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Editorial

Surgical Interventions for Non Insulin Dependent Diabetes Mellitus

Mohammad H Jamal
Department of Surgery, Faculty of Medicine, Kuwait University, Kuwait


Bariatric surgery does not exert its effect through weight loss only, but mainly through its metabolic effects that lead to the resolution of most of the comorbidities associated with obesity including hypertension, hypercholesterolemia, obstructive sleep apnea and Non Insulin Dependent Diabetes Mellitus (NIDDM). Therefore, it is more accurately termed Metabolic Surgery. Early reports in the 1950s showed possible cure of NIDDM in patients undergoing gastric resections for gastric cancer[1]. This finding was reproduced in the field of metabolic surgery.

NIDDM is being treated as a chronic disease with medical management not resulting in cure in the vast majority of patients. Even with the improvement in medical therapy, only 50% of patients achieve desired glycemic control[2].

In 1995, Pories et al[3] reported on 146 patients with NIDDM and 156 patients with impaired glucose tolerance (IGT), 14 years after a Roux En Y Gastric bypass (RYGB). They found that 91% of this cohort had maintained normal values of fasting blood glucose and glycosylated hemoglobin. In particular, 121 patients out of the 146 who had NIDDM, maintained normal values of fasting blood glucose and glycosylated hemoglobin. This effect of bariatric surgery was reproduced in multiple studies, where it was shown to be more effective in curing NIDDM, than medical therapy in multiple randomized controlled studies[4-6].

This dramatic effect of bariatric surgery on NIDDM occurs in the immediate post operative course in majority of cases, even before significant weight loss. The more simplistic theory explaining Diabetes resolution post bariatric surgery focuses on weight loss only, as the main mechanism. Patients are not consuming much food in the immediate post op period leading to a state of starvation that is known to improve diabetes control. In the early post operative period, they are consuming less calories than they need, leading to a negative energy balance, which in turn improves glucose tolerance. The continued weight loss in turn leads to improved insulin sensitivity and beta cell function, thus leading to a better diabetes control[7].

Metabolic theories suggest a major rule of gut hormones behind diabetes resolution post bariatric surgery, particularly the malabsorptive procedures. These metabolic theories may explain better the resolution of diabetes in patients who fail to loose weight post bariatric surgery and in those with lower BMI who get bariatric surgery. The hindgut theory states that the rapid delivery of nutrition to the distal bowel enhances the production of gut hormones that are instrumental in glucose homeostasis. The main and most studied gut hormone is the Glucagon Like Peptide- 1 (GLP-1), which is produced by the L cells of the distal bowel. It is shown to stimulate insulin secretion and enhance the proliferation of pancreatic beta cells. GLP-1 increases by 10 - 20 folds after a RYGB, thus exerting a beneficial effect on diabetic patients[8]. GLP-1 also inhibits gastric emptying and may limit food intake[9].

A second metabolic theory is the foregut theory, which states that the exclusion of duodenum and the proximal jejunum from the nutrition path prevent the secretion of substances that augment insulin resistance and NIDDM. The fact that even patients with a BMI below 35 benefit from bariatric surgery in terms of diabetes resolution may also support indirectly, the metabolic effects independent of weight loss.

The area of diabetes resolution post metabolic surgery is a very interesting area for research, since it will produce knowledge that not only help surgeons and endocrinologists select patients for surgery, but also enable them to better understand
the pathophysiology of NIDDM. What is clear now by strong medical evidence is that, metabolic surgery can be a very effective option in the treatment of NIDDM in a selected group of patients.

REFERENCES

Diabetes: A Fast Evolving Epidemic

Ali H Ziyab, PhD, Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait. Tel: (+965) 24636545; Fax: (+965) 25338948. Email: aziyab@hsc.edu.kw

ABSTRACT

Diabetes is one of the most common and major chronic diseases of the 21st century that affect people living in most parts of the world. Global trends suggest that diabetes has more than doubled over the past three decades and is projected to dramatically increase in the coming years. In addition to the clinical burden associated with the disease, diabetes has emerged as a global public health challenge. Most challenging is the shift in the disease paradigm from mainly being a disease of older ages to increasingly affecting children, adolescents, and young adults. Specifically, type 2 diabetes mellitus (T2DM), by far the most prevalent form of diabetes, and prediabetes, a high-risk state for developing T2DM, are rapidly emerging among the youth. Despite the magnitude of the epidemic and its consequences for individuals, their families, and society as a whole, the global response to diabetes as a public health threat has been slow. Today, many countries have still not been able, or seen fit, to put in place the type of national prevention and mitigation strategies or programs that are needed to deal with the growing challenge. To this end, the history, pathophysiology, epidemiology, and global trends of diabetes are discussed in this review. Moreover, the rising epidemic of T2DM and prediabetes among the youth and its risk factors, consequences, and prevention strategies are discussed.

KEY WORDS: epidemiology, gestational diabetes, prediabetes, prevention

INTRODUCTION

Diabetes has become a global public health challenge and a leading cause of morbidity, serious disability, and death in both developed and developing countries. In 2013, over 382 million people were estimated to be living with diabetes and this figure is expected to rise to 592 million by 2035(1). When it does, diabetes will become one of the most significant disease burdens the world has ever experienced. In 2013, globally, 8.4% of all-cause mortality was attributed to diabetes in adults aged 20 - 79 years, i.e., around 5.1 million people died from diabetes(2-3). In India alone, diabetes is estimated to be killing over 1 million people every year(3), while the lives and wellbeing of millions of other people are being impaired by a combination of diabetes-prompted physical and psychosocial insults. The World Health Organization (WHO) projects that as diabetes becomes the seventh leading cause of death globally over the next 15 years, most of the countries affected will be in Africa and Asia, which are already having difficulties coping with their traditional infectious disease burdens(4).

In this review article, we provide a brief history of diabetes, review the pathophysiology of the different types of diabetes, and discuss the epidemiology and global trends in diabetes and prediabetes, predisposing factors, comorbidities and implications for diagnosis and treatment, and prevention strategies.

DIABETES IN HISTORY

Despite the magnitude of the epidemic and its consequences for individuals, their families, and society as a whole, the global response to diabetes as a public health threat has been slow. Today, many countries have still not been able, or seen fit, to put in place the type of national prevention and mitigation strategies or programs that are needed to deal with the growing challenge(5). Ironically, diabetes is not a new condition. It had already been named two thousand years ago by the Greek scholar, Aretaeus, and its symptoms had been described in detail by Avicenna(6-9). In their writings on diabetes, they were able to describe the urinary dysfunctions of diabetes and the typical “sweet urine” associated with diabetes.
In the 1600s this “sweet urine” was qualified with the term mellitus (honey). By 1889, the role of the pancreas in diabetes was beginning to be understood, and some twenty years later, the role of insulin was identified by Banting and Best in a way that made it possible for the hormone to be prepared industrially and hence made more widely accessible as a treatment for diabetes[20].

**REASONS FOR LATE ATTENTION**
A number of factors may have contributed to the late attention given to diabetes as a public health challenge. The first is the fact that for a long time the numbers of people known to be affected by diabetes remained relatively low in comparison to other major diseases of the time, and that it was seen as a disease unique to wealthy people and not as a problem facing societies as a whole[11, 12]. Another factor is that even today, diabetes remains a silent and highly personal disease that many people choose not to discuss openly[13]. The fact that until recently, it has been viewed as a clinical challenge and has inspired significant biomedical research, may have helped eclipse its public health significance.

**TYPES OF DIABETES**
With time three major types of diabetes have emerged: (a) type 1 diabetes mellitus (T1DM), involving inadequate insulin production and requiring daily insulin administration, which develops primarily in children (aged <14 years) and account for 5-10% of the total cases of diabetes worldwide[14]; (b) type 2 diabetes mellitus (T2DM), prompted by the ineffective use of insulin and also requiring insulin where changed nutritional behavior and exercise are insufficient, predominantly develops among adults and accounts for 90 - 95% of all diabetes cases[15]; and (c) gestational diabetes mellitus (GDM), defined as glucose intolerance whose onset appears at, or is first diagnosed during pregnancy and usually resolves soon after giving birth[16].

**PATHOPHYSIOLOGY OF T1DM**
T1DM is regarded as an autoimmune disease that is manifested as a result of the destruction of the pancreatic β cells, therefore decreasing the production of insulin and resulting in hyperglycemia. It has been well established that T1DM is triggered by a genetic predisposition and environmental factors, which cause the immune system to target its own pancreatic β cells[17] (Fig. 1). In addition, due to the destruction of the β cells, the function of pancreatic α-cells becomes compromised resulting in abnormal and excessive secretion of glucagon. This combination of insulin deficiency and increased glucagon levels can cause major metabolic disruption and lead to ketoacidosis[18].

Insulin deficiency results in uncontrolled lipolysis and elevated levels of plasma free fatty acids, which in turn prohibits glucose metabolism in the peripheral tissues and the skeletal muscle[19]. Several genes are regulated by insulin, in turn these genes regulate protein metabolism by increasing the rate of protein synthesis and reducing the rate of protein degradation[20]. Insulin deficiency leads to elevated plasma amino acid concentration as a result of protein degradation. Amino acids serve as precursors for gluconeogenesis, which result in hyperglycemia in people with T1DM[21, 22].

Genetic susceptibility of T1DM is determined by polymorphisms/mutations in multiple genes. More than 60 genes have been identified which influence the progression of T1DM, with the human leukocyte antigen (HLA) loci having the greatest impact amongst these genes. HLA genes are found on chromosome 6 and are involved in the regulation of the immune response in humans. The genes encode for HLA class I (A, B and C) and class II (DR, DQ and DP) antigens. It has been well established that the HLA- classes I and II alleles are substantially associated with T1DM, and have shown to vary amongst populations and ethnicities. In Caucasian populations, the mutations on the HLA class II DR gene differ from those present in the Japanese and Chinese populations. These different variations in the HLA pattern in these populations can, in part be responsible for the difference in the prevalence T1DM[23].

**PATHOPHYSIOLOGY OF T2DM**
The major components in the regulation of blood glucose are insulin secretion and insulin sensitivity. T2DM develops due to the decline in β-cell function, whereby studies have shown that diabetes and prediabetes manifest when β-cells fail to release insulin when blood glucose levels are elevated[23-25] (Fig. 2). The ability of β-cells to secrete adequate amount of insulin in response to the peripheral blood glucose level are influenced by complex interplay between genetic and environmental factors[19, 24, 26, 27].

Initially it was believed, that insulin resistance was the main abnormality in T2DM and β-cell
dysfunction was a later manifestation. However, this idea was changed with findings that a feedback loop is responsible for maintaining the glucose homoeostasis and blood glucose concentrations[28]. The feedback loop depends on the communication between β cells and insulin-sensitive tissues. Insulin-sensitive tissues feed-back information to the islet cells about their need for insulin[28, 29]. In turn β-cells are stimulated to release insulin, facilitating the uptake of glucose, amino acids and fatty acids by insulin-sensitive tissues. In a scenario where insulin resistance is present, which often occurs in obese individual, insulin secretion from β-cells is increased to maintain normal blood glucose levels. However, blood glucose levels will stay elevated, if the β cells capacity to produce insulin is diminished[29].

Elevations in blood glucose levels are associated with the continuous decline in β-cell function. The further deterioration of the β-cell function is attributed to evolution of the disease from impaired glucose tolerance (pre-diabetes) to T2DM[30]. Studies have shown that certain groups are at increased risk of diabetes due to reduced β-cell function, such as first-degree relatives of patients with T2DM[31], and women with history of GDM[32] or polycystic ovary syndrome[33].

**PATHOPHYSIOLOGY OF GDM**

Although the underlying pathophysiology of GDM is still unclear, insulin resistance combined with β cell dysfunction is known to play an important role[16, 34]. In GDM, insulin resistance often precedes the development of overt diabetes. During pregnancy, towards the second trimester, increases in the concentration of pregnancy-related hormones, such as prostaglandin and estrogen cause postprandial glucose concentrations to increase and tissue sensitivity to insulin to decrease[16]. To counter this, the mother’s pancreatic β-cells increase their secretion of insulin, however, for women suffering from gestational diabetes this increased secretion is insufficient to counteract their resistance to insulin[35]. The end result is high levels of maternal blood glucose. Several physiological mechanisms have been implicated in this process, including the down-regulation of the insulin receptor substrate-1, which helps mediate glucose uptake by muscle cells[34, 35].

Since glucose can pass freely from the mother to fetus but insulin cannot, GDM exposes the fetus to excess doses of glucose forcing it to produce more of its own insulin[16]. Unfortunately, since insulin is a growth factor this can cause the fetus to grow more than usual and become macrosomic (excessive birth weight for gestational age)[36, 37]. Insulin sensitivity in late gestation therefore, has a strong relationship with birthweight. Maternal insulin resistance also gives rise to excessive fetal growth through increased placental transfer of other growth substrates, such as amino acids and lipids. This Pedersen hypothesis is supported by the strong correlation found between fetal size and umbilical total insulin and C-peptide shown in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[38]. This study showed a linear relationship between maternal glucose and umbilical cord C-peptide.

The HAPO study improved our understanding of the mechanisms of GDM. It demonstrated that the risk of adverse maternal, fetal and neonatal outcomes continuously increased with maternal glucose levels, even within ranges previously considered normal for pregnancy[39, 40]. It also showed that both GDM and obesity are independently associated with adverse perinatal outcomes, but that the combination of both obesity and GDM synergistically increase the odds of poor pregnancy outcomes compared to either factor alone[41].

**EPIDEMIOLOGY AND TRENDS OF DIABETES**

By far, the most prevalent form of diabetes is T2DM and most global statistics and reference to diabetes tend to reflect this type. Today the global diabetes threat comes from this form of the disease. Of the three types of diabetes listed above, however, T1DM has been characterised for the longest and its management is understood the best. T1DM constitutes only approximately 5 - 10% of all diabetes cases, and is most commonly seen in Caucasian populations[14]. The number of new cases of T1DM is increasing however, the reasons for this are still unclear but may be due to changes in environmental risk factors, infant feeding practices, or viral infections[42-44]. Similarly, GDM is a major and growing public health problem in most parts of the world, with a global prevalence of between 2% to 6% (and as high as 20% in high-risk populations).
Relatively little is known about GDM, in part because the characterisation of GDM came later than that of type 1 and 2[47], but also because until recently it had not been recognised as a priority by decision makers[48]. The exact prevalence of GDM, however, is difficult to estimate given that in many countries it is not systematically screened for or reported[49, 50]. As a result, many cases of GDM are thought to be listed as diabetes in pregnancy, that is to say pre-existing diabetes in pregnant women as opposed to the transitory form of diabetes that is diagnosed around the 24th and 28th week of pregnancy.

The International Diabetes Federation (IDF) projects that he global prevalence of diabetes among adults aged 20 - 79 years has increased from 6.4% in 2010 to 8.3% in 2013 and is expected to rise to 8.8% by 2035, if the current trends in incidence continue[1, 51]. However, wide variations in the prevalence of diabetes exist across nations and world regions[1, 15, 52]. The highest regional prevalence of diabetes in 2013 was reported for the Middle East and North Africa (MENA) region at 10.9%[1]. In contrast, the Africa region had the lowest estimated prevalence of diabetes at 5.7% in 2013[1]. Although all world regions will experience increases in the number of people with diabetes, it is projected that the Africa region will witness the largest increase in the number of adults with diabetes by 2035 (Fig. 3). Globally, the number of adults with diabetes will rise from 381.8 million in 2013 to 591.9 million in 2035, representing a 55% increase[1].

Geographically, some countries have a particularly high burden of diabetes. Furthermore, very high prevalence of diabetes has long been reported in specific populations such as the Pima Indians in the USA and Pacific Islanders[52, 53]. Elsewhere, and more clearly linked to changing lifestyles, diabetes prevalence rates have grown quickly in the USA and the Caribbean, where the prevalence is now estimated to be around 11%[3]. In 2013, the ten countries with very high prevalence rates of diabetes were Tokelau (37.5%), Federated States of Micronesia (35%), Marshall Islands (34.9%), Kiribati (28.8%), Cook Islands (25.7%), Vanuatu (24%), Saudi Arabia (23.9%), Nauru (23.3%), Kuwait (23.1%) and Qatar (22.9%)[1]. In Europe, the overall prevalence of diabetes is around 8.5%, but Turkey has a reported prevalence of approximately 15%[54]. With the exception of La Reunion with an estimated prevalence of 15.4%, rates of diabetes in Africa appear to have remained relatively low[55], but under-diagnosis and under-reporting of diabetes may be a factor in this regard[54, 55].

Major variations in the prevalence of diabetes have emerged between the MENA region countries, but countries of the Gulf Co-operative Council (GCC) have followed relatively similar epidemiological paths and now have some of the highest diabetes prevalence in the world. Saudi Arabia (23.9%), Kuwait (23.1%), and Qatar (22.9%) were ranked among the top ten most diabetes affected countries around the world[56, 57]. Of the top ten countries for prevalence of diabetes within
the MENA region, GCC counties occupied the top five places (Fig. 4). The rapid increases in the prevalence of diabetes in GCC countries is mirroring the upsurge in overweight and obesity in these nations\(^6\). For instance, in Kuwait, obesity affects 58.6\% and 43.4\% of women and men, respectively, aged \(\geq 20\) years\(^5\). These alarming rates of obesity will further fuel the vicious cycle of diabetes-obesity.

**PREDIABETES: THE RISING EPIDEMIC**

The progression from normoglycemia (normal blood glucose) to hyperglycemia (diabetes; high blood glucose) involves an intermediate stage referred to as ‘prediabetes’ (intermediate hyperglycemia), a situation in which blood glucose levels are above the normal but lower than the diabetes thresholds\(^5, 6\). Usually impaired glucose tolerance (IGT; defined as higher than normal blood glucose levels after eating) and/or impaired fasting glucose (IFG; defined as high blood glucose after a specific period of fasting) are used to define prediabetes\(^5, 6\). More recently, an International Expert Committee and the American Diabetes Association introduced and recommended the use of glycated hemoglobin A1c (HbA1c) to identify people at high risk of diabetes\(^5, 6\). A diagnosis of prediabetes is usually made if: (a) fasting plasma glucose test is between 5.6 – 6.9 mmol/L (indicating IFG), (b) oral glucose tolerance test based on 2-hour 75 g post-load plasma glucose level between 7.8 – 11.1 mmol/L (indicating IGT), and/or (c) HbA1c test of 5.7\% – 6.4\% (indicating high risk for diabetes)\(^6\).

People with prediabetes are at increased risk of developing T2DM and share similar risk profiles of micro- and macro-vascular complications as those with established diabetes\(^5, 6, 7\). In the Strong Heart Study, which aimed to estimate the incidence of diabetes in American Indians – a high risk population – the incidence of T2DM among those with prediabetes at baseline was found to be 66.1 per 1000 person-years, with a hazard ratio of 2.35 (95\% CI: 1.84 – 3.01) when compared to those with normal blood glucose\(^8\). A meta-analysis comparing the incidence rates of T2DM among individuals with prediabetes showed that the progression rates vary according to diagnostic tools/criteria used to define prediabetes, with the highest incidence rate of T2DM being 70.4 per 1000 person-years among those who were classified with prediabetes using both the IFG and IGT criteria\(^9\). A more comprehensive meta-analysis has shown that the annual incidence of T2DM among individuals with prior prediabetes ranges between 5\% and 10\%, and, according to an ADA expert panel, up to 70\% of individuals with prediabetes will eventually develop diabetes in their lifetime\(^5, 6, 7\).

Mirroring the substantial number of people affected by T2DM, prediabetes (defined as IGT) affected 316 million people (i.e., 6.9\% of adults) in 2013 and is projected to affect 471 million people (i.e., 8.0\% of adults) worldwide by 2035, based on estimates and projections provided by the International Diabetes Federation\(^5\). A study based on the National Health and Nutrition Examination Surveys (NHANES) data in the USA examined trends in prediabetes prevalence from 1999 to 2010 and showed that prediabetes prevalence increased from 27.4\% in 1999 – 2002 to 34.1\% in 2007 – 2010 among individuals aged \(\geq 12\) years\(^7\). Moreover,
a study using data collected by the Health Survey for England indicated that the prevalence of prediabetes increased from 11.6% to 35.3% from 2003 to 2011 among Individuals aged ≥ 16 years[52]. Prediabetes heretofore, is a silent epidemic that is rapidly emerging with substantial adverse health effects. Therefore, there is an urgent need for collaborative research to better understand, diagnose, and treat/prevent prediabetes and essentially delay/stop its progression to T2DM.

T2DM AND PREDIABETES IN YOUTH

Traditionally, T1DM has been the predominant type of diabetes in children and adolescents. However, this view has changed due to the increasing incidence/prevalence of T2DM among youth in recent decades[73, 75]. According to findings of a systematic review, the incidence rate and prevalence of T2DM can be as high as 330 per 100,000 person-years and 5300 per 100,000 population, respectively, among children younger than 20 years old[76]. However, there is substantial disparities in the prevalence of T2DM between and within countries that can be explained by race/ethnicity (an indicator of genetic background) and lifestyle factors. For instance, in Australia, the incidence of T2DM is 6-times higher in the Indigenous than the non-Indigenous population[77]. In the SEARCH for Diabetes in Youth Study in the USA, the incidence rate of diabetes was estimated at 24.3 per 100,000 person-years in the total study sample, while demonstrating wide variations according to race/ethnicity and age[78].

In a subsequent analysis of the SEARCH study, the prevalence of T1DM and T2DM (per 1000 population) in 2001 were 1.54 and 0.22, respectively, and in 2009 the estimates were 1.93 and 0.24, respectively, among youth aged < 20 years[79, 80]. This result indicates that T1DM is the predominate type of diabetes among children and adolescent, however, more studies are needed to address whether the gap in the incidence/prevalence between T1DM and T2DM is changing among youth.

More alarming is the increasing trends of prediabetes among the youth, which can fuel the future prevalence pool of T2DM. Data from the NHANES in the USA indicate that the prevalence of prediabetes among youth aged 12 to 17 years has increased from 13.3% in 1999 – 2002 to 17.9% in 2007 – 2010[71]. Several studies have also demonstrated that the prevalence of prediabetes is substantially increased in obese pediatric populations[81, 84]. In Sweden, the prevalence of prediabetes (defines as IFG) among obese children (aged 2 - 18 years) was estimate at 17.1%[84]. In contrast, among overweight/obese school children aged 7 - 18 years in Tianjin, China, the prevalence of prediabetes (defined as IFG or IGT) was 3.3%[83]. Although the magnitude of prediabetes can differ across nations, there is an international consensus that the health complications associated with prediabetes among children and adolescents are alarming and call for the rapid development of preventive strategies the can curb the this ever-growing public health problem[74, 85, 86].

RISK FACTORS

Although increasingly a global phenomenon, the prevalence of diabetes, and especially T2DM, nevertheless varies considerably between socio-geographic “areas” and according to bio-genetic profiles[87, 88]. Socio-behavioural factors are also key to understanding the epidemic, and the push towards more sedentary, urban life has clearly fuelled the spread of diabetes[89]. Middle and high-income urbanized societies have witnessed the emergence of lifestyle that involves less daily routine physical effort and exercise, consumption of industrially prepared, packaged and distributed foods, and dependence on a fast-food industry for main meals[89, 90]. Migration also appears to be playing an important role in creating food acculturation, stress and stress coping dynamics that make people more vulnerable to T2DM[91]. The increasing popularity of industrially prepared and marketed food in low income societies is now prompting concomitant increases in T2DM. To this end, in addition to family history, age, ethnicity, and prediabetes, obesity is the strongest modifiable predisposing factor associated with diabetes development[92, 93]. A meta-analysis has demonstrated that the risk of T2DM in obese individuals is 7-times higher than the risk among those with normal weight[94]. Hence, public health preventive efforts should be employed towards tackling the ever-emerging overweight-obesity epidemic[58].

CONSEQUENCES

As our understanding of the pathophysiology of diabetes and other diseases has improved, it has become increasingly clear that the immune-suppressing character of diabetes facilitates the emergence of opportunistic infections. Chronically elevated blood glucose levels in poorly controlled diabetes can lead to acidosis that severely limits the natural immunologic capacity of people[85], reduces cellular immunity and lowers the body’s ability to fight infections such as tuberculosis (TB) and Hepatitis C virus (HCV)[96]. In settings where these infections are common, they can present a serious threat to people with diabetes and can produce difficult-to- manage complications[97, 98]. In these situations, classic diagnostic and treatment protocols may not be relevant and opportunities for early management of co-infections may be lost. Results from China indicated that early stage bi-directional screening for diabetes and TB is feasible and effective[99, 100]. As far as treatment is
concerned, there is evidence that drugs used to treat TB can interact with oral anti-diabetic drugs and lead to suboptimal glycemic control, thus calling for careful follow up and monitoring of people with co-morbidity[89].

