>
<td>AlShalfan F</td>
<td>146</td>
</tr>
<tr>
<td>Al-Summait BAA</td>
<td>69</td>
</tr>
<tr>
<td>Al Jumah ES</td>
<td>135</td>
</tr>
<tr>
<td>Alqalaf F</td>
<td>135</td>
</tr>
<tr>
<td>Altnova S</td>
<td>113</td>
</tr>
<tr>
<td>AlTarrah MY</td>
<td>146</td>
</tr>
<tr>
<td>Altooky MH</td>
<td>20</td>
</tr>
<tr>
<td>Alwan MH</td>
<td>251</td>
</tr>
<tr>
<td>Al Zanki MBY</td>
<td>227</td>
</tr>
<tr>
<td>Andersen RE</td>
<td>40</td>
</tr>
<tr>
<td>Anjali T</td>
<td>287</td>
</tr>
<tr>
<td>Artas H</td>
<td>316</td>
</tr>
<tr>
<td>Ashok K</td>
<td>341</td>
</tr>
<tr>
<td>Asker W</td>
<td>190</td>
</tr>
<tr>
<td>Ates C</td>
<td>316</td>
</tr>
<tr>
<td>Azab HS</td>
<td>20</td>
</tr>
<tr>
<td>Azizieh F</td>
<td>277</td>
</tr>
<tr>
<td>Babacan T</td>
<td>125</td>
</tr>
<tr>
<td>Bahzad M</td>
<td>322</td>
</tr>
<tr>
<td>Bal B</td>
<td>125</td>
</tr>
<tr>
<td>Baykara M</td>
<td>215</td>
</tr>
<tr>
<td>Bendhifari F</td>
<td>297</td>
</tr>
<tr>
<td>Beytur A</td>
<td>113</td>
</tr>
<tr>
<td>Bhandari S</td>
<td>30</td>
</tr>
<tr>
<td>Bonajmah AA</td>
<td>35</td>
</tr>
<tr>
<td>Borazan H</td>
<td>121</td>
</tr>
<tr>
<td>Ceylan C</td>
<td>113, 316</td>
</tr>
<tr>
<td>Ceylan GG</td>
<td>316</td>
</tr>
<tr>
<td>Chakravorti</td>
<td>224</td>
</tr>
<tr>
<td>Chandrashekhar B</td>
<td>341</td>
</tr>
<tr>
<td>Chen PC</td>
<td>347</td>
</tr>
<tr>
<td>Dagogo-Jack S</td>
<td>274</td>
</tr>
<tr>
<td>Danisman A</td>
<td>215</td>
</tr>
<tr>
<td>Dawoud I</td>
<td>190</td>
</tr>
<tr>
<td>DeMarco SL</td>
<td>40</td>
</tr>
<tr>
<td>Ego AU</td>
<td>291</td>
</tr>
<tr>
<td>Elaaser EM</td>
<td>20</td>
</tr>
<tr>
<td>Elkady AA</td>
<td>20</td>
</tr>
<tr>
<td>Ellatf MEA</td>
<td>190</td>
</tr>
<tr>
<td>El Morshidy AF</td>
<td>219, 244</td>
</tr>
<tr>
<td>El Sharakawy AI</td>
<td>297</td>
</tr>
<tr>
<td>Erdogru T</td>
<td>215</td>
</tr>
<tr>
<td>Ermutlu C</td>
<td>92</td>
</tr>
<tr>
<td>Faeizi F</td>
<td>46</td>
</tr>
<tr>
<td>Feng J</td>
<td>239</td>
</tr>
<tr>
<td>Gelidan A</td>
<td>231</td>
</tr>
<tr>
<td>Gibson S</td>
<td>143</td>
</tr>
<tr>
<td>Greenough WB</td>
<td>1, 40</td>
</tr>
<tr>
<td>Gupta MK</td>
<td>183</td>
</tr>
<tr>
<td>Name</td>
<td>Page</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Habib SK</td>