T1DM is usually diagnosed in childhood and once diagnosed is typically managed through injected insulin[101]. As such T1DM intrudes dramatically in the life of children and can be psychosocially problematic, it can interfere with the sports and social life of children and adversely affect their schooling[102, 103]. Furthermore, diabetes can cause severe morbidity, if not effectively managed. Over 1 million amputations are needed as a result of diabetes each year and diabetes is now the single most important cause of blindness in young adults[2].

Women with GDM are more likely to give birth to large-for-gestational-age infants (fetal macrosomia) [37, 104]. GDM may result in obstructed labor, the death of the mother and the baby and even when vaginal deliveries are successful, it may be at the risk of birth injury in babies[16, 37]. It is estimated that women with previous history of GDM are at 7-fold higher risk for developing T2DM later in life than those with no prior history of GDM[108]. The offspring of women with GDM also have a higher risk of morbidity later in life including obesity and T2DM[36, 106, 107].

PREVENTION

Thus far, etiologic research have identified several modifiable and unmodifiable risk factors for T2DM. Excess body weight (overweight/obesity) and prediabetes (a high-risk state for developing T2DM) are two major modifiable risk factors for T2DM[60, 92, 94]. In addition, family history of diabetes, reflecting genetic predisposition and shared familial environment (i.e., cultural practices and behaviors), is a strong predictor of T2DM[108-110]. Although the role of genetics cannot be ignored, the rapid increase in T2DM incidence/prevalence within the past few decades points toward the inevitable role of environmental factors in disease etiology. Therefore, preventive efforts and strategies should target all individuals and particularly those at high-risk of developing T2DM.

Several key lifestyle factors, namely diet, physical activity, smoking, alcohol use, and body mass index (overweight/obesity) appear to be independently associated with diabetes, and in combination can strongly predict the development of T2DM[111, 112]. A study investigating the role of the aforementioned lifestyle factors indicated that up to nine out of 10 new cases of T2DM can be attributed to these five lifestyle factors, and that most cases of T2DM might have been preventable by collectively managing these risk factors[111]. Large-scale clinical trials have shown that even modest changes to diet and exercise can reduce the risk of diabetes in people with pre-diabetes/impaired glucose regulation, and these results have been mimicked in “real world” prevention programs[113-115]. Simple lifestyle modifications (such as increasing physical activity) in people with prediabetes have also been shown to reduce the risk of progression by 40% – 70%[60]. Secondary prevention of health complications through careful monitoring and early identification of diabetic foot signs or retinopathy has similarly been shown to be effective in reducing the impact of diabetes on extremities and vision[116, 117].

Primary and secondary prevention have been shown to benefit healthcare systems as well as people living with diabetes. Even simple preventative interventions have been shown to be cost effective both for health systems and individuals[118, 119]. Diabetes currently accounts for over 10% of the total health expenditure worldwide and most countries spend between 5 – 18% of their national health expenditures on diabetes[2]. In 2013, more than 548 billion dollars are estimated to have been spent on managing diabetes and complications, making it one of the 10 most expensive treatment regimes in the world[2]. Meanwhile in the USA, diabetes was responsible for the loss of more than 69 billion dollars were lost through reduced productivity[120].

CONCLUSION

The prevalence of diabetes has substantially increased over the last decades and is projected to witness further growth. This upsurge in diabetes is placing substantial burden on local as well as global health care systems, economies, and societies as well as individuals. Most noticeably is, the increase of T2DM and prediabetes among the youth, which is predisposing this group of individuals to serious health consequences at younger ages. Changes in lifestyle and environmental factors in addition to genetic susceptibility is contributing to this ever-rising epidemic. Prevention programs suggest that mitigating the obesity epidemic, a major risk factor for diabetes, is the key towards successful prevention strategies. However, further research is needed to determine the effect of other potential risk factors and how such factors work in concert in the development of diabetes.

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Clinical and Laboratory Features, Complications and Treatment Outcome of Tularemia and a Review of Literature

Mehmet Ulug
Private Umit Hospital, Infectious Diseases and Clinic Microbiology, 26140 Eskisehir, Turkey


ABSTRACT

Objective: To define the epidemiological and demographical characteristics, laboratory findings, treatment methods and treatment results of 14 patients with tularemia

Design: Retrospective study

Setting: Department of Infectious Diseases and Clinic Microbiology, Private Umit Hospital, Eskisehir, Turkey

Subjects: Fourteen patients with tularemia admitted to this hospital from April 2011 to May 2012

Main outcome measures: Demographic characteristics, clinical and laboratory findings of the patients with tularemia and the treatment outcomes

Results: A total of 14 patients (nine male, five female; mean age: 41 ± 17 years) with myalgia, cervical lymphadenopathy, sore throat and fever, and failure to respond to beta-lactam antibiotics, were followed up. Ten patients (71.4%) had oropharyngeal tularemia, three (21.4%) had glandular and one (7.1%), oculaglandular. Serum samples were obtained from all patients and in 13 (92.8%) of them microagglutination test yielded positive results (≥1/160) in their first serum samples. The most frequent laboratory findings were high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Complete recovery was obtained in nine (64.3%) patients, while five (35.7%) were nonresponsive to the medical treatment.

Conclusion: Most of the patients of this study were treated without surgical intervention. Interestingly, medical therapy started within three weeks was found successful. However, it should be considered in differential diagnosis of patients with myalgia, cervical lymphadenopathy and pharyngeal hyperemia, and those who did not respond to beta-lactam antibiotics with high levels of CRP and ESR, and those living in rural areas.

KEY WORDS: lymphadenopathy, Tularemia, Turkey

INTRODUCTION

Tularemia, caused by a small intracellular, non-spore forming, encapsulated, non-motile, aerobic Gram-negative bacterium Francisella tularensis, is a multisystemic zoonotic disease in human and some animals[1-3].

Among four subspecies of F. tularensis genus, F. tularensis subsp. tularensis (Jellison type A) and F. tularensis subsp. holarctica (Jellison type B) are the most common subspecies in human diseases. F. tularensis subsp. tularensis, most commonly seen in the U.S., causes a more severe disease posing a higher fatality rate, whereas F. tularensis subsp. holarctica, found predominantly in Europe, Turkey, and Northern Asia, is associated with a milder disease posing lower mortality and is considered responsible for waterborne outbreaks[4,5]. The organism is highly infectious and can be transmitted to humans through arthropod bites, contact with infected animal tissues, ingestion of contaminated food or water, and inhalation of contaminated aerosols generated through agricultural, laboratory or landscaping activities[6]. Person-to-person transmission does not occur[6]. Its incubation period can range from 1 - 21 days, yet, lasts 2 - 5 days on an average[7]. Depending on the route of microbial transmission, different clinical forms of tularemia can be seen, including ulceroglandular (42-75%), glandular (15 - 44%), oropharyngeal (<5%), oculoglandular (4%), pneumatic and systemic (thiphoidal) forms[8]. Diagnosing tularemia is typically a clinical procedure that considers exposure history and clinical manifestations and is confirmed by serologic testing[9]. Streptomycin, gentamycin, tetracycline and fluoroquinolone antibiotics are effective, and early initiation of these agents is important in effective treatment[9].

This study was aimed to review epidemiological and demographical characteristics, laboratory findings,
treatment methods and treatment results of 14 patients with tularemia. This is the second study reported from Eskisehir (located in Central Anatolia), Turkey.

MATERIAL AND METHODS
This study was performed by retrospectively evaluating the files of 14 patients treated and followed-up in an infectious disease clinic of a private hospital from April 2011 to May 2012. Demographic data of the patients—age, sex, occupation, and residence—were obtained from patient files, as was information regarding the presence of risk factors, including consumption of natural spring water, consumption of hunted animals, rodent bites or contact, animal breeding, consumption of food without appropriate cleaning, and travel to endemic regions, as well as the history of illness, symptoms, clinical findings, laboratory results, and therapeutic features.

Blood samples from each patient for the serological evaluation of tularemia were sent to Refik Saydam Public Hygiene Center, a reference laboratory in Turkey for the evaluation of infectious diseases, including tularemia, in Turkey. The diagnosis of tularemia was made after exclusion of other possible causes of lymphadenopathy, such as human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, Toxoplasma and Brucella, and the presence of a positive tularemia microagglutination test (MAT). MAT was performed with a commercial antigen as described by the manufacturer (BD F. tularensis Antigen, Becton Dickinson, Sparks, MD, USA) or with a homemade F. tularensis antigen obtained from the strains isolated from patients with tularemia in Turkey. In this study, having an antibody titer ≥1/160 or a four-fold increase in blood samples taken at different times at least two weeks apart indicated an acute infection [4, 5]. Since the specific recommended security level and special agar for F. tularensis is currently unavailable in our microbiology laboratory, specific blood cultures, throat smears and lymph node aspirates could not be studied for isolation of F. tularensis.

All patients received appropriate antibiotics, including streptomycin (1 g/day IM), ciprofloxacin (1 g/day p.o.), and doxycycline, for at least 14 - 21 days [6, 7]. Therapeutic failure was indicated by presence of one of the following findings: suppuration and draining (spontaneously or by surgical means) of the involved lymph nodes during and after treatment, or an increase in the size of the existing lymphadenopathy [6, 8, 9]. The treatment was considered successful, if the signs and symptoms disappeared and lymphadenopathy resolved without suppuration. A second antibiotic course with a different regime was given in case of therapeutic failure. The tularemia cases were followed up at 3-months interval for an year.

RESULTS
A total of 14 patients were diagnosed as tularemia. Nine (64.3%) of them were male and five (35.7%) of them were female with a mean age of 41.8 ± 17.3 years (age range: 15 - 65 years). None of the patients had a previous clinical history of tularemia. Most of the patients applied in spring months, especially April (n = 4) and May (n = 5). The demographic data of the patients are shown in Table 1.

Twelve (85.7%) of the patients admitted from Eskisehir, one from Kutahya and one from Bozoyuk/Bilecik, and all were living in rural areas, where the spring water was not chlorinated regularly or at all. Drinking water analysis could not be performed as the cases were sporadic. The risk factors of the patients for tularemia are presented in Table 2.

The mean duration between the onset of the symptoms and the hospital visit was 35.5 ± 27.6 days (range, 7 - 90 days). Ten patients (71.5%) had clinical presentation compatible with oropharyngeal

Table 1: Demographic data of the patients

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Occupation</th>
<th>AT (day)</th>
<th>Date of arrival</th>
<th>Clinic form</th>
<th>First MAT titer</th>
<th>Second MAT titer</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>M</td>
<td>Farmer</td>
<td>30</td>
<td>April 2011</td>
<td>Oropharyngeal</td>
<td>1/320</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>M</td>
<td>Farmer</td>
<td>70</td>
<td>April 2011</td>
<td>Oropharyngeal</td>
<td>1/2560</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>Farmer</td>
<td>20</td>
<td>April 2011</td>
<td>Oropharyngeal</td>
<td>1/2560</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
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<td>Housewife</td>
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<td>April 2011</td>
<td>Oropharyngeal</td>
<td>1/1280</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>5</td>
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<td>M</td>
<td>Farmer</td>
<td>21</td>
<td>May 2011</td>
<td>Oropharyngeal</td>
<td>1/1280</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>F</td>
<td>Housewife</td>
<td>30</td>
<td>May 2011</td>
<td>Oropharyngeal</td>
<td>1/80</td>
<td>1/320</td>
<td>Recovery</td>
</tr>
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<td>7</td>
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<td>Farmer</td>
<td>10</td>
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<td>Oropharyngeal</td>
<td>1/2560</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
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<td>M</td>
<td>Shepherd</td>
<td>25</td>
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<td>Oropharyngeal</td>
<td>1/320</td>
<td>-</td>
<td>Recovery</td>
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<tr>
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<td>M</td>
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<td>7</td>
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<td>Oculoglandular</td>
<td>1/320</td>
<td>-</td>
<td>Recovery</td>
</tr>
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<td>M</td>
<td>Farmer</td>
<td>80</td>
<td>September 2011</td>
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<td>1/320</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>M</td>
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<td>30</td>
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<td>Oropharyngeal</td>
<td>1/640</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
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<td>F</td>
<td>Housewife</td>
<td>10</td>
<td>November 2011</td>
<td>Oropharyngeal</td>
<td>1/640</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
<td>13</td>
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<td>Housewife</td>
<td>60</td>
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<td>Glandular</td>
<td>1/320</td>
<td>-</td>
<td>Recovery</td>
</tr>
<tr>
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<td>64</td>
<td>F</td>
<td>Housewife</td>
<td>90</td>
<td>May 2012</td>
<td>Glandular</td>
<td>1/640</td>
<td>-</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

(M: Male, F: Female, AT: Admission time, MAT: Microagglutination test)
form, three (21.4%) with glandular form and one (7.1%) with ocuglandular form. The most frequent symptoms were malacia (100%), swelling on the neck (92.8%) and sore throat (85.7%). Lymphadenopathy (100%), pharyngeal hyperemia (71.5%) and erythema nodosum-like skin rash (21.4%) were the most common signs. The lymphadenopathy was usually unilateral (92.8%) and with predominantly cervical localization (85.7%). The lymph nodes were palpable, slightly tender and even visible. A patient with ocuglandular tularemia presented with conjunctivitis, swelling of the eyelid and tender cervical lymphadenopathy. The symptoms and signs of the patients are shown in Table 3.

Table 3: Clinical findings of the patients with tularemia

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n (%)</th>
<th>Signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>14 (100)</td>
<td>Lymphadenopathy</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Swelling of the neck</td>
<td>13 (92.8)</td>
<td>Cervical</td>
<td>12 (85.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>13 (92.8)</td>
<td>Right</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12 (85.7)</td>
<td>Left</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>Chills</td>
<td>10 (71.5)</td>
<td>Bilateral</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (42.8)</td>
<td>Axillary</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>3 (21.4)</td>
<td>Supraclavicular</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (7.1)</td>
<td>Pharynx hyperemia</td>
<td>10 (71.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin rash</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonsillitis</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conjunctivitis</td>
<td>1 (7.1)</td>
</tr>
</tbody>
</table>

When the laboratory findings of the patients were evaluated, the mean total white blood cell count (WBC) upon admission was 9701 ± 2123/mm³ (NR: 4000 - 10000/mm³; range: 6380 -12002/mm³), erythrocyte sedimentation rate (ESR) was 35.2 ± 27.9 mm/h (NR: 0 - 20 mm/h; range: 4 - 94 mm/h) and C-reactive protein (CRP) was 38.4 ± 48.3 mg/dL (NR: 0 - 5 mg/dL; range: 2 - 138 mg/dL). The WBC count was within the normal limits in nine (64.3%) patients and high in five (35.3%) patients, while CRP and ESR were high in 11 (78.5%) patients and within normal limits in three (21.4%). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine levels were within normal range in all patients. Brucella, toxoplasma, Epstein-Barr virus, cytomegalovirus and human immune deficiency virus serology were negative in all patients. Purified protein derivative (PPD) test was also negative and chest radiographs were normal. Aerobic and anaerobic blood cultures, urine culture and throat swab cultures were negative, too. Diagnosis of tularemia was confirmed in all patients with MAT. MAT titer was ≥1/160 in 13 (92.8%) patients from a single serum sample and four-fold rise of the antibody titer was determined in one (7.1%) patient.

Before the diagnosis, all of the patients had received a treatment of beta-lactam antibiotics by primary and/or secondary healthcare physicians. A combination of streptomycin and doxycycline was recommended for all of the patients for 21 days. Nine (64.3%) of the patients fully recovered, while surgical lymph node drainage was performed in five (35.3%) patients. While six of seven patients (85.7%) treated with antibiotics active against F. tularensis within the first three weeks of their illness fully recovered, complete recovery was observed in only three of seven (42.8%) treated with appropriate antibiotics but delayed by more than three weeks.

Mortality or major complications, such as pneumonia, meningitis, deep neck infection, due to tularemia was not observed in the patients. However, all of the patients were reevaluated for prognosis on the third, sixth and twelfth month after the first visit, and no relapse of the disease was observed.

**DISCUSSION**

Tularemia is an endemic zoonotic disease in Turkey, and it became a major public health problem once it appeared in Thrace, Marmara, and western Black Sea regions, followed by outbreaks, predominantly due to contaminated water, in other regions of our country[1,4,11,13]. Many studies have reported that the main etiological agent of tularemia cases in Turkey is F. tularensis subsp. holarctica[3,14-16]. Tularemia epidemics have seasonal characteristics, and F. tularensis subsp. holarctica causes outbreaks during autumn and winter months. Although tularemia was observed throughout the year in our country, seasonal distribution data demonstrated an increase during late fall and winter months with a gradual decrease in spring and summer. On the other hand, the seasonal distribution of the disease was not same for all geographic areas[1]. Çağlı et al[17] and Korkmaz et al[13] reported that the frequency of outbreaks are at peak during November and December, and December to March, respectively; whereas in another study conducted by Snowden et al[16], the peak period was between May and June. In this study, most of the patients were also seen report in April and May.

It is not completely clear how our patients were infected, but it is well known that tularemia is a highly infective bacterium, and even 10 bacteria are enough
to cause the disease\textsuperscript{11}. Previous data suggest that tularemia is mainly transmitted through unmonitored spring water and consumption contaminated food\textsuperscript{1,8}. Tularemia outbreaks due to contaminated water usually occur in fall and winter, whereas transmission via consumption of hunted animals is more common in summer\textsuperscript{2,8}. The patients who were presented in this study can be regarded as sporadic, because all of them were from different rural areas and there was no history of animal bites among these patients (Table 2). Hence, most of the patients were infected in spring and summer months (Table 1) and the most likely means of transmission in these patients was via consumption of unmonitored spring water.

Males and females are equally affected in all age groups during the epidemics between 1936 and 2005 in our country\textsuperscript{19}. This study did not contain enough cases to make an evaluation on sex and age range. In Maurin et al\textsuperscript{10} study, males were affected more than females, as in this study. In contrast, in a report including 58 tularemia cases, most of the patients were female and 79\% of these cases were housewives\textsuperscript{20}. In this study, all of the female patients were also housewives. In rural areas, contact with non-chlorinated water is more common among women, who do the house and agricultural work; this could be the probable cause of high frequency of female cases reported in other studies. However, in Helvacı et al\textsuperscript{21} and Celebi et al\textsuperscript{11} studies, the patients were between 16 - 40 and 10 - 50 years old, respectively. In contrast, in Gürkan et al\textsuperscript{22} and Christova et al\textsuperscript{23} studies, most of the patients were elderly. In our study, most of the patients were between 15 - 55 years old.

Tularemia may present itself via various clinical manifestations, depending on the virulence of the bacteria, port of entry, extent of the systemic involvement, and immune status of the host \textsuperscript{2,24}. While the most common form worldwide is the ocular, oropharyngeal form comprises the majority of the cases in our country\textsuperscript{1,2}. In contrast, 86.2\% of the patients presented with the glandular form in Koç et al\textsuperscript{20} study. In this study, most of the patients had also clinical presentation compatible with oropharyngeal form.

The hallmarks of oropharyngeal tularemia are severe pharyngitis, fever, cervical lymphadenitis. Oral ulcers and/or an oropharyngeal pseudo-membrane may be present\textsuperscript{21}. In a study by Helvacı et al\textsuperscript{21}, which included patients admitted within a ten-year period, lymphadenopathy was the most common single finding on physical examination. In this study, myalgia, cervical lymphadenitis and pharyngeal hyperemia were observed in the majority of the cases. Epidemiologically or sporadically, few cases of ocular, or pharyngeal tularemia have been reported in Turkey\textsuperscript{11,21,24}. In this study, one case conformed to the ocular, or glandular form and the presenting signs were ocular. It may have been as a result of autoinfection, through transfer of the bacteria in oral secretions by means of the patients’ own hands. However, in all forms of the tularemia, skin rashes may be seen, such as diffuse maculopapular or vesiculopapular eruptions, pustule, acniform lesions, erythema nodosum, erythema multiforme, and urticaria\textsuperscript{3,4,6}. In the present study, erythema nodosum-like skin lesions developed in 21.4\% of the patients. Other studies reported that 14 - 40\% of the patients developed erythema nodosum-like skin lesions\textsuperscript{6,21}.

The diagnosis of tularemia is mainly based on serological analysis, because isolation of the causative agent is time-consuming, extremely hazardous and requires a biosafety level-3 containment in order to avoid risks of laboratory infection\textsuperscript{1,2,10-12}. The MAT is considered as the current reference method for the serodiagnosis of tularemia\textsuperscript{1,7,11,22,26}. In the presence of compatible symptoms, sustained high titers of 1/160 or greater, or detection of a four-fold increase in blood samples taken at different times (at least two weeks) in an acute specimen support a presumptive diagnosis of a tularemia\textsuperscript{1,4}. However, significant antibody levels do not usually increase until the third week of illness\textsuperscript{10,22}. In addition, some of the tularemia cases that tested negative with the MAT were diagnosed only by enzyme-like immunoabsorbant assay or polymerase chain reaction (PCR)\textsuperscript{19}. PCR-based methods provide positive results in the early stage of tularemia, even after antibiotic therapy has been initiated\textsuperscript{12}. The diagnosis of our patients was made the demonstration of a positive tularemia agglutination test. However, the test result was negative in the first sampling in a patient in this study, but the antibody titer of this patient was 1/320 in repeated serum sampling.

The choice of routine laboratory examinations can vary in tularemia\textsuperscript{13}. WBC may be normal or elevated, with a predominance of neutrophils. CRP and ESR are typically elevated and liver function tests may also be elevated\textsuperscript{7}. The WBC count was found within normal limits in 61\% of the patients in Korkmaz et al\textsuperscript{13}, 50\% in Snowden et al\textsuperscript{28} and 71\% in Meriç et al\textsuperscript{29} studies, while in this study, it was 64.3\%. There have been no significant differences in the ESR and CRP levels in other studies. While Korkmaz et al\textsuperscript{13} found high ESR in 72\% and high CRP in 56\%, and Meriç et al\textsuperscript{29} found high ESR in 79\% of the patients, ESR and CRP levels were high in 78.5\% of the patients in this study. I can conclude that there is no specific and easy-to-use routine laboratory finding for the diagnosis of tularemia, except the MAT.

The differential diagnosis of tularemia is extremely broad. Oropharyngeal tularemia must be
differenitated from the streptococcal pharyngitis, infectious mononucleosis, adenoviral infection and diphtheria. The differential diagnosis of ulceroglandular and glandular tularemia includes pyogenic bacterial infections, cat scratch disease, syphilis, tuberculosis and toxoplasmosis[6]. In cases subjected to surgical excision reporting specimens as chronic granulomatous inflammation or caseous necrosis causes the patient to be examined and treated for tuberculosis[4]. Similarly, five of 61 patients had been misdiagnosed with tuberculous lymphadenitis and started anti-tuberculosis drugs in Celebi et al[11] study. None of our patients was misdiagnosed with tuberculous lymphadenitis. Oculoglandular tularemia may be confused with adenoviral infection, pyogenic bacterial infections, cat scratch disease, syphilis and herpes simplex virus infection. Pneumonic tularemia is with difficulty, differentiated from the typical pneumonias, atypical pneumonias and psittacosis. Typhoidal tularemia must be differentiated from other forms of sepsis as well as from enteric fever and brucellosis[6]. The physicians must always bear in mind that he may encounter tularemia cases randomly, and must be especially in cases when symptoms are not alleviated by beta-lactam antibiotic therapy and in cases that were known to have come from a tularemia region.

Antibiotic therapy should be initiated as soon as tularemia is suspected, rather than awaiting results of serologic testing. The illness may be prolonged, complications are more likely to occur, and treatment failure is more frequent if antibiotic therapy is delayed[7]. Antibiotics are usually administered for 2 - 3 weeks[10]. All of the patients in this study were treated with streptomycin plus doxycycline initially and therapeutic failure was observed in 35.7% of the patients. It has been argued, that starting antibiotic treatment in the first three weeks of the disease is essential for complication-free outcome. However, if initiation of treatment is delayed three weeks, the lymph nodes could become suppurated, requiring surgical drainage[4,11,12,24]. In the present study, six patients who started treatment early made a full recovery, whereas lymphadenopathy persisted despite antibiotic treatment when treatment was delayed in four patients. Those patients were followed up by ear-nose and throat outpatient clinic. The prognosis of the patients was good, and no patient died.

CONCLUSION

Tularemia, commonly presenting in the oropharyngeal form, as observed in sporadic and epidemic cases, is not a rare disease in our region. Most of the patients of this study treated without surgical intervention, interestingly, medical therapy started within three weeks was successful. However, it should be considered in differential diagnosis of patients with myalgia, cervical lymphadenopathy and pharyngeal hyperemia, and who have no responded to beta-lactam antibiotics with high levels of CRP and ESR, and in those living in rural areas. Finally, in order to prevent tularemia, community water supplies, including spring water, should be treated using the standard chlorination procedure and checked periodically. Contaminated water should not be used or consumed.

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Conflict of interest: The author declares no conflict of interest.

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Original Article

Mean Platelet Volume, Red Cell Distribution Width and Ischemia Modified Albumin as a Marker of Oxidative Damage and Inflammation in Obese Children

Hakan Aylanc¹, Fatih Battal¹, Sule Yildirim¹, Nazan Kaymaz², Mustafa Tekin³, Hakan Turkon²

¹Department of Pediatrics, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Turkey
²Department of Medical Biochemistry, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Turkey

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ABSTRACT

Objectives: Childhood obesity is an important risk factor for adulthood obesity. The objective of this study was to evaluate the relationship between red cell distribution widths (RDW), ischemia modified albumin (IMA), mean platelet volume (MPV) and childhood obesity.

Design: Prospective case-control study

Setting: General pediatric outpatient clinics of the Department of Pediatrics, Canakkale Onsekiz Mart University Hospital, Turkey

Subjects: One hundred and seven (57 obese and 50 normal weight) children and adolescents (aged 5 - 18 years)

Interventions: Age, gender, body mass index (BMI) were recorded. The serum IMA and complete blood count level of the subjects were measured. RDW, MPV, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red blood cell (RBC), platelet count and white blood cell (WBC) count were measured as part of the automated complete blood count.

Main Outcome Measures: The RDW and IMA were found significantly higher in obese children and adolescents than normal weighted ones (p < 0.001). MPV values were minimally increased in obese subjects as compared to normal weighted peers (p = 0.05).

Results: Hb, MCV, platelet and WBC counts were similar between normal and obese subjects. The Hct and RBC count were significantly higher in obese subjects.

Conclusions: In the present study we demonstrated that IMA and RDW levels are significantly higher in obese children and adolescents as compared to those with normal weight. The IMA and RDW had positive correlation with BMI. These results support that oxidative and inflammatory processes of obesity begin in childhood.

KEY WORDS: body mass index, childhood obesity

INTRODUCTION

Childhood obesity with an increasing incidence in recent years is an important public health problem that impairs the quality of life of children. The increase in the prevalence of obesity in childhood is a major risk factor for adulthood obesity. Obesity increases the incidences of sleep apnea, non-alcoholic fatty liver disease and type 2 diabetes mellitus[9].

Regional adiposity is associated with increased metabolic and cardiovascular risks. Adipose tissue is a complex endocrine organ and produces a variety of molecules which have local and systemic effects[2-3]. In obese subjects, hyperalimentation can cause oxidative stress and activate the nuclear factor (NF)-κB and finally the transcription of pro-inflammatory cytokines increases[4]. These cytokines may lead to insulin resistance in adipose tissue[5].

Increased red cell distribution width (RDW) has been shown to be correlated with different clinical situations such as chronic heart failure, pulmonary embolism and septic shock, either chronic or acute[6-8]. Increased RDW is also related to inflammation and nutritional status[9]. Fujita et al[6] demonstrated that RDW is elevated in overweight subjects and reflects the inflammatory status in overweight children.

Reactive oxygen species can modify the N-terminal region of albumin in oxidative stress that may increase the levels of ischemia modified albumin (IMA). IMA

Address correspondence to:
Sule Yildirim, Department of Pediatrics, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Turkey, 17000. Tel: +90 505 828 07 07, E-mail: sule.yildirim@comu.edu.tr, draglanc@hotmail.com
levels are increased in diseases related to obesity such as metabolic syndrome, hypercholesterolemia, and type 2 DM[10–14].

Mean platelet volume (MPV) is an automatically measured parameter in the peripheral blood count which shows the correlation with platelet functions. Clinical conditions with low-grade inflammation such as diabetes, hypertension, dyslipidemia, obesity and cardiovascular diseases can effect positively MPV[15,16].

In this study, our objective was to evaluate the relationship between RDW, IMA, MPV and childhood obesity.

SUBJECTS AND METHODS

Study population

This study included 107 children and adolescents (aged 5-18 years), who attended the general outpatient clinics of the Canakkale Onsekiz Mart University Hospital, Turkey, from October 2012 to July 2013. Fifty-seven out of them were obese and 50 were with normal weight. The parents and children were informed and written and verbal consent was obtained. Our local ethics committee approved the study.

Exclusion criteria

Children with history of functional and structural cardiovascular diseases (acquired and congenital), hematologic diseases, chronic systemic diseases, hypertension, sleep apnea, endocrinological disorders were excluded. Also children with anemia, abnormal platelet count and platelet dysfunction were excluded.

Baseline variables

All subjects underwent detailed physical examination. Height and weight were measured, and body mass index (BMI) was calculated for each patient.

Body Mass Index (BMI)

The BMI was calculated by the formula; BMI = weight (kg) / height (m)^2. The subjects were labeled as obese, if their BMI exceeded the 95th percentile for sex and age based reference values.

Laboratory investigations

Ischemia modified albumin (IMA) was studied by the method which was previously defined by Bar-Or et al[17]. Hemoglobin (Hb), hematocrit (Hct), MCV (mean corpuscular volume), RDW, MPV (mean platelet volume), red blood cell (RBC) count, platelet count and white blood cell (WBC) count were measured as part of the automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter, CA, USA).

Statistical Analysis

All the results were expressed as mean ± SD. The Kolmogorov-Smirnov test was used to detect the normality distribution of the data. The student’s t-test was used to compare normally distributed variables and Mann-Whitney U test was used for abnormally distributed variables among groups. Chi-square test was used for comparison of categorical variables. Correlations between variables were evaluated by Pearson’s rank correlation test. Multiple linear regression analyses using the stepwise method were performed to assess the independent variables (age, sex, BMI) affecting the dependent variable RDW. SPSS v13.0 (SPSS Inc., Chicago, IL, USA) was used for analyses, with p-values < 0.05 considered statistically significant.

RESULTS

A total of 107 children and adolescents (57 obese and 50 normal weight) were included in the study. Hb, MCV, platelet, WBC were similar between normal and obese subjects. Hct and RBC count were significantly higher in obese subjects. RDW and IMA were found to be significantly higher in obese children and adolescents. MPV values were minimally increased in obese subjects compared to normal weighted peers (p = 0.05). Demographic, clinical characteristics and laboratory parameters of study group are summarized in Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal weight (n = 50)</th>
<th>Obese (n = 57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>25/25</td>
<td>18/39</td>
<td>ns</td>
</tr>
<tr>
<td>Age, years</td>
<td>11.2 ± 2.3</td>
<td>12.2 ± 2.5</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41.1 ± 11.7</td>
<td>73.7 ± 15.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>146.7 ± 13.2</td>
<td>153.5 ± 11.2</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>18.6 ± 2.5</td>
<td>30.9 ± 3.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.77 ± 0.98</td>
<td>12.8 ± 0.98</td>
<td>0.029</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>37.5 ± 3.1</td>
<td>39.8 ± 3.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Red blood cells (106/μl)</td>
<td>4.59 ± 0.38</td>
<td>4.9 ± 0.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MCV (μm3)</td>
<td>81.81 ± 4.71</td>
<td>81.25 ± 5.3</td>
<td>0.568</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>13.5 ± 0.98</td>
<td>14.4 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelet count (103/mm3)</td>
<td>280.64 ± 64.4</td>
<td>287.3 ± 67.4</td>
<td>0.607</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>8.19 ± 0.88</td>
<td>8.55 ± 1.05</td>
<td>0.050</td>
</tr>
<tr>
<td>White blood cells (103/mm3)</td>
<td>8.5 ± 2.3</td>
<td>8.1 ± 1.7</td>
<td>0.257</td>
</tr>
<tr>
<td>IMA (IU/mL)</td>
<td>742.5 ± 114.4</td>
<td>994.8 ± 130</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

M: male; F: female; BMI: Body mass index; MCV: Mean corpuscular volume; RDW: Red cell distribution width; MPV: Mean platelet volume; IMA: Ischemia modified albumin; ns: not significant

There was positive and statistically significant correlation between RDW and BMI (Fig. 1) (r = 0.365; p < 0.001). IMA levels were significantly correlated
Table 2. Association of complete blood count parameters with IMA and BMI

<table>
<thead>
<tr>
<th>Blood parameters</th>
<th>BMI</th>
<th></th>
<th>IMA</th>
<th></th>
<th>RDW</th>
<th></th>
<th>MPV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>r</td>
<td>p-value</td>
<td>r</td>
<td>p-value</td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.284</td>
<td>0.003</td>
<td>0.142</td>
<td>0.146</td>
<td>-0.245</td>
<td>0.011</td>
<td>0.094</td>
<td>0.337</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>0.372</td>
<td>&lt; 0.001</td>
<td>0.215</td>
<td>0.027</td>
<td>-0.080</td>
<td>0.417</td>
<td>0.141</td>
<td>0.148</td>
</tr>
<tr>
<td>Red blood cells (10^6/μl)</td>
<td>0.380</td>
<td>&lt; 0.001</td>
<td>0.278</td>
<td>0.004</td>
<td>0.319</td>
<td>0.001</td>
<td>0.237</td>
<td>0.015</td>
</tr>
<tr>
<td>MCV (μm³)</td>
<td>-0.021</td>
<td>0.832</td>
<td>-0.079</td>
<td>0.424</td>
<td>-0.393</td>
<td>&lt; 0.001</td>
<td>-0.165</td>
<td>0.092</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>0.365</td>
<td>&lt; 0.001</td>
<td>0.255</td>
<td>0.008</td>
<td>-</td>
<td>-</td>
<td>0.235</td>
<td>0.015</td>
</tr>
<tr>
<td>Platelet count (10^9/mm³)</td>
<td>-0.001</td>
<td>0.993</td>
<td>-0.040</td>
<td>0.685</td>
<td>-0.078</td>
<td>0.427</td>
<td>-0.365</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>0.186</td>
<td>0.057</td>
<td>0.090</td>
<td>0.359</td>
<td>0.235</td>
<td>0.015</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WBC (10^3/mm³)</td>
<td>-0.045</td>
<td>0.64</td>
<td>-0.081</td>
<td>0.409</td>
<td>-0.107</td>
<td>0.275</td>
<td>-0.074</td>
<td>0.453</td>
</tr>
<tr>
<td>IMA (IU/mL)</td>
<td>0.640</td>
<td>&lt; 0.001</td>
<td>-</td>
<td>-</td>
<td>0.255</td>
<td>0.008</td>
<td>0.090</td>
<td>0.359</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-</td>
<td>-</td>
<td>0.640</td>
<td>&lt; 0.001</td>
<td>0.365</td>
<td>&lt; 0.001</td>
<td>0.186</td>
<td>0.057</td>
</tr>
</tbody>
</table>

BMI: Body mass index; IMA: Ischemia modified albumin; RDW: Red cell distribution width; MCV: Mean corpuscular volume; MPV: Mean platelet volume; WBC: White blood cells;

with BMI (Fig. 2) \((r = 0.365; p = < 0.001)\). RDW and IMA had statistically significant correlation (Fig. 3) \((r = 0.255; p = 0.008)\). RDW and MPV also had a statistically significant correlation (Fig. 4) \((r = 0.235; p = 0.015)\). No significant correlation was found between MPV, BMI and IMA. All the correlations are shown in Table 2.

![Fig. 1: Correlation between BMI and RDW](image1)
BMI: body mass index, RDW: red cell distribution width

![Fig. 2: Correlation between BMI and IMA](image2)
BMI: body mass index, IMA: ischemia modified albumin

![Fig. 3: Correlation between RDW and IMA](image3)
RDW: red cell distribution width, IMA: ischemia modified albumin

![Fig. 4: Correlation between MPV and RDW](image4)
MPV = mean platelet volume, RDW: red cell distribution width
Table 3: Results of multiple regression analysis for dependent variable RDW*

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>B</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.353</td>
<td>0.06</td>
<td>&lt;0.001</td>
<td>0.029 - 0.091</td>
</tr>
</tbody>
</table>

BMI: Body mass index; RDW: Red cell distribution width; CI: Confidence interval
*RDW was dependent variable, BMI, sex and age were independent variables

DISCUSSION

In this study, we determined that IMA and RDW levels are significantly increased in obese children and adolescents compared to normal weighted peers. IMA and RDW have positive correlation with BMI. These results show that oxidative and inflammatory processes of obesity begin in childhood.

Recent reports showed that atherosclerotic process starts early in children\[18\]. Obese children and adolescents have, increased risk of type 2 diabetes mellitus, hypertension, dyslipidemia and carotid artery atherosclerosis\[19\]. Therefore, detection of the parameters of chronic inflammatory process in childhood obesity will allow us to prevent the long-term complications.

Baysal et al\[20\] and Piva et al\[21\] showed that IMA levels were significantly increased in obese children who have metabolic syndrome and hepatic steatosis. They also showed that IMA was correlated with epicardial fat tissue thickness. In our study, IMA levels were increased in obese subjects but we did not evaluate epicardial fat tissue thickness.

RDW is a quantitative indicator of anisocytosis of red blood cells in circulation. It is calculated by automatic analyzers in the laboratory. It is typically increased in hemolytic anemias and hematologic diseases with ineffective erythropoiesis such as iron deficiency, B12 deficiency but not in hemoglobinopathies\[22\]. Increased levels of RDW may reflect the response of bone marrow to various oxidative stress and mediators. For example, adrenergic activation may increase ineffective erythropoiesis in bone marrow. Increased erythropoiesis causes increased RDW as a result of enhanced heterogen circulating red blood cells\[23\].

In recent studies, RDW was shown to be increased in patients with chronic heart failure, prior myocardial infarction\[22,24\] and chronic inflammation and it was suggested that this could be the underlying reason.

Felker et al\[22\] presented the RDW as an independent predictor of cardiovascular morbidity and mortality. The results of another study indicated that RDW is associated with metabolic syndrome increasing this risk by three-fold\[25\].

The RDW was shown to be related with the components of metabolic syndrome such as abdominal obesity, hypertension, insulin resistance and diabetes mellitus\[26-29\]. Vaya et al\[30\] concluded that abdominal obesity was the only component that shows an association with high RDW. In our study, RDW was significantly increased in obese subjects suggesting chronic inflammation, and this is compatible with similar findings in the literature.

Several studies demonstrated the positive correlation between MPV and diabetes mellitus, dyslipidemia, hypertension, obesity and cardiovascular diseases\[15,16\]. Coban et al\[30\] showed that MPV was independently influenced from obesity even in the presence of renal and cardiovascular disorders. But some studies conducted in obese children with or without metabolic syndrome showed no increase in MPV values\[31\]. In the present study, MPV values were minimally increased in obese subjects compared to normal weighted peers (p = 0.05).

CONCLUSION

Our study determined that IMA, RDW and MPV levels are increased in obese children and adolescents. Our results also demonstrated the positive correlation between BMI, IMA and RDW. RDW was shown to be independently affected by the BMI. Childhood obesity increases risks of comorbidities in adulthood. Therefore, RDW which is an easily-obtained laboratory parameter can be used to indicate the effect of obesity even in the absence of comorbidities in early stages.

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REFERENCES

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Original Article

Arcuate Line Variations: Are They Important for TEP Surgeons?

Maulana M Ansari
Department of Surgery, J N Medical College, Aligarh Muslim University, Aligarh, UP, India


ABSTRACT

Objectives: Wide anatomic variations in Arcuate line have been recently reported by a few clinical investigators using modern technology of laparoscopy, but received little attention of laparoscopic hernia surgeons as well as anatomists, and hence the present study.

Setting: J. N. Medical College Hospital, Aligarh Muslim University, Aligarh, India

Design: Prospective study

Subjects: Twenty-five male patients with uncomplicated primary inguinal hernia (Unilateral 20 and Bilateral 5)

Intervention: Intra-operative measurement and documentation with video recording

Method of analysis: Data computation in terms of Mean ± SD.

Results: Thirty total extraperitoneal (TEP) hernioplasties were performed in 25 male patients with uncomplicated primary inguinal hernia (Unilateral 20 and Bilateral 5) with a mean age of 49.72 ± 17.56 years (range 18 - 80). Arcuate line was observed during 26 operations and found absent in four instances; well-defined in 24 and ill-defined in six; single in 28 and double in two instances. Mean distance from umbilicus to Arcuate line was 5.65 ± SD 1.7 cm (Range 3.5 – 11.5). In presence of Arcuate line variations (absence/multiple and too high/low), significantly increased difficulties were experienced during surgery in terms of endoscopic vision, ease of procedure and operating time, along with a higher incidence of intraoperative peritoneal rent, surgical emphysema and postoperative seroma.

Conclusions: Arcuate line variations were observed in 40% of cases, and they were associated with an increased level of surgical difficulties and a higher rate of peritoneal injuries. TEP surgeons are advised to keenly observe these variations, preferably under high definition endovision, for a smooth and safe surgery.

KEY WORDS: arcuate line, posterior rectus sheath, TEP anatomy, TEP hernioplasty, TEPP

INTRODUCTION

In year 2000, Avisse and associates[1] rightly pointed out that new surgical techniques provide new vision of structures known for centuries and therefore, anatomic research is still useful – a fact so wonderfully exemplified by Standring (2008) in the new bi-laminar concept of all three aponeurosis of the anterior abdominal wall[2]. Wide variations of the Arcuate line (AL) with their importance to the laparoscopic surgeons have been recently emphasized by a number of investigators[3]. Therefore, the aim of the present research was to study the live surgical anatomy of Arcuate line in patients undergoing elective laparoscopic mesh hernioplasty for inguinal hernia through the total extra-peritoneal pre-peritoneal (TEP) approach.

SUBJECTS AND METHODS

Study was designed and conducted from April 2011 to May 2013 in the Department of Surgery, J. N. Medical College and Hospital, AMU, Aligarh, UP, India, after obtaining clearance from the Institutional Ethics Committee. Adult males ≥18 years of age with ASA grade I & II who had uncomplicated primary inguinal hernia were included in the study after written informed consent and pre-anæsthetic clearance of fitness for general anaesthesia. Patients with age <18 years, co-morbid disease (ASA grade >II), complicated or recurrent hernia, previous lower abdominal surgery and refusal for laparoscopic approach were excluded from the study.

Primary outcome measures included the four characteristics (presence/absence, nature, number and...
Fig. 1: Arcuate line (AL) variations: A & B - sharp well-defined AL (green arrow); C & D - absent AL with aponeurotic complete posterior rectus sheath (PRS); E & F - absent AL with grossly attenuated PRS & tendinous bands; G - very low AL; H - absent AL with musculo-aponeurotic PRS.
level) of the Arcuate Line. Secondary outcome measures included endoscopic vision and ease of procedure (both measured on visual analogue score of 1 - 10), operating time (hours), conversion to TAP (Transabdominal preperitoneal)/Open hernioplasty, intraoperative peritoneal injury, surgical emphysema and postoperative seroma.

Surgical technique, as described by the author elsewhere, was followed[6]. Data computations were done in terms of mean ± SD, and a p-value of <0.05 was considered as significant.

RESULTS

TEP mesh hernioplasty was done in a total of 25 patients with uncomplicated primary inguinal hernia (Indirect 27; direct 3). All patients were male and overall mean age of patients was 49.72 ± 17.56 years (range 18 - 80 years). There were 20 unilateral hernias (Right 13; Left seven) and five bilateral hernias, making a total of 30 hernias for analysis in the present study.

Traditionally described Arcuate line was observed in 26 out of 30 cases (86.67%), and it was well-defined (Fig 1a & 1b) in 20 cases (67.9%) and ill-defined in six cases (23.1%). Arcuate line was found single in 24 cases (92.3%) and double in two cases (7%).

Mean distance from Umbilicus to Arcuate line was 5.65 ± SD 1.7 cm (Range 3.5 - 11.5 cm), and Arcuate line was found situated at 1/3rd of the distance from Umbilicus to Symphysis Pubis (mean 15.1 ± SD 1.3 cm; range, 11.5 - 17.0 cm). AL was situated very low (>6 cm) in two patients (Fig. 1G) and very high (<3 cm) in one patient.

Mean distance from Xiphisternum to Arcuate line was 20.5 ± SD 2.1 cm (Range 18.5 - 23.0 cm), and Arcuate line was found situated at about 2/3rd of distance from xiphisternum to pubic symphysis (Mean 29.5 ± SD 1.5 cm; range 28.0 - 32.5 cm). Moreover, Arcuate line was found situated 2.15 ± SD 0.7 cm above the line joining the two anterior superior iliac spines (Range 1.9 - 2.8 cm).

Posterior Rectus Sheath (PRS) was found complete extending up to the pubic symphysis with absence of the Arcuate Line in four patients (13.33 %), and its nature was aponeurotic in two patients (Fig. 1C & 1D), musculo-aponeurotic in one patient (Fig. 1H) and attenuated with thickened aponeurotic bands in one patient (Fig. 1E & 1F).

Results of secondary outcome measures are detailed in the Table 1.

DISCUSSION

Contrary to the general belief, anatomy of the groin is reported to be complex[5,6], and poorly understood by the most practicing surgeons[5-8]. Inadequate understanding of extra-peritoneal anatomy and improper dissection is now regarded as the main cause of difficulties in execution of TEP hernioplasty with a long learning curve[7,9], leading to its lack of popularity despite the obvious advantages and better results[9].

Posterior rectus sheath (PRS) in the lower half of the abdomen is conventionally described to be incomplete with the existence of a sharp, concave downwards, lower border, traditionally known as the Arcuate line of Douglas. Cadaveric studies describe the rectus sheath at great lengths but very little is known about the characteristics of Arcuate Line (AL) of Douglas[10]. Level of Arcuate Line is generally reported to vary from half way to 1/4th down the umbilicus to the pubic symphysis[10-12], although in 1986, Monkkhouse and Khalique[13] documented, after a thorough study of rectus sheath formation in 56 cadaveric specimens (112 sides), that “The position of the Arcuate line was very variable. The summit of the line was on some occasions as high as the umbilicus and on others almost at the pubic bone, thus forming little more than a foramen for the passage of the inferior epigastric vessels. The medial end was usually lower than the lateral; a symmetrical disposition was a rarity”. These investigators beautifully illustrated the inconsistency of shape and position of the Arcuate line as well as its asymmetry on the two sides with a simple diagrammatic representation[13]. Mwachaka and associates (2010) reported not only absence of the

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Secondary outcome measures</th>
<th>Classical arcuate line (n = 18)</th>
<th>Variant arcuate line (n = 12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Endoscopic Vision (VAS score)</td>
<td>8.5 ± SD 1.0</td>
<td>6.3 ± SD 0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>Ease of Procedure (VAS score)</td>
<td>9.0 ± SD 0.5</td>
<td>6.0 ± SD 0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3</td>
<td>Operating Time (Hours)</td>
<td>1.8 ± SD 0.3</td>
<td>3.1 ± SD 0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4</td>
<td>Peritoneal injury</td>
<td>5.6 %</td>
<td>58.3 %</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5</td>
<td>Surgical Emphysema</td>
<td>0</td>
<td>16.7%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>6</td>
<td>Post-op Seroma</td>
<td>5.6 %</td>
<td>16.7 %</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>7</td>
<td>Conversion to Open/TAP¶</td>
<td>Nil</td>
<td>Nil</td>
<td>---</td>
</tr>
</tbody>
</table>

*Visual analogue score (1-10); ¶Transabdominal preperitoneal approach
Arcuate line with complete PRS in 19.6% of the cadaveric dissections but also gender variation not yet reported in the literature (Absent AL in 7% males and ~33% females)\[10].

In a classic paper way back in 1991, Rizk\[14] documented four major variations in PRS:
1. Complete PRS (i.e., absent Arcuate Line) but gradually thinned out in 70%;
2. Complete PRS (i.e., absent Arcuate Line) of nearly normal thickness up to symphysis pubis in 10%;
3. Incomplete PRS with ill-defined/double Arcuate line in 5%; and
4. Dense well-defined transverse band(s) between umbilicus and symphysis pubis in another 10% of the specimens.