<td>30</td>
</tr>
<tr>
<td>Haidari M</td>
<td>211</td>
</tr>
<tr>
<td>Halallkhor HTS</td>
<td>46</td>
</tr>
<tr>
<td>Haleem S</td>
<td>30</td>
</tr>
<tr>
<td>Hamed I</td>
<td>338</td>
</tr>
<tr>
<td>Hammoud MS</td>
<td>141</td>
</tr>
<tr>
<td>Hegde BM</td>
<td>90</td>
</tr>
<tr>
<td>Hutchinson IF</td>
<td>143</td>
</tr>
<tr>
<td>Ibrahim YMAE</td>
<td>335</td>
</tr>
<tr>
<td>Iskandar MM</td>
<td>69</td>
</tr>
<tr>
<td>Ismail ZA</td>
<td>69</td>
</tr>
<tr>
<td>Jaiprakash P</td>
<td>332</td>
</tr>
<tr>
<td>Jayant T M</td>
<td>60</td>
</tr>
<tr>
<td>Joshi R</td>
<td>101</td>
</tr>
<tr>
<td>Kahvic M</td>
<td>329</td>
</tr>
<tr>
<td>Kantoush H</td>
<td>329</td>
</tr>
<tr>
<td>Kara I</td>
<td>121</td>
</tr>
<tr>
<td>Karaoglu N</td>
<td>104</td>
</tr>
<tr>
<td>Karimi A</td>
<td>26</td>
</tr>
<tr>
<td>Khaddadah S</td>
<td>322</td>
</tr>
<tr>
<td>Khajah H</td>
<td>303</td>
</tr>
<tr>
<td>Khan A</td>
<td>303</td>
</tr>
<tr>
<td>Khan HA</td>
<td>53</td>
</tr>
<tr>
<td>Khalifa NM</td>
<td>133</td>
</tr>
<tr>
<td>Khalifa SO</td>
<td>133</td>
</tr>
<tr>
<td>Khalil MF</td>
<td>141</td>
</tr>
<tr>
<td>Khorramabadi MS</td>
<td>211</td>
</tr>
<tr>
<td>Kose S</td>
<td>125</td>
</tr>
<tr>
<td>Kushwaha RAS</td>
<td>183</td>
</tr>
<tr>
<td>Lai HC</td>
<td>255, 347</td>
</tr>
<tr>
<td>Lai SW</td>
<td>154, 255, 347</td>
</tr>
<tr>
<td>Liao KF</td>
<td>154, 255, 347</td>
</tr>
<tr>
<td>Liu J</td>
<td>239</td>
</tr>
<tr>
<td>Mayanglambam RD</td>
<td>287</td>
</tr>
<tr>
<td>Mehmoood K</td>
<td>53</td>
</tr>
<tr>
<td>Memisoglu K</td>
<td>92</td>
</tr>
<tr>
<td>Menori V</td>
<td>60</td>
</tr>
<tr>
<td>Mittal R</td>
<td>133</td>
</tr>
<tr>
<td>Mokaddas E</td>
<td>3</td>
</tr>
<tr>
<td>Mokhtar M</td>
<td>63</td>
</tr>
<tr>
<td>Mondal R</td>
<td>139, 224</td>
</tr>
<tr>
<td>Mothafar FJ</td>
<td>56</td>
</tr>
<tr>
<td>Muo CH</td>
<td>255, 347</td>
</tr>
<tr>
<td>Muqim</td>
<td>56</td>
</tr>
<tr>
<td>Muttikkal TJE</td>
<td>149, 227</td>
</tr>
<tr>
<td>Nafisi MR</td>
<td>26</td>
</tr>
<tr>
<td>Nandi M</td>
<td>139, 224</td>
</tr>
<tr>
<td>Nejad SP</td>
<td>118</td>
</tr>
<tr>
<td>Noor TA</td>
<td>35</td>
</tr>
<tr>
<td>Otelcioglu S</td>
<td>121</td>
</tr>
<tr>
<td>Ozturk A</td>