He found the traditional well defined Arcuate line in only one of his 80 specimens. Unfortunately, these variations of the overriding importance did not receive due attention of the anatomists and the laparoscopic surgeons.

CONCLUSIONS

Arcuate line variations were observed in 40% of TEP hernioplasties with an overlap of ~10% multiple variations (ill-defined 23.1%, double 7.7%, very low 7.7%, very high 3.3% and absent 13.3%), and they were associated with an increased level of surgical difficulties and a higher rate of surgical complications. However, a larger sample study is needed to validate this preliminary but significant report. Conscious and keen search for Arcuate line variations is recommended to execute TEP hernioplasty smoothly and safely, and help of an interested anatomist cannot be overemphasized.

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Conflict of Interest: None

Funding: Nil

REFERENCES

Prevalence of Metabolic Syndrome in Psoriasis Patients

Mohammad Ebrahimzadeh1, Ali Akbar Akaberi2, *Farideh Dehghani1, Parichehr Kafie1, Mohammad Reza Taghizadeh2, Hossein HajHosseini3
1Department of Dedermatology, Yazd University of Medical Sciences, Yazd, Iran
2Department of industrial management, University of Tehran, Tehran, Iran
3Laser Center of Yazd, Yazd, Iran

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ABSTRACT

Objectives: To evaluate the prevalence of metabolic syndrome in patients with psoriasis in Yazd, Iran
Design: A cross sectional study conducted among Iranian patients with psoriasis and age and sex - matched controls.
Setting: Department of Dermatology, Burn and Accident Hospital, Yazd, Iran
Subjects: A total of 110 patients with psoriasis and 110 nonpsoriasis patients were enrolled in this study.
Intervention: Data on age, sex, weight, height, waist circumference and blood pressure of all participants were obtained. Severity of psoriasis was assessed using Body Surface Area (BSA) as mild (< 2% BSA), moderate (3-10% BSA) and severe (>10% BSA). Fasting venous blood samples were collected and the fasting glucose and lipid levels were measured.

Main Outcome Measure: We assessed fasting glucose, lipid profile, blood pressure and metabolic syndrome.
Results: The mean ages of the cases and controls were 14.80 ± 39 years and 14.25 ± 39 years, respectively. The results showed that hypertension is significantly more common in psoriatic patients compared with controls. There was no significant difference in BMI, diabetes mellitus and hyperlipidemia between two groups. Metabolic syndrome was detected in 27.3% of patients with psoriasis and 20.9% of the patients in control group but this difference was not statistically significant (P value = 0.270).
Conclusion: The results of our study revealed that there is no close association between psoriasis and metabolic syndrome in Yazd.

KEY WORDS: hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, psoriasis

INTRODUCTION

Psoriasis is a chronic T-cell mediated inflammatory disease affecting the skin and the joints. Previous studies demonstrated that psoriasis could be associated with cardiovascular disease, obesity, insulin resistance and dyslipidemia, the combination of these risk factors known as metabolic syndrome[1]. The pathogenesis of metabolic syndrome may be related to the increased level of proinflammatory cytokines and adipocytokines (adipocytokines) such as TNF-α and adiponectin. That’s why anti-TNF-α drugs have mentioned as the first-line treatment of psoriasis and metabolic syndrome[2-3].

According to the revised NCEP ATP III (National Cholesterol Education Programme Adult Treatment Panel) criteria, patients who have three or more parameters of these criteria have metabolic syndrome: Abdominal obesity (waist circumference >102 cm in men and 88 cm in women), hypertriglyceridermia (TG >150 mg/dl), reduced high density lipoprotein (HDL) under 40 mg/dl in men and less than 50 mg/dl in women, blood pressure > 130/80 and blood sugar > 100 mg/dl[4]. Although the association of psoriasis and metabolic syndrome has been investigated in several studies[5-9], but in our city, these risk factors have not been reviewed in psoriatic patients. The aim of our study was to determine the prevalence of metabolic syndrome in patients with psoriasis in Yazd, Iran.

SUBJECTS AND METHODS

This cross-sectional study was conducted in the department of dermatology (Yazd, Iran) between May 2011 and October 2012. A total of 110 patients with psoriasis and 110 nonpsoriasis patients were enrolled in this study after obtaining informed consent. Cases were patients with psoriasis more than 18 years of age and the control group was composed of non psoriatic patients attending our dermaology clinic. Data on age, sex, weight, height,
waist circumference, blood pressure and body mass index (BMI) were collected. Severity of psoriasis was assessed by Body Surface Area (BSA) as mild (< 2% BSA), moderate (3 - 10% BSA) and severe (>10% BSA). Venous samples were taken after 12 h fasting overnight and fasting glucose and lipid levels (cholesterol, HDL-cholesterol, and triglycerides) were measured.

Ethics Committees of Yazd University of Medical Sciences approved our study. Data was analyzed using SPSS software version 19. Chi-square test, T-test and Eta coefficient were used for statistical analysis.

RESULTS

Of 110 patients with psoriasis participated in our study, 74 (67.3%) were men and 36 (32.7%) were women and in control group there were 75 men (68.2%) and 35 women (31.8%). The mean age was 48.3 ± 39 years with age ranging from 10 to 75 years. The mean age of controls was 14.25 ± 39. There was no statistically significant difference in age between two groups. The disease duration ranged from two months to a maximum of 45 years in psoriatic patients. The correlation between disease duration and metabolic syndrome was evaluated by Eta coefficient but this relationship was not statistically significant (P-value = 0.9). Sixty-four (58.2%) participants had mild psoriasis and 42 (38.2%) patients had moderate involvement. Severe psoriasis was detected in four (3.6%) patients. The results showed that there was no significant association between the severity of psoriasis and metabolic syndrome (P-value = 0.582). On comparing body mass index, obesity was found in 15.5% of patients with psoriasis and 18.2% of controls, but this difference was not statistically significant (P-value = 0.359). High waist circumference (greater than 102 cm in men and 88 cm in women) was present in 36.4% of patients and 33.6% of control group but no significant difference was noted between psoriasis patients and controls (P-value = 0.389).

Systolic blood pressure higher than 140 mmHg was detected in 22.7% of psoriatic patients and 8.2% of controls. This difference was statistically significant (P-value = 0.003). 18% of patients and 7% of the control group had a diastolic blood pressure more than 90 mmHg. Statistical analysis revealed that this difference was meaningful (P-value = 0.01).

Diabetes mellitus (38.2% vs 37.3%), (P-value = 0.500) and hypertriglyceridemia (45.5% vs 40%), (P-value = 0.248) were more common in patients with psoriasis. Low density lipoprotein (LDL) cholesterol level > 160 mg/dl was detected in 25.5% of patients and 31.8% of the control group, but this difference was not statistically significant (P-value = 0.202). The mean HDL cholesterol level was higher in the control group than in the psoriatic patients. Analysis with chi-square test showed that this difference was statistically significant (P-value = 0.007).

Metabolic syndrome was detected in 30 (27.3%) patients with psoriasis and 23 (20.9%) controls but this difference was not statistically significant (P-value = 0.270). Table 1 shows the mean values measured in both groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>73 ± 15</td>
<td>72.74 ± 15</td>
</tr>
<tr>
<td>Height</td>
<td>169.4 ± 9.96</td>
<td>168.4 ± 9.62</td>
</tr>
<tr>
<td>BMI</td>
<td>25.47 ± 4.68</td>
<td>25.68 ± 4.71</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>94.5 ± 12.87</td>
<td>92.5 ± 12.76</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>124.4 ± 18.8</td>
<td>118 ± 11.3</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>82.8 ± 9.51</td>
<td>78.6 ± 8</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>193.3 ± 40.10</td>
<td>186.6 ± 42</td>
</tr>
<tr>
<td>HDL</td>
<td>56.24 ± 15.65</td>
<td>51.76 ± 11.83</td>
</tr>
<tr>
<td>FBS</td>
<td>106 ± 46.51</td>
<td>103.95 ± 28.34</td>
</tr>
<tr>
<td>TG</td>
<td>164.7 ± 92.80</td>
<td>165.7 ± 120.93</td>
</tr>
<tr>
<td>LDL</td>
<td>113.49 ± 41.10</td>
<td>116.34 ± 53.44</td>
</tr>
</tbody>
</table>

BMI = body mass index, HDL = high density lipoprotein, LDL = Low density lipoprotein, FBS = fasting blood sugar, TG = triglycerides

DISCUSSION

Psoriasis is a chronic inflammatory skin disease characterized by well defined erythematous plaques with silvery scales on the scalp and extensor surfaces of the limbs and trunk. In addition, psoriasis may affect the other organs especially soft tissue and joints. Patients with psoriatic arthritis have worse quality of life than patients with psoriasis alone. The association between psoriasis, cardiovascular disease and metabolic syndrome was considered in several studies, but controversial results were obtained. Some of them showed that metabolic syndrome is more common in patients with psoriasis.

For instance, Choi WJ et al investigated the association between psoriasis and cardiovascular risk factors in Korean patients and demonstrated a higher prevalence of metabolic syndrome (17.8%) and cardiovascular disease (4.6%) in patients with psoriasis or in a large study on 6549 patients aged 20-59 years in America, the prevalence of metabolic syndrome was 40% versus 23% of controls (OR = 2.16). The highest manifestation of metabolic syndrome were abdominal obesity, hypertriglyceridemia and low HDL serum. Previous studies in our country showed that metabolic syndrome is more prevalent in patients with psoriasis.

Ghiasi and her colleagues’ enrolled 304 psoriatic and 300 nonpsoriatic patients in a cross sectional
study and evaluated the association between diabetes mellitus, cardiovascular disease and psoriasis. The results of this study revealed that psoriatic patients are at increased risk of developing metabolic syndrome compared with nonpsoriatic patients[14].

Farshchian et al conducted a case control study in Hamedan, Iran and assessed the risk factors of metabolic syndrome in psoriatic patients. Fifty-five patients with psoriasis were studied from 2011 to 2012 and compared with normal population. Higher prevalence of lipid abnormalities and hypertension was seen in patients with psoriasis[15]. In our study, metabolic syndrome was found in 27.3% of patients and 20.9% of controls, but this association was not statistically significant (P-value = 0.270). These results were in accordance with the study by Kim CR et al and Damevska K et al that they could not find a meaningful relationship between psoriasis and metabolic syndrome[16, 17].

The cause of these conflicting results is unknown. It seems that the variety in racial and genetic background, eating habits and physical activities' status are the most important factors that resulted in a wide range of prevalence rates of metabolic syndrome in different studies[18,19]. Previous investigations showed a high prevalence of metabolic syndrome in Iran[20,21]. In our city, Sadrbafghi SM and his colleagues studied the prevalence of metabolic syndrome among 1110 participants and found that approximately one third of general population of Yazd have metabolic syndrome[22].

Although our results are in consistent with these findings, we could not find a higher prevalence of metabolic syndrome in patients with psoriasis compared with patients without psoriasis. High prevalence of metabolic syndrome in general population and small sample size in our investigation might be the main cause that we could not show a meaningful relationship. A larger sample sized study is needed to demonstrate the association between metabolic syndrome and psoriasis in our city.

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REFERENCES
Original Article

Closed Reduction of Pediatric Nasal Bone Fractures

Ahmed Mohammed Al Arfaj
Division of Facial Plastic Surgery, Department of ENT & HNS, King AbdulAziz University Hospital, King Saud University, Riyadh, Saudi Arabia

Kuwait Medical Journal 2015; 47 (4) : 321 - 324

ABSTRACT

Objective: To review the closed reduction of pediatric nasal bone fractures, presented at different times after trauma
Design: A retrospective study and telephone questionnaire to assess the result of childhood nasal fracture outcome
Setting: Department of Otorhinolaryngology, King AbdulAziz University Hospital (KAUH), King Saud University, Saudi Arabia
Subjects: Children who visited the KAUH Emergency Unit, with nasal bone fracture between January 1, 2009 to December 1, 2014
Intervention(s): Closed reduction of nasal bone
Main Outcome Measure(s): The overall satisfaction rate in terms of nasal function and cosmesis post surgery

Results: Of the 57 pediatric patients/parents contacted and interviewed, 21 patients (37%) expressed complete satisfaction with the functional and aesthetic outcome; 19 patients (33%) were partially satisfied, but would not consider revision surgery; and 17 (30%) patients, not satisfied and would consider revision surgery.

Conclusion: 30% of our patients were not satisfied with closed reduction procedure and are considering rhinoplasty. Such further surgical intervention has socioeconomic impact on the patient’s family. A general practitioner should be aware of this trauma and refer such patients to professionals such as facial plastic or maxillofacial consultants.

KEY WORDS: maxillofacial injuries, nasoseptal trauma, pediatric, rhinoplasty

INTRODUCTION

Although maxillofacial injuries as a whole are relatively uncommon in children when compared with adults, an estimated one-third of all nasal fractures occur in the pediatric population[1]. Among children, the nasal bones are the 2nd most common site of injury, representing between 41% and 60% of all pediatric facial fractures[2]. The incidence of pediatric facial fractures increase by age. Pediatric facial fractures are much more common in males than females. It has been estimated that boys account for 63 to 76% of facial fractures[3-4]. Common causes of nasal fractures in particular include motor vehicle accidents, sports, violence, falls, and other accidents. Intrauterine and birth trauma are infrequent causes of injury to the external nose and/or septum requiring acute management, yet may be the occult origin of internal or external deviations presenting years later in a patient with no identifiable inciting traumatic event.

It is essential for a physician to have anatomy and embryology intelligence of the nose and midface in order to manage nasoseptal trauma. Many injuries to the nasoseptal framework, which may initially be missed or ignored by the patient, can result in a progressive deformity of the nose and midface, with both functional and aesthetic consequences. In children, the nasal framework is more cartilaginous than bony and has less frontal projection. In younger children, the nasal bones are separated in the midline by an open suture line, and laterally the nasal bones overlap the frontal processes of the maxilla[5]. As the nose and midface grow, these structures take on the more familiar adult anatomy. The majority of nasal growth occurs in two distinct postnatal growth spurs, ages 2 - 5 years and again during puberty. Growth is usually completed by age 16 to 18 in girls and 18 to 20 in boys, although additional growth of the nasal septum may occur up to the age of 25 years[6,7]. Between these two rapid growth phases, there is a period of moderate nasal growth[7]. An understanding of growth periods has led many surgeons to delay rhinoplasty surgery until after the adolescent nasal growth phase.

The most common locations of injury to the nose are the nasal tip, dorsum, and nasal root region, and
32% of injuries involve the nasal skeleton\textsuperscript{[8]}. The long-term surgical outcome of a nasal bone fracture in a pediatric population is important because of the growing characteristics, whereby even a minor trauma could cause a major deformity, as the patient becomes older\textsuperscript{[9]-[10]}. Pediatric nasal bone fractures should be attended earlier than adult fractures, within 3 - 7 days\textsuperscript{[1]-[11]}.

The purpose of this study is to review the age, gender, causes and the treatment outcome of pediatric nasal trauma cases treated in King Abdulaziz University hospital over a 6-year period.

**MATERIALS AND METHODS**

A review of Hospital Information System (HIS) system was used to pull out all the files of patients who were diagnosed with fracture of nasal bone in King AbdulAziz University Hospital, King Saud University, from January 1, 2009 to December 1, 2014.

We found 57 cases of closed reduction or splint application. All patients had a follow-up of three years, except two children (aged 11 & 13), who had a follow-up of 6 months after surgery. All the patients who presented two weeks post-trauma were excluded from the study. All those patients’ files were retrieved and the patients and parents were interviewed through telephone. The author was able to review all of the 57 patients. The caller would introduce himself, explain the study and take verbal consent for their participation in the study. The caller asked a fixed format of 12 questions about the outcome and entered the feedback in the datasheet. These datasheets would then be completed from information gathered from the file. All the data were statistically analyzed by Chi-square (X\textsuperscript{2} test) or Fisher’s exact test and the significant level was set at p = 0.05 or less, using SPSS version 16 Software (SPSS Inc., Chicago IL).

**RESULTS**

Fifty-seven children were enrolled in the study, with a mean age of 10.2 years (3 - 15 years). For the interview, response was from 51 mothers and 6 fathers; mean = 28.6). Forty-one (72%) of them were male and 16 (28%) were female. Thirteen (23%) presented to the ER within three days of trauma, 15 (25%) within seven days of trauma and 29 (51%) presented after seven days of trauma. There was no relation between ER appeal day and satisfaction (Fisher’s, p = 0.09).

The most common complaint was nasal deformity in 51 (89%) patients; and the next was nasal obstruction in 6 (10%). Satisfaction rates were similar among the deformity type groups (Fisher’s, p = 0.8). The causes of nasal bone fracture in our patient are described in Table 1.

On radiology (Table 2), the most common finding was a depressed fracture in 29 patients (51%); a greenstick fracture in eight (14%) and communicated fracture in eight (14%). Remaining children had no radiological fracture. Twenty-one patients (37%) were completely satisfied with their outcome, 19 (33%) were partially satisfied and not interested to go ahead for any corrective procedures and 17 (30%) were totally unsatisfied and planning to undergo rhinoplasty. Of the six patients whose primary complaint was nasal obstruction; three were totally satisfied and the remaining three, totally dissatisfied. Among the 51 patients whose primary complaint was nasal deformity, 23 were fully satisfied; 17 were partially satisfied but did not consider revision surgery and 11 were totally unsatisfied and considered revision surgery.

With regard to their time of initial presentation post trauma, the most satisfied were 29 (51%) children, who presented seven days after trauma, as compared to 15 (26%), who presented between 4 - 7 days after trauma, and 12 (21%), who presented 1 - 3 days after trauma. The least satisfied were those who presented 1 - 3 days after nasal trauma (Table 3).

<table>
<thead>
<tr>
<th>Table 1: Number of patients according to gender and type of trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender Type</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Radiological study showing type of fracture and number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Fracture</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Depressed (In fracture)</td>
</tr>
<tr>
<td>Comminuted</td>
</tr>
<tr>
<td>Greenstick</td>
</tr>
<tr>
<td>No radiology done</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Long term satisfaction survey of pediatric patient with nasal bone fracture based on time of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Median age (range)</td>
</tr>
<tr>
<td>Nasal Deformity</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Satisfaction</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Nasal Obstruction</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Satisfaction</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>
DISCUSSION

Among children, the nasal bones are the most common site of injury, representing 41% to 63% of all pediatric facial fractures. The incidence of pediatric facial fractures increases with advancing patient age. In our study, the male groups were more involved in nasal trauma than females, by a ratio of 2.5:1.

In very young children, nasal fractures are not common because of the underdeveloped nasal bones and the relative projection of the soft part of the nose with compliant cartilage, which easily bends during trauma. Low quality radiography and difficulty in taking computer Tomography (CT) scan at this age is also a contribution factor. In adolescence, a nasal bone fracture pattern more closely follows that of adults.

In 2007, Verwoerd and Verwoerd-Verhoef described in detail the developmental anatomy of the nose. They described two growth centers of the nasal septum, one that extends from the sphenoid to the nasal dorsum and termed the sphenoidal zone, and a second that extends from the sphenoid to the anterior nasal spine, which is termed the sphenoidal zone. Vertical growth in the sphenoidal zone results in increased length and height of the nasal dorsum, and sagittal growth in the sphenoidal zone contributes to anterior projection of the nose and maxilla. Injury to either of these growth centers may lead to a loss of vertical height and sagittal projection of the nose and subsequently the midface, as the developmental organization provided by the nasal septum suffers.

Another proposed model for nasomaxillary growth is based on the septo-premaxillary ligament. In this model, the growth of the nasal septum is an important “starter mechanism” during fetal development for the initiation of downward and forward growth of the maxilla. The septopremaxillary ligament is described as a bundle of fibers arising from the anterior-inferior border of the nasal septum and coursing posteroinferiorly to insert on the nasal spine of the premaxillary bone.

In 1988, Precious et al described repercussions to nasofacial growth following traumatic injury to the nasal septum. Grymer et al in 1985 reported the longterm results of 57 adults who suffered nasal fractures as children and were treated by closed reduction at a single center and compared them to a control group. The group with nasal fractures had a significantly higher incidence of dorsal hump, saddling, bony pyramid and cartilaginous vault deviations, columnar dislocation, septal deviation, and septal spines. Despite 70% of the patients with nasal deformities were initially satisfied, the deformities had developed gradually as the nose grew following injury.

According to Moran, the most commonly seen pattern is the lateral fracture, in which an in-fracture is noted on the side of the traumatized nasal bone at the point where the ascending process of the maxilla and the nasal bone meet, and an out-fracture is seen in the opposite nasal bone, similar to our study, where we had 29 (51%) as depressed in fracture (Table 2).

In an adult population, nasal bone fractures may be reduced 7 - 10 days after injury. Pediatric patients, however, have been known to need reduction sooner, as osteogenesis is faster in children. Some authors, have suggested reduction of the fracture within 3 - 5 days, whereas others, have suggested that it should be within 10 days. We found that the most satisfied children were those whose reductions were done seven or more days after trauma. Our finding is similar to that of D.H. Lee et al. Time to surgery is not a relevant factor in predicting long-term surgical outcome.

The general practitioner or ER physician, as the first person to see most of trauma nose cases, should not neglect nasal trauma and should refer them to professionals like facial plastic or maxillofacial surgeon for assessment. We recommend that once a nasoseptal fracture has been diagnosed and any emergent problems (e.g., epistaxis, hematoma etc.) treated, the patient is instructed to follow up in 3 - 5 days to be reexamined. Once the edema has improved and the follow-up exam completed, the surgeon must consider: (a) whether a surgical intervention is indicated; and if indicated, to plan it within 7 - 14 days post trauma for best result. The ultimate goal of any intervention should be to restore the nasal airway, return the nose to its premorbid appearance, and preserve the integrity of the nasal growth centers for future development.

After fracture reduction, the nasal bones remain mobile for approximately two weeks and can be depressed by force for up to six weeks. Thus, it is recommended that children with nasal fractures refrain from all sports activities for two weeks and contact-sports (e.g., football, wrestling..), for six weeks.

CONCLUSION

Facial trauma affects facial growth. Thirty percent of our patients consider advanced surgical procedure in the future. A parents should be aware of the effect of facial trauma on the child, and it’s socio-economic impact. Also General practitioners and trauma doctors should be aware of this and refer all nasal traumas professionals like facial plastic or maxillofacial consultants. Late intervention (7 - 14 days) has better outcome as compared to early intervention (1 - 7 days). Further studies designed to prospectively investigate long-term effects of surgical intervention are necessary to maximize successful outcome in the pediatric population.
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Prevalence and Risk Factors of Severe Perineal Injuries during Childbirth in Saudi Arabia

Lateefa O. Al-Dakhil, Assistant Professor and Consultant, King Saud University/King Khalid University Hospital, Department of Obstetrics and Gynecology, P.O. Box 7805, Riyadh, 11472 Saudi Arabia. Mobile: +966500044280. Email: lateefa95@hotmail.com

ABSTRACT

Objectives: To estimate the prevalence and risk factors for obstetric anal sphincter injuries (OASIS) in Saudi Arabia using data in a tertiary care University Center

Design: A retrospective case-control study

Setting: King Khalid University Hospital, Kingdom of Saudi Arabia

Subjects: All women with third and fourth degree perineal tears over a 10-year period

Interventions: We conducted this study by creating an obstetric database compiled over a period of 10 years (2002 – 2012) screening all for third and fourth degree perineal tears and too control matched by the time of delivery and delivery team (midwife and obstetrician).

Main Outcome Measures: The prevalence of perineal injuries was calculated in cases and controls. Maternal and obstetric parameters were analyzed and compared between the two groups.

Results: Of 31,665 vaginal deliveries, seventy-three patients (0.23 %, 95% CI by the adjusted Wald method: 0.18% - 0.29%) had a recognized third (n=66) or fourth-degree (n=7) perineal tear. The following three variables were independently associated with OASIS on multivariate logistic regression models adjusting for potential confounders: primiparity (OR 3.32) instrumental delivery (OR 7.19) and episiotomy (OR 4.92).

Conclusion: The overall prevalence of third- and fourth-degree perineal tears in our population is low; avoidance of certain obstetric interventions including instrumental delivery and episiotomy may decrease such complications.

KEY WORDS: anal sphincter, obstetric, perineal injury, vaginal delivery

INTRODUCTION

Obstetric anal sphincter injuries (OASIS) are serious adverse outcomes of vaginal delivery. OASIS are third- and fourth-degree severe perineal injury. This classification has been used by the International Consultation on Incontinence[1].