<td>92</td>
</tr>
<tr>
<td>Parsian H</td>
<td>46</td>
</tr>
<tr>
<td>Pospula W</td>
<td>35</td>
</tr>
<tr>
<td>Prakash C</td>
<td>35</td>
</tr>
<tr>
<td>Prasad AS</td>
<td>180</td>
</tr>
<tr>
<td>Prasad KV</td>
<td>60</td>
</tr>
<tr>
<td>Prasad R</td>
<td>183</td>
</tr>
<tr>
<td>Pratish S</td>
<td>341</td>
</tr>
<tr>
<td>Quiejq D</td>
<td>46</td>
</tr>
<tr>
<td>Rao ACK</td>
<td>332</td>
</tr>
<tr>
<td>Raina A</td>
<td>141</td>
</tr>
<tr>
<td>Raghupathy R</td>
<td>277</td>
</tr>
<tr>
<td>Ramadan A</td>
<td>303</td>
</tr>
<tr>
<td>Rawdhan H</td>
<td>101</td>
</tr>
<tr>
<td>Rezanejad J</td>
<td>211</td>
</tr>
<tr>
<td>Ronald M</td>
<td>251</td>
</tr>
<tr>
<td>Rotimi VO</td>
<td>63</td>
</tr>
<tr>
<td>Saad E</td>
<td>235</td>
</tr>
<tr>
<td>Sadeq FJAA</td>
<td>149, 227</td>
</tr>
<tr>
<td>Saha AK</td>
<td>143</td>
</tr>
<tr>
<td>Sahin N</td>
<td>92</td>
</tr>
<tr>
<td>Salam SA</td>
<td>50</td>
</tr>
<tr>
<td>Salah M</td>
<td>200</td>
</tr>
<tr>
<td>Saleh AAM</td>
<td>20</td>
</tr>
<tr>
<td>Saleem M</td>
<td>183</td>
</tr>
<tr>
<td>Sanam M</td>
<td>118</td>
</tr>
<tr>
<td>Saritas TB</td>
<td>121</td>
</tr>
<tr>
<td>Sarkar S</td>
<td>139</td>
</tr>
<tr>
<td>Seker M</td>
<td>104</td>
</tr>
<tr>
<td>Serfoglu EC</td>
<td>113</td>
</tr>
<tr>
<td>Shamsah M</td>
<td>101</td>
</tr>
<tr>
<td>Sharma D</td>
<td>30</td>
</tr>
<tr>
<td>Sharma PK</td>
<td>326</td>
</tr>
<tr>
<td>Shirzad H</td>
<td>26</td>
</tr>
<tr>
<td>Singh NG</td>
<td>329</td>
</tr>
<tr>
<td>Sung FC</td>
<td>255, 347</td>
</tr>
<tr>
<td>Tuncer S</td>
<td>121</td>
</tr>
<tr>
<td>Uwatoronye NC</td>
<td>291</td>
</tr>
<tr>
<td>Valiathan M</td>
<td>332</td>
</tr>
<tr>
<td>Varshney R</td>
<td>30</td>
</tr>
<tr>
<td>Valente SA</td>
<td>40</td>
</tr>
<tr>
<td>Vijay MK</td>
<td>326</td>
</tr>
<tr>
<td>Vijay P</td>
<td>326</td>
</tr>
<tr>
<td>Wei SM</td>
<td>308</td>
</tr>
<tr>
<td>Wraikat AA</td>
<td>344</td>
</tr>
<tr>
<td>Yan ZZ</td>
<td>308</td>
</tr>
<tr>
<td>Yorulmaz H</td>
<td>125</td>
</tr>
<tr>
<td>Yuce H</td>
<td>316</td>
</tr>
<tr>
<td>Yuce S</td>
<td>215</td>
</tr>
<tr>
<td>Zamanzad B</td>
<td>26</td>
</tr>
<tr>
<td>Zhou S</td>
<td>239</td>
</tr>
<tr>
<td>Zhou J</td>
<td>308</td>
</tr>
</tbody>
</table>