A third-degree perineal tear is defined as a partial or complete disruption of the anal sphincter muscles, which may involve either or both, the external anal sphincter (EAS) and internal anal sphincter (IAS) muscles. Therefore, third-degree tear has been classified as 3A, 3B or 3C in order to standardize classification (Table 1). A fourth-degree tear is defined as a disruption of the anal sphincter muscles with a breach of the rectal mucosa.

Studies have shown that the failure of proper management may lead to chronic perineal pain, dyspareunia and fecal incontinence in up to 60% of cases, which severely affect the physical and psychological well-being of postpartum women[2-8]. Various obstetric parameters have been reported as risk factors for severe perineal injuries, including assisted instrumental delivery, a birth weight of more than 4000 g, primiparity, episiotomy, persistent occipitoposterior position, maternal age, postdate pregnancies, induction of labor, prolonged second stage of labor, precipitate labor, epidural anesthesia and various maternal birth positions[4, 6, 9-22]. Instrumental delivery, nulliparity and large birth weight have emerged as the risk factors with the strongest independent associations with a higher risk of OASIS[21-24].

The reported prevalence of third- and fourth-degree tears is relatively variable between different countries, ranging between 0.1% and 15%[3-8]. These discrepant
observations may be related to under diagnosis of this obstetric complication, racial disparities or differences in obstetric practices. Numerous previous reports have indicated the higher prevalence of OASIS among Asian ethnicity[7,8]. To the best of our knowledge, there are no published data from our area regarding the prevalence or risk factors for such injuries. In view of the former considerations, we conducted a case-control study to estimate the prevalence and risk factors for OASIS in Saudi Arabia, using data retrospectively collected in a tertiary care University Center.

Various obstetric parameters have been reported as risk factors for severe perineal injuries, including assisted instrumental delivery, a birth weight of more than 4000 g, primiparity, episiotomy, persistent occipito-posterior position, maternal age, postdate pregnancies, induction of labor, prolonged second stage of labor, precipitate labor, epidural anesthesia and various maternal birth positions[4, 6, 9-22]. The most significant independent risk factors reported were instrumental delivery, nulliparity and large birth weight[23,24].

MATERIAL AND METHODS

Retrospective data collection was performed for all women who delivered at King Khalid University Hospital (KKUH) over a 10-year period (January 2002 to December 2012), using labor and delivery records.

Cases with severe perineal tears (OASIS) (3rd and 4th degree tears) identified in records were retrieved. We used the same definition and classification used by the International Consultation on Incontinence as described in the introduction[11]. When there is suspicion of a third and fourth degree tear, the patient was examined by the senior obstetrician on duty to confirm the diagnosis.

For each case of third or fourth degree perineal tear, two matched controls, by time of delivery and labor and delivery team (midwife and obstetrician), were included. The following demographic and clinical characteristics were collected: maternal age, maternal body mass index (BMI) and gestational age, maternal and obstetric parameters. Obesity was defined as a BMI of ≥30 kg/m².

Midwives and obstetricians perform deliveries at KKUH, with the assistance of training residents. A prolonged second stage of labor is defined as duration of more than 2 or 3 hours, depending on parity and the use of epidural anesthesia, as proposed by the American College of Obstetricians and Gynecologists[25]. Almost all episiotomies are medio-lateral and are performed according to the attending physician’s or midwife’s preference. Episiotomies are routinely performed in cases of suspected macrosomia, non-reassuring fetal heart monitoring or a prolonged second stage, which may necessitate instrumental delivery. Assisted vaginal delivery is usually performed using vacuum extraction, whereas forceps delivery is rarely performed.

The Institutional Review Board of our institution approved the research protocol prior to data collection.

Statistical Analyses

Continuous variables are presented as mean ± SD (normal distribution) and as median with interquartile range (skewed distribution). Categorical variables are presented as percentages with corresponding 95% confidence intervals (CI). The adjusted Wald method, which provides the best coverage for binomial CI when samples are less than 8%150 [26], was used for computation of 95% CI of reported prevalence. Pearson’s Chi-Square test was used to detect univariate associations between cases and controls with respect to all categorical variables. Similarly, independent sample t-test was compared cases and controls in terms of continuous variables.

The association of different risk factors identified in univariate analyses with the risk of OASIS was further investigated by means of multivariate conditional logistic regression analyses to account for the matched design. The odds ratio (OR) and 95% CI, which were computed with the control group as reference, were used as a measure of association. The computed p-values correspond to Wald statistics. In the initial univariate analyses (chi-square and un-paired t-test), a threshold of p < 0.1 was used to identify candidate variables (because of the risk of type II error due to low statistical power in such an analysis) for inclusion in the multivariate conditional logistic regression model. The final multivariate analyses were conducted using a backward selection procedure and statistical significance was achieved if p < 0.05. To confirm the robustness of the multivariate conditional regression models, all analyses were repeated using a forward-selection procedure. Finally, the goodness of fit for the multivariate model had been tested using the Hosmer and Lemeshow’s goodness of fit test. A p-value ≥ 0.05 means that the model’s estimates fit the data at an acceptable level. The Statistical Package for Social Science (SPSS Inc, version 22.0 for Windows) was used for statistical analyses.

RESULTS

During the study period, 31,665 women had vaginal deliveries. A total of seventy-three women (0.23%, 95% CI by the adjusted Wald Method: 0.18% - 0.29%) had recognized severe perineal tears, of whom 66 women had a third-degree tear (3a: 17 women; 3b: 44 women; and 3c: 5 women) and four women had a fourth-degree tear. Since we were unable to follow up the majority of patients, we could not assess presence of fecal incontinence or any other long-term complications of vaginal delivery.
The mean age of our study population was 28 ± 3.5 years (range: 18 - 44 years). All patients were Saudi, and 124 (56.6%) were primiparous. Obstetric risk factors for severe perineal tears were compared between the study and the control groups, including primiparity, BMI, IOL, the use of an epidural analgesia, prolonged second stage, episiotomy, high birth weight and instrumental deliveries (Table 1).

### Table 1. Baseline characteristics in patients and controls

<table>
<thead>
<tr>
<th>Characteristics/Risk Factor</th>
<th>Cases (n = 73)</th>
<th>Control (n = 146)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.8 ± 4.9</td>
<td>29.1 ± 5.7</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI</td>
<td>29.2 ± 4.95</td>
<td>30.7 ± 5.1</td>
<td>0.046</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>31 (42.5%)</td>
<td>76 (52.1%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Primiparity</td>
<td>51 (69.9%)</td>
<td>73 (50%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>9 (12.3%)</td>
<td>7 (4.8%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Epidural Analgesia</td>
<td>15 (20.5%)</td>
<td>9 (6.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of second stage of labor</td>
<td>177.2 ± 23.1</td>
<td>108.5 ± 84.4</td>
<td>0.025</td>
</tr>
<tr>
<td>Instrumental deliveries</td>
<td>32 (43.9%)</td>
<td>6 (4.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>63 (86.3%)</td>
<td>48 (32.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight &gt; 4000 g</td>
<td>9 (12.3%)</td>
<td>9 (6.2%)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

*BMI* = Body Mass Index

The following factors were associated with OASIS (p < 0.1) in initial univariate analyses: primiparity, body mass index, obesity instrumental delivery, induction of labor, prolonged second stage of labor epidural anesthesia, and episiotomy. The former factors were entered as candidate variables in the final conditional multivariate logistic regression models. The following three factors emerged as independent predictor of higher risk of OASIS (Table 2): primiparity (OR 1.862), instrumental delivery (OR 1.352) and episiotomy (OR 1.333).

### Table 2. Independent Risk Factors associated with higher risk of Severe Perineal Laceration on conditional multivariate logistic regression analyses.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primiparity</td>
<td>3.32</td>
<td>[1.55 - 7.14]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>7.19</td>
<td>[2.9 - 17.86]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>4.92</td>
<td>[1.9 - 10.53]</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

OR = Odds Ratio; CI = Confidence Interval

**DISCUSSION**

Severe perineal injuries are rare complications of vaginal delivery that are associated with substantial morbidity, since even if the laceration is recognized and repaired, significant complications have been reported. In our study, the prevalence of severe perineal injuries was very low (0.2%), which could be due to missed cases. Among vaginal deliveries worldwide, the reported prevalence of third- and fourth-degree tears is variable, ranging from 0.1% (China, Cambodia and India) to 15.0% (Philippines).[7] Other studies from North America have reported prevalence up to 19%.[6] This wide range of reported prevalence rates may be associated with under-diagnosis of third- and fourth-degree perineal lacerations, especially in developing countries. Other possible causes could be potential racial disparities and differences in obstetric practices. Interestingly, previous investigators have reported that Asian women were more likely to suffer perineal trauma (in particular, severe perineal trauma) in comparison to non-Asian ethnicities.[8, 27-29]

Several risk factors for severe perineal injuries have been reported,[5,7], which are inconsistent. This variation in the reported risk of each parameter could reflect differences in practices at different institutions. Among these factors are advanced maternal age, increased maternal BMI, primiparity, persistent occipito-posterior position, instrumental delivery, macrosomia, a prolonged second stage of labor, induction of labour (IOL), episiotomy and epidural analgesia. In contrast, certain studies have identified IOL, mediolateral episiotomy, epidural analgesia and instrument-assisted delivery in the occipito-anterior position to be protective.[2, 30]. We found that primiparity, instrumental delivery and episiotomy are significant risk factors for severe perineal injuries. Second stage duration, epidural anesthesia and higher BMI were initially associated with severe perineal tears, but the former association lost its significance in the final multivariate logistic regression model adjusting for all potential confounders. The findings of the present cohort indicate that primiparity and instrumental vaginal delivery were found to be the three independent risk factors associated with a higher risk of OASIS in the final multivariate model. These observations are consistent with the majority of published data concerning the risk factors for anal tears.[31] In our study, macrosomia did not emerge as an independent risk factor for a higher risk of OASIS and this may be due to the lower prevalence of macrosomia in our study population (8%).

At our institution, whenever an episiotomy is performed, it is invariably of the mediolateral type because of the suggested advantages of fewer extensions and thus fewer third- and fourth-degree tears during the midline procedure. Therefore, mediolateral episiotomy is considered to be safer.[32, 33]. It is now well established that mediolateral episiotomy itself does not protect the anal sphincter during delivery.[34]. In our study, mediolateral episiotomy was also identified as an independent risk factor for OASIS. However, it should be noted that, whether mediolateral episiotomy is a risk factor for severe perineal tears, still remains an issue of controversy and debate.[30, 38]. More specifically, in an analysis of 2967 first vaginal deliveries, 50 (1.7%) cases of severe
perineal tears were identified. Multivariate analysis
declared five significant risk factors for such tears,
including episiotomy (both mediolateral and midline)
[19]. However, the investigators found that the angle of
a mediolateral episiotomy from the perineal midline
could affect the rate of extension to a third- or fourth-
degree tear with a smaller angle (30 degrees) being
associated with a higher risk of severe extension[20].

The clinical practice in our Institution dictates
most straightforward deliveries to be performed by
midwives, and in case of any complication such as
fetal distress or prolonged second stage, a physician
intervenes and performs the delivery. Moreover, all
instrumental deliveries are performed by attending-
level obstetricians. This is the reason why deliveries
conducted by physicians had a higher OASIS risk,
in comparison to deliveries by midwives in initial
univariate analyses. However, the former association
did not persist after adjustment for potential
confounders in multivariate logistic regression
models.

Our findings are in line with the recently published
results of a survey conducted in 215 maternity units
in UK (81% of national sample) [30]. In this survey,
the investigators established that the national rate of OASIS
was 2.9% of all vaginal deliveries, with some units
reporting rates as high as 8%. By contrast, the Royal
College of Obstetricians and Gynaecologists guidelines
indicate an acceptable rate of 1% [37]. Although the
variation found in this study may reflect differences in
obstetric practice, it could also be due to over-diagnosis
of OASIS. The perceived increase in the incidence of OASIS has been attributed to improvements in
accuracy of diagnosis by clinicians, as encouraged by
National Institute of Clinical Excellence, including the
requirement for routine rectal examinations prior to
suturing perineal trauma [38]. Furthermore, with regard
to changes in patient demographics, the use of the
‘hands off’ technique and the associated reduction in
the use of episiotomy, where indicated, may also have
contributed to the increase in OASIS rates that was
detected in the present report.

CONCLUSION
In conclusion, significant risk factors for perineal
injuries during delivery include primiparity,
instrumental vaginal delivery and episiotomy.
Techniques for prevention of perineal injuries should
be considered especially in the presence of other
risk factors for severe perineal damage, and careful
assessment of potential complications should be
performed after delivery in high-risk women.
The identification of women who are at risk may facilitate
the use or avoidance of certain obstetric interventions,
to decrease the risk of severe and morbid perineal
injuries.

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Case Report

Carbimazole-Induced Agranulocytosis Treated with Granulocyte Colony-Stimulating Factor (GCSF): A Report of Two Cases

Norasyikin A Wahab, Rozita Mohd, Suehazlyn Zainudin
Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia

Kuwait Medical Journal 2015; 47 (4): 330 - 332

ABSTRACT

Agranulocytosis is the most serious and potentially fatal side-effect of antithyroid drug therapy. We report two cases presenting with carbimazole-induced agranulocytosis. The first patient received 20 mg of carbimazole daily, and developed agranulocytosis within one month of commencement of therapy. The second patient presented with agranulocytosis complicated by a thyroid storm following ingestion of 60 mg of carbimazole, daily for two months. Both patients were treated with 300 mg of granulocyte colony-stimulating factor (GCSF) subcutaneously (in addition to discontinuation of their anti-thyroid drugs) and broad-spectrum antibiotics for neutropenic sepsis. The total white and neutrophil counts returned to baseline following five and six days of treatment, respectively, with the resolution of sepsis. This rare complication of anti-thyroid drugs and the use of GCSF in the treatment will be being discussed.

KEY WORDS: agranulocytosis, carbimazole, granulocyte colony-stimulating factor (GCSF), neutropenia

INTRODUCTION

Thyrotoxicosis is a common endocrine disorder affecting approximately 2% of females mainly in the childbearing age and 0.2% of males [1]. Patients are usually treated with anti-thyroid drugs. The commonest antithyroid drug used in the UK and several Commonwealth states is carbimazole [2]. A rare but potentially fatal serious side effect of the treatment is agranulocytosis, which has been reported to have an incidence ranging between 0.3 - 0.6 % [1].

We encountered two thyrotoxic patients who developed agranulocytosis shortly following treatment with carbimazole. We aim to increase the awareness of physicians regarding this uncommon side effect of carbimazole which is commonly used for the treatment of thyrotoxicosis.

CASE REPORTS

Case 1

A 39-year-old female initially presented with symptoms of thyrotoxicosis secondary to Grave’s disease of one year duration. She was prescribed 20 mg of carbimazole daily. Following four weeks of treatment, she was admitted with a one-day history of fever, sore throat and diarrhea. She claimed compliance to carbimazole and denied taking any other medications. During admission, she was febrile with a temperature of 38 °C. Her blood pressure (BP) was 116/64 mmHg and pulse rate (PR) was 122 beats/min. The tonsils and pharynx were inflamed. Otherwise, the examination of all other systems did not reveal any abnormality. Her total white cell count (WCC) was 0.8 x 10^9/L and neutrophils were absent. Renal, liver and coagulation profiles were normal. Thyroid function test revealed elevated free T4 of 41.53 pmol/L (NR: 9.10 - 23.80 pmol/L) with suppressed TSH < 0.01 uIU/ml (NR: 0.32 - 5.00 uIU/ml). Septic work-up did not yield any significant growth. Anti-thyroid medication was promptly discontinued and her thyroid activity was controlled with high dose of beta blocker propranolol 80 mg tds with Lugol’s iodine, 10 drops tds. She was prescribed broad-spectrum antibiotics and nursed in isolation.

However, after three days of treatment she remained febrile with high temperature and with no improvement in her WCC. Subcutaneous granulocyte colony-stimulating factor (GCSF) 300 mg was administered daily. After six days of GCSF, her total

Address correspondence to:
Dr Norasyikin A Wahab, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +60129810882 (Mobile), E-mail: Nawa8282k@gmail.com
WCC rose to 6.8 x 10⁹/L with a neutrophil count of 3.7 x 10⁹/L. She was discharged well after completion of the empirical antibiotic therapy. Her propranolol was continued whilst her Lugol’s iodine was tapered slowly to 10 drops daily for three weeks followed by 5 drops daily for a week. She was initially agreeable to radioactive iodine (RAI) therapy a month later but subsequently refused. As a result of the delay, she only underwent total thyroidectomy three months from her presentation. Throughout this period, her thyroid status was monitored twice weekly and she remained biochemically in subclinical hyperthyroidism.

**Case 2**

A 29-year-old female was admitted with a two-day history of confusion, agitation and mild jaundice. This was preceded by worsening sore throat, high fever and diarrhoea of two weeks duration. She had been diagnosed with thyrotoxicosis secondary to Grave’s disease three months prior to admission and was prescribed 60 mg daily of carbimazole by a primary care doctor. She continued with same treatment, until the current presentation. There was no history of other concurrent medications.

During admission, she was delirious with Glasgow Coma Scale (GCS) of 14/15. Her BP was 125/60 mmHg, PR was 120 beats/min and temperature was 39 °C. She was clinically thyrotoxic and jaundiced with hepatomegaly. There was also tonsillitis and pharyngitis.

Liver function test (LFT) showed hyperbilirubinaemia of direct bilirubin with high alanine transaminase as a result of thyrotoxicosis. Her coagulation profile was normal and full blood picture showed agranulocytosis with a WCC of 2.0 x 10⁹/L and absence of neutrophils. Ultrasound examination of the liver revealed hepatomegaly with no evidence of obstruction. Her thyroid function test revealed a raised free T4 of 60.47 pmol/L (NR: 9.10 - 23.80 pmol/L) with significantly suppressed TSH of < 0.01 uIU/ml (NR: 0.32-5.00 uIU/ml). Carbimazole was discontinued, septic work-up was performed and she was empirically treated with broad-spectrum intravenous antibiotics in an isolation room. In view of a suspicion of thyroid storm, propranolol 60 mg tds was commenced with lugol’s iodine and intravenous hydrocortisone. Plain computed tomography (CT) scan of the brain revealed no abnormalities.

Unfortunately, she remained febrile with minimal improvement on the second day of admission. The WCC and neutrophil counts did not improve and she was commenced on subcutaneous GCSF 300 mg daily. Her fever settled after three days of GCSF therapy. The WCC and neutrophil counts rose to 14.2 x 10⁹/L and 10 x 10⁹/L respectively after five days of GCSF. Bacteriologic cultures remained sterile. Her free T4 decreased to upper limit of normal after a week of treatment following which lugol’s iodine and Hydrocortisone were tapered off. She was discharged well with normal WCC and LFT with oral propranolol. She was subsequently referred for radioactive iodine therapy within a month following discharge.

**DISCUSSION**

Agranulocytosis due to antithyroid drugs may occur in any age group, with the elderly being most vulnerable [2,3]. There has been no reported gender predominance [2,3]. It is defined as an absolute neutrophil count of less than 0.5 x 10⁹/L. Agranulocytosis is said to occur in approximately 0.37% and 0.35% of patients who received prophyluracil and methimazole, respectively [2]. Interestingly, a prior uncomplicated use of an antithyroid drug does not exclude the occurrence of agranulocytosis in future use of the same drug [3].

Agranulocytosis is thought to be an autoimmune-mediated medical entity. Most cases occur within the first six months of the commencement of therapy, the earliest case reported after seven days but may be delayed for up to one year [1,2]. This observation was consistent with both our patients as they had developed agranulocytosis between one to three months following initiation of antithyroid drugs. Fever and sore throat were the commonest symptoms [3]. Difficulty in diagnosing may arise with the presence of rapid onset of fever and prostration as thyroid storm needs to be suspected and managed immediately. This was demonstrated in the second case. Interestingly, Tajiri et al showed about 78% of patients with antithyroid drug-induced agranulocytosis were asymptomatic at the time of diagnosis and only detected on routine white blood cell monitoring [4].

Side effects of anti-thyroid drugs are believed to be dose-related [3]. The higher dosage of carbimazole received by our second patient may have contributed to her more severe sepsis with multi-organ involvement. Perhaps an appropriate dose related prescription should be considered according to the patient’s weight before prescribing the higher dose. Treatment includes prompt discontinuation of anti-thyroid drugs. We replaced the antithyroid drug with Lugol’s iodine for the purpose of controlling the thyrotoxic state of both our patients. The use of lugol’s iodine alone would be able to reduce thyroid activity rapidly as it inhibits the release of pre-stored hormones. The effect is reported to last for only 2 - 3 weeks as most patients would escape from the inhibitory effect and return to hyperthyroidism, if no other treatment was instituted [6]. However, in our
patient, we found that despite being exposed to a total four weeks of Lugol’s iodine, she experienced no rebound of hyperthyroidism and remained subclinical until surgery.

Overall, the resolution of agranulocytosis was observed within 1-2 weeks following discontinuation of antithyroid drugs \(^{[3,7]}\). However, as neutrophil recovery depends on the myeloid precursor cells in the bone marrow, in severe cases recovery time may be prolonged up to 56 days \(^{[7]}\). The GCSF has emerged as a potent stimulus for neutrophil proliferation and maturation in vitro and in vivo. It proved to be a useful treatment. GCSF can hasten the marrow recovery time to approximately one week and facilitate good infection control with reductions in the duration of antibiotics and hospitalization to approximately 4.5 days and 2.5 days, respectively, resulting in significant reduction in the total cost of agranulocytosis management \(^{[8]}\). Tajiri et al showed that GCSF therapy could shorten the recovery period and benefit patients with granulocyte count greater than 0.1 x 10\(^9\) /L \(^{[9]}\). This recommendation had prompted us to administer GCSF in the first patient, as despite withholding anti-thyroid drug for three days and initiating broad spectrum antibiotic, the patient persistently had very high temperatures, little clinical improvement and unresolving neutropenia. In contrast, the patient described in case 2, received GCSF much sooner in view of the severe sepsis and multi-organ dysfunctions. Both patients subsequently demonstrated extremely good response with WCC returning to normal by day 5 and 6, respectively, after commencing GCSF. The GCSF was ceased as soon as neutropenia resolved.

Mortality rate as a result of agranulocytosis has decreased significantly in the past two decades because of the availability of more potent antibiotics and GCSF \(^{[10]}\). However, thyrotoxicosis is a common endocrine disease, which affects a relatively young population and majority would opt for pharmacotherapy rather than the surgical or radionuclear options. Therefore, emphasis must be placed on the importance of this antithyroid drugs complication. Although most administrative bodies do not recommend routine WCC monitoring due to its lack of cost effectiveness, physicians must be aware of other prognostic factors including age and other co-morbidities.

CONCLUSION

In conclusion, antithyroid drug-induced agranulocytosis is uncommon but due to its potential fatality if untreated, a high index of suspicion must be adopted. This should be followed by early detection, diagnosis and prompt action. GCSF should be considered as a treatment option to facilitate the recovery of WCC and to shorten hospital stay in selected patients, especially those with evidence of bacteraemia.

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Case Report

Rare Case of Non-Parasitic Chyluria in Pediatric Population Treated with Dietary Modification in a Four-year-old Male Child

Umang G Thakkar¹, Aruna V Vanikar², Hargovind L Trivedi³
¹Department of Regenerative Medicine and Pediatrics
²Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology
³Department Nephrology and Transplantation Sciences
IKDRC and ITS, Ahmedabad, Gujarat, India

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ABSTRACT

Chyluria is the passage of milky urine composed of albumin, chylomicron, and fibrin in various proportions due to the leakage of lymph into the urinary tract as a result of communication between the lymphatics and the urinary system. Intermittent mild proteinuria and hematuria may be found at routine urinalysis. The conventional diagnostic approach involves confirmation of chyle in urine and the demonstration of lymphaticourinary fistulae by radiological study. It occurs predominantly in adults and is rare in children. We present an unusual case of a four-year-old male child with proteinuria, hematuria and milky urine which was subsequently diagnosed as idiopathic non-parasitic chyluria with spontaneous remission. The child recovered with dietary management for about five weeks after starting a low-fat, high-fiber diet.

KEYWORDS: dietary treatment, hematuria, proteinuria, lymphoscintigraphy

INTRODUCTION

Idiopathic chyluria is a rare benign disease of childhood presenting with alarming findings of milky urine due to lymphatico-urinary fistula diagnosed by lymphoscintigraphy. Therapy ranges from conservative dietary management to surgical intervention in spite of which recurrence is common. It is a benign yet an alarming condition rarely reported in children[1].

CASE REPORT

A four-year-old male child presented with a complaint of passing milky urine after waking up from bed in the morning, since one month (Fig. 1). The mother of the child informed that her son passed a small sludge in urine and from next day he began passing milky urine initially followed by normal colored urine. The patient lived in a village and had not traveled to areas known for endemic filariasis. On examination, he had normal vital signs with no lymphadenopathy, no abdominal masses or edema and an unremarkable systemic examination. Urinalysis showed milky color with alkaline reaction and albumin (3+). Microscopic examination revealed 18 - 20 crenated and fresh RBCs / high power field and culture report was sterile. A 24-hour urine sample contained 3600 mg protein (reference range: 20 - 150 mg / 24 hours) and 874 mg triglycerides (normal range: ≤ 10mg / 24 hours). Vigorous shaking of urine for few minutes with equal amount of ether cleared opacity, indicating positive ether test. Urine electrophoresis revealed severe albuminuria and non-specific proteinuria. Urine cytopsin analysis revealed lymphocyte dominant (88%) fluid and suggested that urine was mixed with lymphatic fluid. Complete blood count was normal (hemoglobin 13.6 g/dl, hematocrit 36.3%, WBC count, 5.4 x 10⁹/µl and platelet count, 2.15 x 10⁹/µl) with no evidence of microfilaria or eosinophilia on peripheral smear. Repeat examination

Address correspondence to:
Dr. H L Trivedi, FRCP (C), D.Sc., Department Nephrology and Transplantation Sciences, G R Doshi and K M Mehta Institute of Kidney Diseases & Research Centre (IKDRC), Dr H L Trivedi Institute of Transplantation Sciences (ITS), Civil Hospital Campus, Asarwa, Ahmedabad - 380016, Gujarat, India. Tel: +91 79 22685608, Fax: +91 79 2268 5454, E-mail: ikdrcad1@sancharnet.in, umangpaedia@yahoo.co.in
Fig. 1: On the left, a photograph of a 4-year-old male child with collected sample of milky urine and on the right is a photograph of containers of chylous urine with milky appearance.

Fig. 2: Retrograde pyelogram showing pyelolymphatic backflow into renal lymphatics due to abnormal communication of lymphatic and urinary system depicted by arrow.

of thick blood smear at midnight revealed absence of microfilaria. In biochemical serum analysis, blood urea nitrogen, creatinine, sodium, potassium, protein and albumin was 12 mg/dl, 0.3 mg/dl, 136 mEq/l, 4.1 mEq/l, 6.7 gm/dl, and 4.2 gm/dl respectively. Cystoscopy showed chylous efflux from the right ureteral orifice. A retrograde pyelogram (RGP) showed pyelolymphatic backflow into the renal lymphatic sinuses (Fig. 2). Lymphoscintigraphy was performed three weeks later and was normal. Renal ultrasonography confirmed kidney with normal anatomy. Chest X-ray and abdomino-pelvic CT scan did not demonstrate a cause for the chyluria and other diseases were excluded. A diagnosis of idiopathic non-parasitic chyluria was, therefore, established. The patient was treated with conservative management (a low-fat, high-fiber diet) and the chyluria disappeared after five weeks. We concluded that rarely seen idiopathic non-parasitic chyluria is an alarming symptom with benign course in pediatric patients and can disappear spontaneously without any medication or surgical intervention. Our case was successfully treated conservatively using a low-fat and high-fiber diet without recurrence till six months of follow-up.

**DISCUSSION**

Chyluria, the passage of intestinal lymph in urine, though an uncommon symptom has been recognized since the time of Charak (300 BC) who described it as ‘Shuklameha’ [2]. The disease is significantly higher in males (86%) than in females (14%). It has been more frequently reported on the left side [2]. Majority of the cases present in the second and third decade of life. It has been recognized as a tropical disease more prevalent in the rural and poverty stricken population. Classification of chyluria based on etiological factors is mentioned in Table 1. Chyluria is graded into mild (34 - 50%, intermittent milky urine; no clot colic / chylous coagulum / urinary retention / weight loss; involvement of single calyx on RGP), moderate (33 - 40% Intermittent continuous milky urine with occasional clot colic / chylous coagulum; no urinary retention / weight loss; involvement of two or more calices on RGP), severe (15 - 26% intermittent continuous milky urine with occasional clot colic / chylous coagulum;
no urinary retention / weight loss; involvement of two or more calices on RGP)\(^3\). On anatomical basis, there is a short circuiting of chyle drainage from intestinal lacteals to renal lymphatics. Presence of lymphocytes and fat globules in the urine form the basic diagnostic criteria. Vigorous shaking (for a few minutes) of milky urine with equal amount of ether clears opacity\(^3\). Lymphoscintigraphy is a non-invasive, safe and simple technique for investigating the lymphatic system for lymphatic urinary communication and has an established role in providing important physiological and anatomical information relevant for diagnosis and management especially when surgical intervention is contemplated\(^4\), but confirmed by RGP. In this case, the chyluria spontaneously disappeared and the urine became clear and yellowish after a RGP. But the chyluria recurred three days later. The patient was treated with conservative management (i.e., a low-fat, high-fiber diet) and chyluria disappeared after five weeks. Spontaneous remission of chyluria is reported\(^3\). As most cases of non-parasitic chyluria showed spontaneous remission, surgical treatment should be restricted to patients with severe symptoms, not responding to conservative treatment and sclerotherapy. The prognosis of non-parasitic chyluria (or idiopathic chyluria) is usually very good and the treatment is mostly conservative\(^4\). A long-term remission rate of 62% in the conservatively managed group (DEC- Diethylcarbamazine Citrate and fat restricted diet), and a cure rate of 90% in patients in the operated group has been reported. Postoperative recurrence rate was 10%. There was more weight gain and dietary freedom along with a longer chyluria free period in the operated group relative to the conservatively managed group\(^6\).

**CONCLUSION**

We conclude that spontaneous remission of idiopathic non-parasitic chyluria is possible in pediatric population with dietary modification. This avoids the surgical intervention.

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**REFERENCES**

Case Report

Scimitar Syndrome: Two Cases in Different Age Groups

Salah Maklad, Sameer Humad, Muneera Al-Adwani
Department of Radiodiagnosis, Al Jahra Hospital, Kuwait

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ABSTRACT

Scimitar syndrome is a very rare and variable congenital cardio-pulmonary disorder characterized by an anomalous pulmonary venous connection. It can present in the neonatal period as well as later in life. We report two cases of anomalous pulmonary venous connection that presented at different ages. The first case was a four-week-old female child who presented with multiple serious chest problems. The second case was a twenty-two-year-old adult male patient, discovered incidentally by screening during a pre-employment chest X-ray examination. Both cases were accurately diagnosed by multi-detector computed tomography (MDCT) imaging modality.

KEY WORDS: bronchial abnormality, congenital disorder, MDCT, pulmonary venous drainage

INTRODUCTION

Scimitar syndrome is mostly seen in early infancy. However it can be seen in adults. Scimitar syndrome is a rare and variable congenital disorder characterized by an anomalous connection of the pulmonary vein with the inferior vena cava (IVC) [1].

The scimitar syndrome was named by Neill in 1960, describing a syndrome of complete or partial anomalous pulmonary venous return of the right lung into the IVC, partial systemic arterial blood supply and hypoplasia of the affected lung with bronchial abnormalities. Co-existent cardiovascular abnormalities can also occur [1].

The syndrome involves mainly the right lung. Rarely, scimitar syndrome of the left lung has been described. The anomalous vein might produce a vascular shadow, resembling a scimitar, to the right of the heart, on the frontal view chest X-ray examination [2].

The aim of this case report was to emphasize that scimitar syndrome can present in the early infancy as well as later in life, with different clinical manifestations and radiological findings. We also wanted to focus upon the role of multi-detector computed tomography (MDCT) in the diagnosis of scimitar syndrome.

CASE 1

A 4-week-old female infant was referred to the radiology department for CT chest examination due to persistent pneumonia and few cyanotic attacks. The initial chest X-ray revealed shifting of the heart to the right side (dextroposed), scattered bilateral small patches of pulmonary consolidation, and small atelectatic bands (Fig. 1).

Contrast enhanced multi-detector computer tomography (CE-MDCT) was done on our outpatient MDCT machine (light speed VCT / GE-64 slice). The MDCT chest examination was carried out after intravenous injection of 10 ml of non-ionic contrast medium (Visipaque / iodixanol). After the scanning all source images were reconstructed and delivered to the workstation for post-processing.

MDCT and its applications showed dextroposition of the heart and an anomalous right pulmonary vein joining the inferior vena cava at its right postero-lateral aspect just before joining the right atrium. CE-MDCT also showed a hypoplastic right main pulmonary artery, hypoplasia of the right lung as well as small sequestrated right basal lung segment (Fig. 2 and 3).

MDCT also showed an abnormal arterial supply to the right basal lung lobe, from the abdominal aorta through an anomalous artery originated from left lateral side of the abdominal aorta just above the origin of the left renal artery. It curved anteriorly around the aorta and passed through the liver medial to the IVC, to reach the basal segments of the right lower lobe and then divided into two main branches. (Fig. 4 a & b)

CASE 2

A twenty-two-year-old male patient was referred to our radiology department for routine pre-employment
chest X-ray examination. There was no previous respiratory or cardio-vascular complaint in the past history.

Chest X-ray revealed a classical Turkish sword appearance of the anomalous vein in the right paracardiac region descending downwards towards the diaphragm. Also, the dextroposed heart is noted with a hypoplastic right lung (Fig. 5). Further assessment by post-contrast CT chest examination clearly showed the abnormal partial venous drainage of the right lung into the IVC. The anomalous vein was seen joining the IVC just before its entry into the right atrium. Also, the CT scan demonstrated hypoplasia of the right lung and relatively dextroposed heart. (Fig. 6).
pulmonary vein drains blood from the lung into the IVC resulting in an increased risk of developing right ventricular failure due to longstanding right ventricular overload \[9\].

The conservative management is usually adequate and enough in milder and asymptomatic cases. Surgical intervention should be limited to those patients with lung sequestration or recurrent serious chest infections of the affected lung or those with right ventricle overload due to a major left - right shunt. Surgical options include re-implantation of the anomalous vein into the left atrium, ligation or embolization of vascular supply as well as pneumectomy of the sequestered lung lobe \[9,10\].

**CONCLUSION**

We report two cases of scimitar syndrome. The first case showed the full blown syndrome in a newborn and the second case was of an adult with classical chest X-ray showing Turkish sword appearance of the anomalous pulmonary vein.

**REFERENCES**

Case Report

Left Main Coronary Artery Stenting in a Patient with L-I Type Single Coronary Artery

Jeng-Feng Lin, Yu-Lin Ko, Heng-Chia Chang
Division of Cardiology, Department of Internal Medicine, Buddhist Tzu-Chi Hospital, Taipei, Taiwan
School of Medicine, Tzu Chi University, Hualien, Taiwan

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ABSTRACT

Single coronary artery, with both the left and right coronary arteries arising from it, is a rare congenital coronary anomaly. In this report, we present the case of a 75-year-old man whose coronary angiography revealed single coronary artery arising from left coronary sinus, severe ostial stenosis of the left main coronary artery (LMCA), and anomalous right coronary artery (RCA) originating as a continuation of the distal left circumflex artery (LCX).

Under the backup of pre-existent permanent pacemaker, percutaneous coronary intervention (PCI) with bare metal stent was performed successfully for LMCA stenosis without intra-aortic balloon pump support. The patient was symptom free after PCI. Follow-up angiography and intravascular ultrasound seven months later demonstrated 29% in-stent restenosis of the LMCA with a minimum lumen area of 8.7 mm².

KEY WORDS: coronary angiography, percutaneous coronary intervention

INTRODUCTION

Single coronary artery is extremely rare and occurs in 0.044 to 0.066% of patients undergoing coronary angiography[1,2]. Most patients with single coronary artery are diagnosed incidentally during coronary angiography and generally have a benign clinical course[2].

In patients with significant left main coronary artery (LMCA) stenosis with or without normal coronary artery origin, coronary artery bypass grafting (CABG) has been the conventional treatment of choice[3]. Recent studies have shown that percutaneous coronary intervention (PCI) with stenting is feasible and has a similar long-term outcome[4,5]. However, unprotected LMCA stenting in a patient with single coronary artery theoretically represents a considerable challenge and risk because the blood supply of the entire myocardium may be jeopardized during the procedure. In this report, we present a patient with a single coronary artery undergoing successful LMCA stenting without complications.

CASE HISTORY

A 75-year-old man was admitted to our hospital because of hypotension and chest tightness, precipitated by hemodialysis, for one month. He had a history of diabetes mellitus, hypertension, end stage renal disease on hemodialysis, and atrioventricular block status post permanent pacemaker implantation. Before admission, myocardial perfusion scan showed moderate anteroseptal and inferior ischemia. Echocardiography revealed calcified aortic valve with valve area of 1.0 cm², maximal pressure gradient 29 mmHg, and normal left ventricular (LV) ejection fraction. Coronary angiography revealed 66% ostial stenosis of the LMCA, 73% stenosis of the middle left anterior descending artery (LAD), and anomalous right coronary artery (RCA) arising from left circumflex artery (LCX) (Fig. 1A, B). Aortography confirmed the absence of RCA ostium. On continuous pull back pressure trace recording from LV to ascending aorta, the mean pressure gradient was 25 mmHg. The cardiac output was 5.3 lpm measured by thermodilution technique. Aortic valve area was 0.88 cm² calculated by Gorlin equation. Medical treatment was recommended for normal-flow low-gradient moderate to severe aortic stenosis[6,7]. PCI for ostial stenosis of LMCA was performed initially with a 3.5 x 15 mm balloon (Sprinter Legend, Medtronic). The patient did not have any chest tightness or

Address correspondence to:
Heng-Chia Chang, MD, Division of Cardiology, Department of Internal Medicine, Buddhist Tzu-Chi Hospital, Taipei branch, 289 Jianguo Road, Xindian District, New Taipei City 231, Taiwan. Tel: 886-2-6628-9779 Ext: 5709, Fax: 886-2-6628-9009, E-mail: hccmd@ms4.hinet.net
hypotension during 15 seconds of balloon dilatation. The middle LAD lesion was then dilated with a 3.0 × 15 mm balloon (Sprinter Legend, Medtronic). Subsequent angiography revealed 33% and 29% residual stenosis in the LMCA and LAD artery, respectively. A 4.0 × 18 mm bare metal stent (Vision, Abbott) was placed from LMCA ostium to proximal LAD artery successfully, although the procedure was accomplished with

Fig. 1: Before percutaneous coronary intervention, (A) Right anterior caudal view and (B) Shallow left cranial view of left coronary angiography showing ostial stenosis of left main coronary artery (black arrowhead) and anomalous right coronary artery (RCA) originating as a continuation of distal left circumflex artery (LCX)

Fig. 2: Seven months after coronary intervention, (A) Right anterior caudal view and (B) Shallow left anterior cranial view of left coronary angiography showing no significant restenosis of left main coronary artery (black arrowhead). Right coronary artery (RCA) arose from distal left circumflex artery (LCX) and tapered off to the anticipated RCA ostium (white arrowhead). Intravascular ultrasound study in the stent implantation site revealed (C) minimal neointimal hyperplasia in proximal left anterior descending artery (white arrow), (D) slight malposition of stent at distal LMCA (white arrows), and (E) patent proximal left main coronary artery.
great difficulty because of severe LMCA calcification. There was no significant plaque shift or stenosis of LCX ostium after the procedure. Under the backup of pre-existent permanent pacemaker, the patient’s hemodynamic state was constantly stable during PCI, not requiring intra-aortic balloon pump (IABP) support. The patient was free of chest tightness during hemodialysis after PCI. Seven months later, follow-up myocardial perfusion scan revealed improved anteroseptal perfusion. Coronary angiography showed 29% restenosis of LMCA and 32% restenosis of LAD (Fig. 2A, B). Intravascular ultrasound disclosed only minimal neointimal hyperplasia at proximal LAD and slight malposition of stent at distal LMCA (Fig. 2C, D, E). The minimum lumen diameter and minimum lumen area of distal LMCA were 3.2 mm and 8.7 mm², respectively. Repeated PCI was not performed.

**DISCUSSION**

Single coronary artery is a rare congenital anomaly of the coronary arteries. There are several angiographic patterns of single coronary artery. The Lipton classification is a practical one and has classified single coronary artery into groups depending on ostial location (right or left) and anatomical distribution (I, II, or III)\(^\text{[12]}\). The patient presented here corresponds to L-I group. The group is characterized by dominant LCX perfusing the entire heart, RCA originating as a continuation of distal LCX, and congenital absence of RCA ostium\(^\text{[8-11]}\). The tapering course from LCX to RCA can help us to differentiate this L-I anomaly from RCA total occlusion with collaterals fed by LCX\(^\text{[8,10,12]}\). These rare L-I anomalies generally have a benign clinical course\(^\text{[12]}\).

When a single coronary artery was found incidentally by coronary angiography in patients with angina or myocardial infarction, 46% of the patients had significant coronary artery narrowing\(^\text{[13]}\). Out of the remaining patients without significant coronary artery narrowing, 22% of patients still had evidence of myocardial ischemia or infarction, as shown by electrocardiography, exercise stress test, or thallium scan\(^\text{[13]}\). Thus, myocardial ischemia in patients with single coronary artery can be caused by the coronary anomaly itself or by accompanied coronary artery narrowing\(^\text{[13]}\). In the present case, follow-up myocardial perfusion scan suggests that myocardial ischemia is related to stenosis of LMCA ostium and LAD and was relieved by PCI.

We reviewed the literature for PCI in patients with RCA originating from left coronary artery. The culprit lesions treated in previous reports included LAD\(^\text{[5,11-14]}\), LCX\(^\text{[7]}\), and RCA\(^\text{[10]}\). To the best of our knowledge, this is the first report suggesting that PCI for LMCA in a patient with type L-I single coronary artery is feasible and effective.

**CONCLUSION**

Our case demonstrates that LM stenting can be done successfully and without complication in a patient with single coronary artery with the backup of a permanent pacemaker and without IABP support.

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Conflicts of Interest: None

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Case Report

Primary Hodgkin’s Lymphoma of the Uterine Endometrium: A Case Report

Rashmi Patel, Aruna Vanikar, Kamlesh Suthar
Department of Pathology, Laboratory Medicine and Transfusion Services and Immunohematology, G R Doshi and K M Mehta Institute of Kidney Diseases & Research Centre (IKDRC), Dr. H L Trivedi Institute of Transplantation Sciences (ITS), Civil Hospital Campus, Ahmedabad, Gujarat, India

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ABSTRACT
Primary Hodgkin’s lymphoma of the female genital tract has been rarely reported. We report the case of a 65-year-old lady, who presented with postmenopausal bleeding following percutaneous nephrolithotomy for left ureteric calculus. Eventually, she was subjected to abdominal hysterectomy with right-sided salpingoophorectomy. Histopathological examination revealed Hodgkin’s lymphoma - mixed cell type, involving the endometrium.

KEY WORDS: percutaneous nephrolithotomy, postmenopausal bleeding, polypoid mass, uterine calculus

INTRODUCTION
Primary lymphoma occurring in female reproductive system is very rare. It accounts for 0.54 - 0.64% of extra-nodal non-Hodgkin’s lymphoma (NHL)\(^2\). Malignant lymphoma can present in endometrium, myometrium or both. It typically occurs in elderly patients, 75% being postmenopausal who present with bleeding and a polypoid mass. The most common lymphoma is NHL - large B-cell type\(^2\). We present this case of a 65-year-old woman with postmenopausal bleeding found to have primary extra-nodal Hodgkin’s lymphoma (HL) of endometrium.

CASE HISTORY
A 65-year-old lady presented with postmenopausal bleeding. She had hypertension and renal stone disease. The right-sided renal stone was removed by open surgery 15 years ago. Since the last eight months, she had bilateral flank pain. She had no fever or lower urinary tract symptoms. She had an unremarkable obstetric history with four full-term normal deliveries, and tubal ligation was performed 30 years ago. She was menopausal for last 20 years.

On presentation her complete blood counts and renal function tests were normal. She had recently developed diabetes mellitus. Urine albumin was absent and microscopy showed 25 - 30 pus cells / high power field. The urine culture was sterile. Her ultrasonography (USG) showed the right kidney to be 11 x 4.2 cm and unremarkable in appearance. The left kidney was 13 x 6 cm with hydronephrosis and a 20 mm calculus in the upper ureter. The urinary bladder was normal. The gall bladder showed two calculi measuring 20 and 19 mm in size. She underwent retrograde pyelography and DJ stenting. However the stone was not removed in next fortnight. A left percutaneous nephrolithotomy (tubeless) was done and the stone removed. She was discharged with anti-hypertensive, anti-diabetic and antibiotic medication.

On follow-up after one month, she complained of two episodes of postmenopausal bleeding. On examination, she was found to be obese with a soft abdomen. A per-speculum examination was grossly normal. At per-vaginal examination, the uterine size could not be assessed due to obesity. An USG showed a uterine mass of 31 x 25 mm suspected to be a fibroid. The endometrial thickness was 9 mm. An endometrial biopsy was performed which showed simple cystic hyperplasia (Fig. 1). She was put on hormonal therapy. After five months, she came back
with postmenopausal bleeding off and on with pain in abdomen. The USG findings showed a uterus 8 x 6 x 5.8 cm³ with bulky heterogenous echotexture, an endometrial thickness of 12 mm with a polypoid mass. The Fallopian tubes and ovaries were normal. A transvaginoscopic examination revealed a uterine size of 10 x 8 x 8 cm³ with an endometrial polypoid mass measuring 5.4 x 4.9 cm in size. The liver, spleen and pancreas were normal. No abdominal, mediastinal, or neck lymphadenopathy was noted. She was subjected to abdominal hysterectomy with right-sided salpingoophorectomy and specimen was sent for histopathology evaluation.

On gross examination the uterus with cervix weighed 300 grams and measuring 9 x 8 x 5 cm³ in size. The myometrium was 2.5 cm thick at the fundus and a polypoid growth, greyish brown in colour and occupying the whole of the endometrial cavity measuring 5.5 x 2.5 cm in size was noted (Fig. 2). The Fallopian tube and ovary measuring 3.5 x 2 cm in size were unremarkable. The microscopic examination of the polypoid growth arising from endometrium showed a fair number of lymphoplasmacytic cells, eosinophils, Reed-Sternberg giant cells as well as popcorn type multinucleated giant cells in loose stroma (Fig. 3a, b). These small cells were infiltrating the myometrium. Normal endometrium was replaced by tumor cells. Epithelial membrane antigen, CD-20 (Fig. 3c) and neuron-specific enolase were positive, whereas desmin and vimentin were negative. The cervix had mild chronic non-specific inflammation. The ovary and the Fallopian tube were unremarkable.
Based on these findings a diagnosis of primary HL-mixed cell type, of the endometrium was made. She was referred to gynec-oncology special services after which she was lost to follow-up.

DISCUSSION
About 30% of NHLs occur in tissues other than lymph node referred to as extranodal lymphoma, and in 1/4th cases, the most prevalent subtype of NHL is diffuse large B-cell lymphoma[1,4,5]. Isolated lymphomatous involvement of the female genital organs is rare accounting for approximately 1% of extra-nodal NHLs. Nearly 75% of affected women are postmenopausal, and present with vaginal bleeding. It affects the cervix more frequently than uterus and vagina[6,7]. Primary extra-nodal presentation of Hodgkin’s disease is extremely rare and only a few cases of primary genital HL - mixed cell type involving the cervix and ovary, HL-nodular sclerosis type in the vagina, HL-lymphocyte depletion type in uterine corpus have been reported in literature similar to our case[4,7,8,9].

CONCLUSION
Primary HL of the uterine endometrium as noted in our patient aged 65 years with postmenopausal bleeding is rarely reported. Due to the unexpected site, it may be misdiagnosed either as an inflammatory lesion or another malignant tumor.

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REFERENCES
Case Report

Cerebral Cryptococcoma - Why?

Avirup Guha, Lee Ann Merchen
Department of Internal Medicine, Georgia Regents University, Georgia, USA

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ABSTRACT

We report a case of cryptococcal abscess in an immunocompetent individual. She was found to have normal T-cell line with appropriate number of CD4, CD3 and CD8 cells. She was noted to have poor T-helper cell immunity which has been correlated to such kinds of manifestation in mice models of pulmonary cryptococcosis. We performed the candida antigen and tetanus toxoid mediated T-cell assay to see the aforementioned point. Although a presentation of this kind has been mentioned in literature before, such reasoning has never been cited earlier.

KEYWORDS: abscess cryptoccus, immunocompetent, T-helper cells

INTRODUCTION

Cryptococcus is the most common fungus causing central nervous system (CNS) infection with the most common presentation being meningo-encephalitis. Ring enhancing lesions in immunocompetent patients with fungal etiology is rare[1]. In 2008 Quang et al reviewed 17 cases of cryptococcoma in immunocompetent patients[2], out of which, just 7% were caused by cryptococcus. In this case report, we present this rare manifestation.

CASE REPORT

A 66-year-old African-American female with past medical history of hypertension, diabetes mellitus type 2 and hyperlipidemia presented to the emergency room with a one week history of global limb weakness, anorexia and cough. Several weeks prior to her presentation, she had suffered two grand mal seizures and was found to have a brain mass on magnetic resonance imaging (MRI) (Fig. 1, 2), with plan for operative approach shortly. She had recently been started on phenytoin and dexamethasone tapering dose for the brain lesion and resultant seizures. She described her current neurological symptoms as heaviness in left leg and tremor in the right arm. On history, she mentioned night sweats for a few months but denied headache, nausea, vomiting, repeated infections, dyspnea, fever or rashes. There was no history of travel, change in diet, change of housing conditions, sick contacts, similar illness in family, or drug abuse and she also was in a monogamous relationship. At home, she was taking phenytoin, dexamethasone, amlodipine, glipizide, metformin, valsartan, nystatin swish and swallow and potassium supplements. Relevant physical examination findings included grade 4 / 5 power in the right upper extremity and bilateral lower extremities both proximally and distally. An MRI demonstrated a 10.8 mm ring enhancing mass lesion seen in the post central gyrus with varied changes of ischemia in PICA area of distribution. She also had a right lenticular nucleus associated with microvascular white matter disease. The intracranial mass was resected and was found to be Cryptococcus neoformans with a positive mucicarmine stain. Of note, she had an HbA1C of 7% and negative HIV, HBV, HCV markers. A workup for all fungal and bacterial disease associated with low T-cell mediated immunity was negative. Counts for CD3, CD4 and CD8 were 1696, 604, 1075 cell/microliter of blood respectively, which was interpreted as low CD4 / CD8 ratio with normal CD8 counts and mildly low CD4 count. Proliferation of lymphocytes of CD3 and CD45 marker in response to candida antigen and tetanus toxoid was poor which was interpreted as poor function of memory T cells. It was recommended that she receive four weeks of liposomal amphotericin B and flucytosine; however, due to increased transaminases and worsening acute anemia in the setting of anemia of

Address correspondence to:
Avirup Guha, MBBS, Georgia Regents University, 1120 15th St Bl 5070 Augusta, GA 30912, USA. Tel: 001- 706-267-5675, Fax- 706-721-6918, E-mail: aguha@gru.edu
chronic disease, flucytosine was discontinued. She was treated with amphotericin B for six weeks. High dose induction therapy with fluconazole with continued treatment for a year was recommended. Her creatinine was followed closely during the treatment and she followed up with neurosurgery with improved neurological function with no new symptoms.

**DISCUSSION**

This patient’s only risk for immunosuppression was long standing diabetes which was controlled (Hb A1C 7%). In addition, her low normal CD4 and CD3 T-cells were idopathic and had been found to be associated with this condition\(^1\). The new finding which had not been mentioned in previous case reports is low T-helper cell reactivity to Candida antigen and Tetanus toxoid. It is known that T-helper mediated immunity is related to CNS manifestation of Cryptococcus\(^4\) but the manifestation in human brain is not known. Mutation of cytokine pathways have been shown to make the infection worse\(^8\) and might be the reason for an otherwise immunocompetent patient to develop cryptococcosis. The bottomline is that the quantity of the CD4 matters as known traditionally but the quality of the response also plays an important role in helping us understand the disease manifestation in immunocompetent patient.

Another learning point in this case is considering Cryptococcus as a differential for ring enhancing lesion also in immunocompetent patients.

**CONCLUSION**

In this case, we see how quality of CD4 cell response matters and also how Cryptococcus is a rare but possible etiology in immunocompetent patients with ring enhancing lesions.

**REFERENCES**

Case Report

Spontaneous Pneumomediastinum Mimicking Angioedema in an Asthmatic Teenager

Mohammed H AlShati, Mohamed Osama Hegazi, Mohammed M Yaktien
Departments of: Respirology, Internal Medicine, and Radiology; Al Adan Hospital, Kuwait

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ABSTRACT

Spontaneous pneumomediastinum (SPM) often presents with chest pain, cough, and/or dyspnea. The presentation with facial swelling is less frequently mentioned and may be misinterpreted as angioedema. A palpable subcutaneous crepitus, an audible mediastinal crunch, and subcutaneous or mediastinal air in chest X-ray should be carefully sought. We present a boy with an asthma exacerbation and bronchopneumonia who developed facial swelling following an antibiotic injection. Careful scrutiny of the Chest X-ray for an evidence of subcutaneous air would have negated an initial thinking of angioedema. SPM should be included in the differential diagnosis of acute swelling of the face during asthma exacerbations.

KEY WORDS: asthma, bronchopneumonia, facial swelling

INTRODUCTION

Spontaneous pneumomediastinum (SPM) refers to air within the mediastinum without preceding trauma, surgery, or any instrumental tracheal or esophageal procedures. Air may further spread through the connective tissues causing subcutaneous emphysema of the chest wall, neck, and face. Asthma exacerbations represent one of the most common accompaniments of SPM. Other triggers include cough, vomiting, exercise and valsalva maneuver. The presentation with facial swelling may be misdiagnosed as angioedema.

CASE HISTORY

A 12-year-old boy with bronchial asthma presented with acute swelling of the face and a sharp central chest pain. Three days ago, he has been diagnosed with asthma exacerbation and left lower lobe pneumonia. He was started on treatment with IV ceftriaxone 1 gm daily and inhaled steroids/bronchodilators. The current presentation was coincidentally following the second ceftriaxone injection.

Clinically he showed heart rate: 104/min, respiratory rate: 32/min, and blood pressure: 110/70 mmHg. Chest showed bilateral rhonchi and left lower zone bronchial breathing. The face was markedly swollen with considerable puffiness of eyelids. Room air oxygen saturation was 88% with arterial blood gases showing PaO₂ = 7.2 KPa, PaCO₂ = 3.2 KPa, pH = 7.43, and HCO₃ = 20 mmol/l. The rest of laboratory investigations including full blood count, hepatic and renal profiles, and microbiological workup for upper and lower respiratory infections were unremarkable.

The thought of angioedema was initially entertained. However, a crepitus suggesting subcutaneous emphysema was felt on palpating the face, neck and chest. The previous chest X-ray (CXR), showed an initially overlooked area of subcutaneous emphysema at the root of the neck (Fig 1). Computed tomography (CT) of the chest revealed air in the mediastinum and subcutaneous emphysema at the lower face, neck, and chest wall (Fig 1). The diagnosis of SPM along with asthma exacerbation and pneumonia was thus made.

The patient was managed conservatively with high flow oxygen, nebulized bronchodilators, systemic steroids, and the current antibiotic. Eventually, He showed a remarkable recovery and his face and eye

Address correspondence to:
Mohamed Osama Hegazi, Department of Respirology, Al Adan Hospital, Kuwait. Address: P.O.Box: 46969, Postal Code: 64020, Kuwait. Tel: +96537403085; Email: drosama02@gmail.com
swelling fully improved within seven days. The subcutaneous crepitis and the air in CXR disappeared in two and three weeks respectively.

**DISCUSSION**

SPM may occur in patients with or without an underlying lung disease\[^{1, 2}\]. It is an uncommon, yet a well-known complication of acute episodes of bronchial asthma\[^{1, 2}\]. In an analysis of 62 cases, the presenting symptoms included chest pain (63%), cough (45%), dyspnea (44%), neck pain (18%), light-headedness (18%), dysphagia (5%), and dysphonia (5%)\[^{1}\]. However, the presentation with facial swelling is mentioned less often\[^{3, 4}\]. The presentation with acute facial swelling and eye puffiness may raise the possibility of angioedema or anaphylaxis\[^{3}\]. A palpable subcutaneous crepitis, an audible mediastinal crunch (An air crepitus with each heart beat on auscultation), and mediastinal or subcutaneous air in CXR should be carefully sought. A chest CT will confirm and further delineate the SPM and the associated chest condition if any.

Hypoxemia may accompany the onset of SPM in patients with asthma exacerbations\[^{5, 6}\]. The coexistence of pneumonia will likely aggravate ventilation/perfusion mismatch and add to the severity of hypoxemia as was the case in our patient.

The clinical course of SPM is usually self-limiting and mainly influenced by the severity of the underlying lung disorder\[^{2}\].

**CONCLUSION**

The diagnosis of SPM can be easily missed without a high index of suspicion. The travel of air through the subcutaneous tissues to the neck and face may invite other diagnostic possibilities. A palpable
subcutaneous crepitus, and an audible mediastinal crunch, may give clues to diagnosis. A careful look for mediastinal or subcutaneous air in CXR is warranted. This case illustrates the need to include SPM in the differential diagnosis of acute face swelling during asthma exacerbation; that may be misinterpreted as angioedema.

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Letter to the Editor

Student-Centered Teaching to Enhance Learning in Histology Lab

Jian-Jun Wang1, Chao-Jin Xu2
1 School of Stomatology, Wenzhou Medical University, Wenzhou 325035, China
2 Department of Histology and Embryology, Wenzhou Medical University, Wenzhou 325035, China

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What problems were addressed?
Histology is a major discipline within medical and other life science curricula, which can be described as the study of normal tissue morphology[1]. Histology is, in general, difficult to recognize and comprehend, thus, we want to evaluate whether student-centered teaching (SCT) would help students retain knowledge in lab classes. SCT is active learning theory styles, in which learners are active sense makers, who seek to build coherent and organized knowledge.

What was tried?
The study took place in the Wenzhou medical university. All teachers were involved in the research project with histology-related PhD. All teachers agreed to participate with their student groups. Each teacher and his/her student group were assigned to one learning environment. The class was divided into two groups (5 members = one group) in a crossover study to remove bias. One group of students was shown to six different histology slides and asks them to observe under the microscope in 15 mins, then discuss with each other in another 6 mins. The second group was lectured the same slides by the histology teacher without any pauses for discussion, then watch the same slides with the group one. Two different instructive models assessment with single answer, multiple-choice questions (MCQs) was performed after teaching, to assess efficacy.

The test results in both groups with or without SCT showed an overall significant improvement. However, the improvement was more significant when students watched slices with strategic pauses and discussion (p < 0.05, Wilcoxon signed rank test).

Additionally, we administered the questionnaires to investigate the preferences of students for particular teaching modes and was analyzed by the total number of responses to determine the preferences of students for each instructive styles. Over all, 85% of students preferred the SCT model, whereas the minority (6.5% of students) preferred the passive teaching model and 8.5% of students preferred the two instructive styles.

What lessons were learned?
As most students preferred the SCT, demonstrating this active teaching model in histology lab is feasible, and also makes them to learn effectively as well as have the improved self-reported confidence. Furthermore, SCT encouraged students’ access to different histology related materials to discuss in lab class and were to motivate to provide the feedback to the instructors, themselves. The collaboration among students is also strengthened. Therefore, the value of the SCT value in the histology lab should be considered. We believe that SCT to improve observing the slides level has great effects on an undergraduate histology lab study and future development.

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REFERENCE
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**Oral Antibiotics in Trans-Rectal Prostate Biopsy and Its Efficacy to Reduce Infectious Complications: Systematic Review**

Yaghi MD, Kehinde EO

1Ministry of Health in Kuwait, Al-Jahra Health Region, Saad Al-Abdullah Specialized Medical Institute, Kuwait University, Kuwait

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For the diagnosis of prostate cancer trans-rectal prostate biopsy (TRPB) is used commonly, the procedure is associated with infective complications. There is evidence that antibiotics (ABs) decrease infective events after TRPB, but different regimens are used. To systematically review different regimens of prophylactic oral ABs in TRPB. MEDLINE, EMBASE, clinical trials site, and Cochrane library were searched, experts were consulted for relevant studies. Randomized clinical trials conducted in the last 20 years, which investigated the different oral antibiotic regimens in TRPB, and compared their efficacy to reduce infectious complications were analyzed. Primary outcomes were bacteriuria, urinary tract infection (UTI), fever, bacteremia, and sepsis. Secondary outcomes were the hospitalization rate and the prevalence of ABs-resistant bacteria. Nine trials were eligible with 3012 patients. ABs prevented bacteriuria (3.5% vs. 9.88%), UTI (4.46% vs. 9.75%), and hospitalization (0.21% vs. 2.13%) significantly in comparison with placebo or no treatment. No significant difference was found in all the outcomes of the review between the single dose regimen and the 3 days. The single dose regimen was as effective as the multiple doses except in bacteriuria (6.75% vs. 3.25%), and the prevalence of ABs-resistant bacteria (1.57% vs. 0.27%). Quinolones reduced only UTI significantly in comparison with other ABs (chloramphenicol, trimethoprim-sulfamethoxazol). It is essential to prescribe prophylactic ABs in TRPB. No conclusive evidence could be claimed about the superiority of the multiple or the 3 days regimens to the single dose regimen. Unexpectedly, ABs-resistant bacteria were identified more often in the single dose cohorts.

**Diversity of Multi-Drug Resistant *Acinetobacter Baumannii* Population in a Major Hospital in Kuwait**

Vali L, Dashti K, Opazo-Capurro AF, Dashiti AA, Al Obaid K, Evans BA

1Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University Sulaibekhat, Kuwait

2Laboratorio de Investigación en Agentes Antibacterianos, Departamento de Microbiología, Facultad de Ciencias Biológicas, Universidad de Concepción Concepción, Chile

3Microbiology Department, Amiri Hospital Kuwait City, Kuwait

4Department of Biomedical and Forensic Sciences, Faculty of Science and Technology, Anglia Ruskin University Cambridge, UK


*Acinetobacter baumannii* is one of the most important opportunistic pathogens that causes serious health care associated complications in critically ill patients. In the current study we report on the diversity of the clinical multi-drug resistant (MDR) *A. baumannii* in Kuwait by molecular characterization. One hundred *A. baumannii* were isolated from one of the largest governmental hospitals in Kuwait. Following the identification of the isolates by molecular methods, the amplified bla OXA-51-like gene product of one isolate (KO-12) recovered from blood showed the insertion of the ISAba19 at position 379 in bla OXA-78.
Of the 33 MDR isolates, 28 (85%) contained bla OXA-23, 2 (6%) bla OXA-24 and 6 (18%) bla PER-1 gene. We did not detect bla OXA-58, bla VIM, bla IMP, bla GES, bla VEB, and bla NDM genes in any of the tested isolates. In three bla PER-1 positive isolates the genetic environment of bla PER-1 consisted of two copies of ISPα12 (tnpA1) surrounding the bla PER-1 gene on a highly stable plasmid of ca. 140-kb. Multilocus-sequence typing (MLST) analysis of the 33 A. baumannii isolates identified 20 different STs, of which six (ST-607, ST-608, ST-609, ST-610, ST-611, and ST-612) were novel. Emerging STs such as ST15 (identified for the first time in the Middle East), ST78 and ST25 were also detected. The predominant clonal complex was CC2. Pulsed-field gel electrophoresis and MLST defined the MDR isolates as multi-clonal with diverse lineages. Our results lead us to believe that A. baumannii is diverse in clonal origins and/or is undergoing clonal expansion continuously while multiple lineages of MDR A. baumannii circulate in hospital ward simultaneously.

Spatial-Temporal Variations and Diversity of the Bacterioplankton Communities in the Coastal Waters of Kuwait

Almutairi A^1

^1Kuwait University, Faculty of Science, Department of Biological Sciences, P.O. Box 5969, Safat 13060, Kuwait.
E-mail: a.almutairi@ku.edu.kw


The dynamics and composition of the bacterial community in the coastal waters of Kuwait are poorly understood. In this study, the spatial-temporal variations in the bacterial composition in the surface water along the Kuwaiti coast was examined by 16S rRNA denaturing gradient gel electrophoresis (DGGE) fingerprinting and phylogeny analyses. The sampling sites were Kuwait Bay, Al-Sabbiya (north of the bay) and Al-Khairan (to the south). The bacterial composition was more variable in the summer for all sites. A cluster analysis of the DGGE fingerprint revealed two main clusters, indicating a temporal similarity between sites. Kuwait Bay and Al-Khairan were more similar to each other than to Al-Sabbiya. The bacterial community composition exhibited distinctive spatial variations, with more diversity at Al-Khairan and less diversity at Al-Sabbiya. At all sites, the dominant bacteria were Alphaproteobacteria, in particular Rhodobacteraceae, followed by Alteromonadaceae (Gammaproteobacteria) and Bacteroidetes.

A Comparison of Continuous Subcutaneous Insulin Infusion Vs. Multiple Daily Insulin Injection in Children with Type I Diabetes in Kuwait: Glycemic Control, Insulin Requirement, and BMI

Majedah M. AbdulRasoul, Mousa M^1, Al-Mahdi M^2, Al-Sanaa H^3; Dalia Al-AbdulRazzaq, Al-Kandari H^4

^1Department of Community Medicine, Kuwait University, Jabiya City, Kuwait
^2Department of Pediatrics, Adan Hospital, AlAhmadi City, Kuwait
^3Department of Pediatrics, Amiri Hospital, Kuwait city, Kuwait
^4Department of Pediatrics, Farwania Hospital, Farwaniya City, Kuwait


Objective: Continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDI) are two methods currently used to manage type I diabetes mellitus (T1DM). Here we compare our experiences with CSII and MDI in a large cohort of pediatric patients in Kuwait.

Methods: Data on 326 patients with T1DM who were started on CSII between 2007 and 2012 were retrospectively compared with those of 326 patients on MDI. They were matched for sex, age at diagnosis,
T1DM duration, glycemic control, insulin requirement, and body mass index (BMI). Data were collected at baseline and every three months and included glycated hemoglobin (HbA1c), insulin dose, and adverse events (severe hypoglycemia, diabetic ketoacidosis, and skin problems).

**Results:** The main reason for switching to CSII was to achieve better glycemic control (37%), followed by reducing hypoglycemia, and improving the quality of life (13.3% each). Although HbA1c decrease was most significant in the first year, it continued to be significantly lower in the CSII group compared to the MDI throughout the study period. Total daily insulin requirements were significantly lower in the CSII group. BMI increased in both groups, but the difference was significant only at the end of the fifth year. There was no significant change in the rate of diabetic ketoacidosis in either group. The CSII patients had more severe hypoglycemic episodes at baseline; however, it significantly decreased throughout the study period. Only five patients discontinued CSII therapy and two of these restarted within three months.

**Conclusion:** CSII is a safe intensive insulin therapy in youngsters with T1DM and achieved markedly fewer severe hypoglycemic episodes and lower daily insulin requirements.

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**Prognostic Indicators of Secondary Progression in a Paediatric-Onset Multiple Sclerosis Cohort in Kuwait**

Akhtar S1, Alroughani R2, Ahmed SF3, Al-Hashel JY4

1Department of Community Medicine and Behavioural Sciences, University of Kuwait, Kuwait.
E-mail: saeed.akhtar@hsc.edu.kw

2Division of Neurology, Amiri Hospital, Kuwait/Neurology Clinic, Dasman Diabetes Institute, Kuwait

3Department of Neurology, Ibn Sina Hospital, Kuwait/Department of Neurology and Psychiatry, Minia University, Egypt

4Department of Neurology, Ibn Sina Hospital, Kuwait/Department of Medicine, University of Kuwait, Kuwait


**Background:** The frequency of paediatric-onset multiple sclerosis (POMS) and the precise risk of secondary progression of disease are largely unknown in the Middle East. This cross-sectional cohort study assessed the risk and examined prognostic factors for time to onset of secondary progressive multiple sclerosis (SPMS) in a cohort of POMS patients.

**Methods:** The Kuwait National MS Registry database was used to identify a cohort of POMS cases (diagnosed at age <18 years) from 1994 to 2013. Data were abstracted from patients’ records. A Cox proportional hazards model was used to evaluate the prognostic significance of the variables considered.

**Results:** Of 808 multiple sclerosis (MS) patients, 127 (15.7%) were POMS cases. The median age (years) at disease onset was 16.0 (range 6.5-17.9). Of 127 POMS cases, 20 (15.8%) developed SPMS. A multivariable Cox proportional hazards model showed that at MS onset, brainstem involvement (adjusted hazard ratio 5.71; 95% confidence interval 1.53-21.30; P=0.010), and POMS patient age at MS onset (adjusted hazard ratio 1.38; 95% confidence interval 1.01-1.88; P=0.042) were significantly associated with the increased risk of a secondary progressive disease course.

**Conclusions:** This study showed that POMS patients with brainstem/cerebellar presentation and a relatively higher age at MS onset had disposition for SPMS and warrant an aggressive therapeutic approach.

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**Normal Reference Ranges for Cardiac Valve Annulus in Preterm Infants**

Abushaban L1, Vel MT, Rathinasamy J, Sharma PN

1Chest Diseases Hospital, Ministry of Health, Kuwait City, Kuwait. E-mail: lulu@hsc.edu.kw

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**Objective:** The purpose of this study was to establish normal reference ranges for the cardiac valve annulus size in preterm infants and their correlation with gestational age, body weight and chronological age.
Subjects and Methods: In a prospective study, 268 pre-term babies, who fulfilled the criteria for inclusion, were examined in Kuwait during the years 2008 - 2010. Echocardiograms were performed to measure the aortic, pulmonary, mitral and tricuspid valve annulus size on 0 - 6 day(s) of life and at weekly intervals until they reached 36 weeks. The gestational age was grouped into three: 24 - 27, 28 - 31 and 32 - 35 weeks, and body weight into five: ≤ 999, 1000 - 1499, 1500 - 1999, 2000 - 2499 and ≥ 2500 g. The overall group differences were compared for each period of life: 0 - 6 days, 1 - 2, 3 - 4 and ≥ 5 weeks.

Results: The mean gestational age was 29.8 (± 2.38 SD) weeks, ranging between 24 and 35, and the mean body weight 1479 (± 413 SD) grams, ranging between 588 and 3380. At the first scan (0 - 6 days of life), all cardiac valve measurements correlated well with both body weight and gestational age (P < 0.001). In the subsequent weeks valve diameters correlated well with body weight, while gestational age was found to have significant correlation (P < 0.01) with aortic and mitral valves only. A significant gradual increase was noticed in all valve annulus measurements with body weight during each period of life. Overall, a progressive and significant increase for all four cardiac valve annulus measurements was observed during the first nine weeks of life.

Conclusion: The cardiac valve annulus measurements were found to have significant correlation with body weight. All the cardiac valve measurements correlated well with gestational age (P < 0.01) only up to 2 weeks. The study also provides reference data, which can be used as a normal reference tool for cardiac valve diameters for preterm infants against the gestational age, body weight and chronological age.

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Pediatric-Onset Multiple Sclerosis Disease Progression in Kuwait: A Retrospective Analysis

Alroughani R¹, Ahmed SF², Al-Hashel J³

¹Division of Neurology, Amiri Hospital, Arabian Gulf Street, Sharq, Kuwait; Neurology Clinic, Dasman Diabetes Institute, Dasman, Kuwait. E-mail: alroughani@gmail.com
²Department of Neurology, Ibn Sina Hospital, Safat, Kuwait; Department of Neurology and Psychiatry, Minia University, Minia, Egypt
³Department of Neurology, Ibn Sina Hospital, Safat, Kuwait; Department of Medicine, Faculty of Medicine, Kuwait University, Safat, Kuwait


Background: Pediatric and adults patients share basic aspects of multiple sclerosis; however, pediatric patients may have distinctive clinical features and disease course.

Objective: To compare the demographic and clinical characteristics between patients of pediatric-onset and adult-onset multiple sclerosis.

Methods: Using the Kuwait National Multiple Sclerosis Registry, multiple sclerosis patients with disease onset at age ≤17 years (pediatric-onset multiple sclerosis) or >17 years (adult-adult multiple sclerosis) were identified. Several demographics and clinical characteristics were analyzed. Disability measures and time to reach secondary progressive multiple sclerosis were compared between the two cohorts using chi-square and Student t tests.

Results: A total of 984 records of multiple sclerosis patients were assessed, of which 111 (11.3%) had disease onset at age ≤17 years. The female to male ratio did not differ between the two groups (P = 0.19). The mean age at onset of pediatric- and adult-onset multiple sclerosis was 14.9 and 27.68 years, respectively. Pediatric-onset multiple sclerosis patients were more likely to have brainstem/cerebellar (P < 0.03) and multifocal (P < 0.01) presentations at onset. The mean number of relapses did not differ between the two cohorts (3.4 ± 2.1 versus 3.05 ± 2.2; P = 0.14). The mean expanded disability status scale score at last visit was lower in the pediatric-onset cohort compared with the adult-onset cohort (2.38 ± 1.72 versus 3.02 ± 2.18; P = 0.003). The time to develop secondary progressive multiple sclerosis was longer in the pediatric-onset cohort (14.6 ± 4.6 years versus 11.0 ± 5.3 years; P < 0.04).

Conclusions: Pediatric-onset multiple sclerosis patients were more likely to have brainstem/cerebellar and multifocal symptoms at onset. Although the number of relapses was comparable to the adult-onset cohort, multiple sclerosis patients with pediatric-onset had lower expanded disability status scale scores and a longer time to reach secondary progressive course at last follow-up visits.
Forthcoming Conferences and Meetings

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10th International Conference on Healthcare & Biological Research
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Dec 18 - 19, 2015
United States / New York
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789
Fax: 925-969-1795

1st Annual Bit World Congress of Digestive Diseases
Dec 18 - 20, 2015
China / Nanjing
Contact: Mandy Han, Program Coordinator, Bit Congress, Inc.
Phone: 011-86-411-8479-9609 Ext. 804
Fax: 011-86-411-8479-9609
Email: mandy@bitcongress.com

Infectious Diseases in the Adult Patient: A Primary Care Update
Dec 28 – 31, 2015
United States / Florida / Sarasota
Contact: Tara Esteves, Live Cme Manager, American Medical Seminars, Inc.
Phone: 866-267-4263; Fax: 941-365-7073
Email: testeves@ams4cme.com

17th Annual Dermatology for the Non-Dermatologist
Jan 1 - 5, 2016
United States / Florida / Key West
Contact: University Of South Florida Health
Phone: 813-224-7860 or 800-852-5362; Fax: 813-224-7864

New Zealand CME Cruise: Internal Medicine & Geriatrics
Jan 5 – 19, 2016
Australia / Sydney
Contact: Sea Courses Cruises
Phone: 888-647-7327; Fax: 888-547-7337
Email: cruises@seacourses.com

2016 British Fertility Society (BFS) Annual Meeting;
Gamete Formation, Preservation & Donation
Jan 7 - 8, 2016
United Kingdom / Newcastle Upon Tyne
Contact: Bfs Secretariat, Bioscientifica
Phone: 011-44-14-5464-2217; Fax: 011-44-14-5464-2222
Email: bfs@bioscientifica.com

2016 Genitourinary Cancers Symposium
Jan 7 - 9, 2016
United States / California / San Francisco
Contact: Customer Service, American Society of Clinical Oncology
Phone: 888-282-2552 or 703-299-0158
Email: customerservice@asco.org

49th Annual Conference of Urological Society of India
Jan 7 - 10, 2016
India / Hyderabad
Contact: Conference Manager, Kuoni Destination Management
Phone: 011-91-98-4844-0272
Email: thirupathi.atkapuram@in.kuoni.com

9th International Conference on Healthcare & Life Science Research
Dec 27 - 28, 2015
Malaysia / Kuala Lumpur
Contact: Prof. Davis Lazarus, Prof., Global Research & Development Services
Phone: 011-91-94-6283-2013
Email: Info@Malaysiaichlsr.Com

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

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

10th International Conference on Healthcare & Biological Research
Dec 17 - 18, 2015
Thailand / Bangkok
Contact: Prof. Davis Lazarus, Prof., Global R & D Services
Phone: 011-91-94-6283-2013
Email: Info@IchbIRTHailand.Com

64th Neurological Society of India (NSI) Annual Conference
Dec 17 - 20, 2015
India / Hyderabad
Contact: Conference Secretariat, Cim Global
Phone: 011-91-80-2608-0700; Fax: 011-91-80-2608-0702
Email: Info@Nsicon2015.Com

2015 European Society for Medical Oncology (ESMO) Asia Congress
Dec 18 - 21, 2015
Singapore / Singapore
Contact: Daura, Ms., Esmo
Phone: 011-41-91-973-1900; Fax: 011-41-91-973-1902
Email: daura.mella@esmo.org

21st Annual Conference on Challenges in Gynecology
Dec 18 - 19, 2015
United States / New York
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789
Fax: 925-969-1795

1st Annual Bit World Congress of Digestive Diseases
Dec 18 - 20, 2015
China / Nanjing
Contact: Mandy Han, Program Coordinator, Bit Congress, Inc.
Phone: 011-86-411-8479-9609 Ext. 804
Fax: 011-86-411-8479-9609
Email: mandy@bitcongress.com

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United States / Florida / Sarasota
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Phone: 866-267-4263; Fax: 941-365-7073
Email: testeves@ams4cme.com

17th Annual Dermatology for the Non-Dermatologist
Jan 1 - 5, 2016
United States / Florida / Key West
Contact: University Of South Florida Health
Phone: 813-224-7860 or 800-852-5362; Fax: 813-224-7864

New Zealand CME Cruise: Internal Medicine & Geriatrics
Jan 5 – 19, 2016
Australia / Sydney
Contact: Sea Courses Cruises
Phone: 888-647-7327; Fax: 888-547-7337
Email: cruises@seacourses.com

2016 British Fertility Society (BFS) Annual Meeting;
Gamete Formation, Preservation & Donation
Jan 7 - 8, 2016
United Kingdom / Newcastle Upon Tyne
Contact: Bfs Secretariat, Bioscientifica
Phone: 011-44-14-5464-2217; Fax: 011-44-14-5464-2222
Email: bfs@bioscientifica.com

2016 Genitourinary Cancers Symposium
Jan 7 - 9, 2016
United States / California / San Francisco
Contact: Customer Service, American Society of Clinical Oncology
Phone: 888-282-2552 or 703-299-0158
Email: customerservice@asco.org

49th Annual Conference of Urological Society of India
Jan 7 - 10, 2016
India / Hyderabad
Contact: Conference Manager, Kuoni Destination Management
Phone: 011-91-98-4844-0272
Email: thirupathi.atkapuram@in.kuoni.com

9th International Conference on Healthcare & Life Science Research
Dec 27 - 28, 2015
Malaysia / Kuala Lumpur
Contact: Prof. Davis Lazarus, Prof., Global Research & Development Services
Phone: 011-91-94-6283-2013
Email: Info@Malaysiaichlsr.Com
1st Annual Mayo Clinic update on infectious diseases for primary care
Jan 9 - 10, 2016
United States / Arizona / Phoenix
Contact: Mayo School of Cpd, Meeting Planner, Mayo Clinic
Phone: 480-301-4580; Fax: 480-301-8323
Email: mca.cme@mayo.edu

Practical Approach to Breast Imaging & Optional Digital Mammography
Jan 10 - 15, 2016
United States / Hawaii
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

7th International Course on Ophthalmic & Oculoplastic Reconstruction & Trauma Surgery
Jan 13 - 15, 2016
Austria / Vienna
Contact: Helmut Weissmann, Advanced Ophthalmic Trainings
Phone: 011-43-2243-20898
Fax: 011-43-2243-20898 ext. 15
Email: office@ophthalmictrainings.com

13th Annual Canadian Paediatric Review Program (CPRP)
Jan 13 - 17, 2016
Canada / Ontario / Hamilton, Ontario
Contact: Louise Bruns, Program Coordinator, CPRP
Phone: 519-699-9232; Fax: 519-218-8919
Email: brunso@paediatricreview.ca

6th Emirates Otorhinolaryngology, Audiology & Communication Disorders Congress
Jan 13 - 15, 2016
United Arab Emirates / Dubai
Contact: Nadia Ansari, Marketing Executive, Mci Middle East
Phone: 011-971-4-311-6300; Fax: 011-971-4-311-6301
Email: Nadia.Ansari@Mci-Group.Com

7th International Course on Ophthalmic & Oculoplastic Reconstruction & Trauma Surgery
Jan 13 - 15, 2016
Austria / Vienna
Contact: Helmut Weissmann, Advanced Ophthalmic Trainings
Phone: 011-43-2243-20898
Fax: 011-43-2243-20898 Ext. 15
Email: office@ophthalmictrainings.com

Cataract Surgery: Telling It Like It Is
Jan 13 - 17, 2016
United States / Florida / Naples
Contact: University of Cincinnati
Phone: 513-569-3679; Fax: 513-569-3879
Email: Jmosher@CincinnatiEye.Com

2016 World Congress on Recurrent Pregnancy Loss
Jan 14 – 17, 2016
France / Cannes
Contact: Secretariat, Paragon Group
Phone: 011-41-22-533-0948
Fax: 011-41-22-580-2953
Email: secretariat@wrpl.com

21st Annual International Atrial Fibrillation Symposium
Jan 14 – 16, 2016
United States / Florida / Orlando
Contact: Advanced Medical Education
Phone: 508-614-5413
Fax: 508-519-0789
Email: info@afsymposium.com

Updates In Abdominal Wall Reconstruction
Jan 14 – 16, 2016
United States / Florida / Orlando
Contact: Cleveland Clinic Foundation
Phone: 216-444-9990

2016 American Professional Society of ADHD & Related Disorders (APSARD) Annual Meeting
Jan 15 – 17, 2016
United States / District of Columbia / Washington
Contact: Apsard
Phone: 615-649-3083

2016 Orlando Dermatology Aesthetic & Clinical Conference
Jan 15 - 18, 2016
United States / Florida / Orlando
Contact: Dana Turner, Sanovaworks
Phone: 646-453-5718
Email: info@orlandoderm.org

3rd International Workshop on Lung Health, Asthma & COPD: Converging or Diverging Chronicity?
Jan 15 - 17, 2016
Monaco / Monaco-Ville
Contact: Lung Health Team, Publi Creations
Phone: 011-377-9797-3555
Email: lunghealth@publiccreations.com

Principles & Treatment of Spinal Disorders for Residents
Jan 15 - 16, 2016
United States / Nevada / Las Vegas
Contact: Continuing Medical Education, AO North America
Phone: 800-769-1391 or 610-695-2459
Fax: 610-695-2420
Email: customerservice@aona.org
14th Mild Cognitive Impairment Symposium & Early Alzheimer’s Diagnostic & Treatment Workshop  
Jan 16 - 17, 2016  
United States / Florida / Miami Beach  
Contact: Wien Center for Alzheimer’s Disease & Memory Disorders, Mount Sinai Medical Center  
Phone: 224-938-9523  
Email: meetings@worldeventsforum.com

1st Middle Eastern Conference for Stereotactic & Functional Neurosurgery  
Jan 16 - 18, 2016  
United Arab Emirates / Dubai  
Contact:  
Phone: 011-971-4-457-7966  
Email: Info@mfsns.org

11th International Conference on Healthcare & Biological Research  
Jan 17 - 18, 2016  
United Arab Emirates / Dubai  
Contact: Prof. Davis Lazarus, Prof., Global Research & Development Services  
Phone: 011-91-94-6283-2013  
Email: info@ichbrdubai.com

2016 Tutorials in Diagnostic Radiology Course  
Jan 17 - 21, 2016  
United States / Hawaii / Maui  
Contact: Mayo School of Continuous Professional Development  
Phone: 800-323-2688  
Email: cmereg@ucalgary.ca

18th International Conference on Dialysis: advances in kidney disease  
Jan 20 - 22, 2016  
United States / Florida / Miami  
Contact: Ingrid Adelsberger, Renal Research Institute  
Phone: 212-331-1700; Fax: 212-331-1774  
Email: iadelsberger@rriny.com

Comprehensive Colposcopy  
Jan 20 - 23, 2016  
United States / Florida / Tampa  
Contact: American Society for Colposcopy & Cervical Pathology  
Phone: 800-787-7227 or 301-733-3640  
Fax: 240-575-9880

2016 Gulf Arrhythmia Congress  
Jan 21 - 23, 2016  
United Arab Emirates / Dubai  
Contact: Magdalena Mikusova, Marketing and Business Development, Diaedu  
Phone: 011-971-4-453-2975  
Email: mag@diaedu.com

HDR & Electronic Brachytherapy for Skin Cancer  
Jan 21 - 22, 2016  
United Kingdom / Manchester  
Contact: The Christie NHS Foundation Trust  
Phone: 011-44-16-1918-7409  
Email: Info@brachytherapy.com

2016 Progress & Controversies in Gynecologic Oncology Conference  
Jan 22 - 23, 2016  
Spain / Barcelona  
Contact: Prime Oncology, Prime Oncology  
Phone: 011-31-70-306-7190; Fax: 011-31-70-331-8335  
Email: gyncongress2016@primeoncology.org

32nd Annual Emergency Medicine for Rural Hospitals  
Jan 22 - 24, 2016  
Canada / Alberta / Banff Rural  
Contact: Office of CME, University of Calgary  
Phone: 403-220-7032  
Email: cmereg@ucalgary.ca

Current Treatment of the Athlete’s Knee: Innovative Surgical Solutions for Complex Problems  
Jan 22 - 24, 2016  
United States / Illinois / Chicago  
Contact: American Orthopaedic Society for Sports Medicine  
Phone: 847-292-4900

2016 Winter Rheumatology Symposium  
Jan 23 - 29, 2016  
United States / Colorado / Snowmass  
Contact: American College of Rheumatology  
Phone: 404-633-3777 Ext. 381  
Email: education@rheumatology.org

49th Annual Winter Conference on Brain Research  
Jan 23 - 28, 2016  
United States / Colorado / Breckenridge  
Contact: Michelle Chappell, Project Manager, Parthenon Management Group, Inc.  
Phone: 615-649-3075  
Email: info@winterbrain.org

52nd Society of Thoracic Surgeons (STS) Annual Meeting & STS/AATS Tech-Con  
Jan 23 - 27, 2016  
United States / Arizona / Phoenix  
Contact: STS  
Phone: 312-202-5800; Fax: 312-202-5801

23rd International Symposium in Oral & Maxillofacial Surgery  
Jan 25 - 29, 2016  
United States / Hawaii / Kauai  
Contact: University of California, San Francisco  
Phone: 415-514-0778
30th Annual San Diego International Conference on
Child & Family Maltreatment
Jan 25 - 29, 2016
United States / California / San Diego Pediatrics
Contact: Registration Coordinator, Rady Children’s
Hospital San Diego
Phone: 858-966-4972
Email: sdconference@rchsd.org

Adult Sexual Assault Forensic Examiner Training for
Healthcare Professionals
Jan 25 - 29, 2016
United States / California / Sacramento
Contact: Sheila Cavanagh, California District
Attorneys Association
Phone: 916-930-3057
Email: sheila.cavanagh@ccfmtc.org

Virtual Colonography
Jan 25 - 27, 2016
Canada / Ontario / Toronto
Contact: Milla Bond, Hons B.A., Chrp, Advanced
Imaging And Education Centre, University Of Toronto
Phone: 416-340-4800 Ext. 5108
Email: milla.bond@uhn.ca

2016 British Institute of Radiology (BIR) UK MRI
Course
Jan 26 - 29, 2016
United Kingdom / Liverpool
Contact: BIR
Phone: 011-44-20-3668-2220; Fax: 011-44-20-3411-6354
Email: conference@bir.org.uk

2016 Viruses: At the Forefront of Virus–Host
Interactions
Jan 26 - 28, 2016
Switzerland / Basel
Contact: Delia Costache, Conference Secretariat, Mdpi
Phone: 011-41-79-572-1597
Email: viruses@mdpi.com

2016 British Society of Paediatric Gastroenterology,
Hepatology & Nutrition (BSPGHAN) Annual
Meeting
Jan 27 - 29, 2016
United Kingdom / Bristol
Contact: Administrator, BSPGHAN
Email: carla@bspghan.org.uk

2016 Mayo Clinic Cardiovascular Reviews in Bahrain
Jan 27 - 30, 2016
Bahrain / Manama
Contact: Charlene Tri, Mayo Clinic Cardiovascular
Cme
Phone: 800-283-6296
Email: cvcme@mayo.edu

42nd Annual British Paediatric Neurology
Association (BPNA) Conference
Jan 27 - 29, 2016
United Kingdom / Sheffield Neurology
Contact: Bpna Secretariat
Phone: 011-44-120-452-6002
Fax: 011-44-120-452-8394
Email: info@bpna.org.uk

2016 International Master Course on Aging Skin
(IMCAS) Annual World Congress
Jan 28 - 31, 2016
France / Paris
Contact: IMCAS Team, IMCAS
Phone: 011-33-1-4073-8282
Email: contact@imcas.com

23rd International Symposium on Pancreatic & Biliary
Endoscopy
Jan 28 - 31, 2016
United States / California / Los Angeles
Contact: Cedars-Sinai Medical Center
Phone: 310-423-5548

8th Annual T-Cell Lymphoma Forum
Jan 28 - 30, 2016
United States / California / San Francisco
Contact: Damaris Cruz, Jonathan Wood & Associates
Phone: 201-594-0400 Ext. 106
Fax: 201-594-0409
Email: info@jwoodassoc.com

Complex Facial Injuries: Controversies &
Multidisciplinary Perspectives
Jan 28 - 31, 2016
United States / Colorado
Contact: Continuing Medical Education, Ao North
America
Phone: 800-769-1391 or 610-695-2459
Fax: 610-695-2420
Email: customerservice@aona.org

2016 Canadian Breast Cancer Symposium
Jan 29 - 30, 2016
Canada / British Columbia / Whistler
Contact: HAYMATICk
Phone: 778-882-4389
Email: info@haymatick.com

2016 Electives in Hand Surgery
Jan 29 - 30, 2016
United States / Louisiana / New Orleans
Contact: Diana Shkap, American Society For Surgery
of The Hand
Phone: 312-880-1900
Email: dshkap@assh.org
2016 **Traumatic Brain Injury** Conference  
Jan 29, 2016  
*Canada / Ontario / Toronto*  
Contact: Conference Services, University Health Network  
Phone: 416-597-3422 Ext. 3448  
Email: conferences@uhn.ca

**Malignant Melanoma & Beyond:** An Introduction to Targeted Treatments & Cancer Immunotherapy  
Feb 2, 2016  
*United Kingdom / London*  
Contact: Education and Conference Centre, The Royal Marsden NHS Foundation Trust  
Phone: 011-44-20-7808-2334  
Fax: 011-44-20-7808-2334  
Email: conferencecentre@rmh.nhs.uk

2016 Aspen **Anesthesia**  
Jan 30 - Feb 6, 2016  
*United States / Colorado / Snowmass*  
Contact: Holiday Seminars  
Phone: 877-859-0550 Or 970-923-9650  
Fax: 970-923-9640  
Email: office@holidayseminars.com

**Musculoskeletal** MR Imaging  
Jan 31 - Feb 2, 2016  
*United States / California / Rancho Mirage*  
Contact: Office of Continuing Medical Education, University of California, San Francisco  
Phone: 415-476-5808; Fax: 415-502-1795  
Email: info@ocme.ucsf.edu

**Abdominal & Pelvic Imaging:** CT/MR/US  
Feb 3 - 5, 2016  
*United States / California*  
Contact: Office of Continuing Medical Education, University of California, San Francisco  
Phone: 415-476-5808  
Fax: 415-502-1795  
Email: info@ocme.ucsf.edu

6th Advanced Course in **Knee Surgery**  
Jan 31 - Feb 5, 2016  
*France / Val D’isère*  
Contact: Congress Centre Henri Oreiller  
Phone: 011-33-4-7906-2123; Fax: 011-33-4-7906-1904  
Email: KneeCourse@Valdisere-Congres.Com

**Abdominal & Pelvic Imaging:** CT/MR/US  
Feb 3 - 5, 2016  
*United States / California*  
Contact: Office of Continuing Medical Education, University of California, San Francisco  
Phone: 415-476-5808  
Fax: 415-502-1795  
Email: info@ocme.ucsf.edu

**6th Advanced Course in Knee Surgery**  
Jan 31 - Feb 5, 2016  
*France / Val D’isère*  
Contact: Congress Centre Henri Oreiller  
Phone: 011-33-4-7906-2123; Fax: 011-33-4-7906-1904  
Email: KneeCourse@Valdisere-Congres.Com

**2016 Arrhythmias & the Heart:** A Cardiovascular Update  
Feb 1 - 5, 2016  
*United States / Hawaii / Maui*  
Contact: Charlene Tri, Mayo Clinic Cardiovascular CME  
Phone: 800-283-6296  
Email: cvcme@mayo.edu

**Recent Advances in Anaesthesia, Critical Care & Pain Management**  
Feb 3 - 5, 2016  
*United Kingdom / London*  
Contact: Meetings and Events, Royal College of Anaesthetists  
Phone: 011-44-20-7092-1670; Fax: 011-44-20-7092-1730  
Email: events@rcoa.ac.uk

**15th Annual Symposium on Current Concepts In Spinal Disorders**  
Feb 4 - 6, 2016  
*United States / Nevada / Las Vegas*  
Contact: Cedars-Sinai Medical Center  
Phone: 310-423-5548

**34th Annual Infectious Diseases Conference**  
Feb 5 - 6, 2016  
*United States / California*  
Contact: Vickie Hidalgo, Marketing, UC Davis  
Phone: 916-734-5390; Fax: 916-734-0776  
Email: vmhidalgo@ucdavis.edu

**Geriatrics & Rheumatology:** Practical Topics in Overlapping Specialties  
Feb 1 - 5, 2016  
*United States / Florida / Sarasota*  
Contact: Tara ESTEVES, Live CME Manager, American Medical Seminars, Inc.  
Phone: 866-267-4263 (Toll Free) Or 941-388-1766  
Fax: 941-365-7073  
Email: testeves@ams4cme.com

**Cardiology Meeting**  
Feb 5 - 6, 2016  
*Australia / Melbourne*  
Contact: Meeting Manager, ARINEX  
Phone: 011-61-3-9417-0888; Fax: 011-61-3-9417-0899  
Email: 4ccardiology@arinex.com.au
2016 Symposium on **Clinical Interventional Oncology**
Feb 6 – 7, 2016
*United States / Florida / Hollywood*
Contact: Jonas Nash, Complete Conference Management
Phone: 305-279-2263; Fax: 305-279-8221
Email: jnash@ccmcme.com

28th International Symposium on **Endovascular Therapy**
Feb 6 – 10, 2016
*United States / Florida / Hollywood*
Contact: Jonas Nash, Complete Conference Management
Phone: 305-279-2263; Fax: 305-279-8221
Email: jnash@ccmcme.com

4th Annual Advances in **Gastroenterology & Hepatology** Conference
Feb 6, 2016
*United States / California / San Diego*
Contact: Maureen Helinski Clarke, University of California, San Diego
Phone: 858-534-1302
Email: mbelinski@ucsd.edu

**Neuro & Musculoskeletal Imaging**
Feb 7 - 12, 2016
*United States / Hawaii / Big Island*
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

Topics in **Anesthesia**: Emphasis on Trauma
Feb 8 – 12, 2016
*United States / California / Lake Tahoe*
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065; Fax: 509-547-1265
Email: coleen@nwas.com

49th Annual Recent Advances in **Neurology**
Feb 10 - 12, 2016
*United States / California / San Francisco*
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

**2016 Sleep Medicine Trends**
Feb 11 - 14, 2016
*United States / Arizona / Phoenix*
Contact: American Academy of Sleep Medicine National Office
Phone: 630-737-9700; Fax: 630-737-9790

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22nd Annual Advances in Diagnosis & Treatment of **Sleep Apnea & Snoring**
Feb 12 - 13, 2016
*United States / California / San Francisco*
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

16th Annual International Symposium on Congenital **Heart Disease**
Feb 13 - 16, 2016
*United States / Florida / St. Petersburg*
Contact: All Children’s Hospital
Phone: 800-456-4543 or 727-898-7451
Email: info@allkids.org

29th Annual State-of-The-Art **Echocardiography**: Echo Southwest
Feb 13 - 16, 2016
*United States / Arizona / Tucson*
Contact: American Society of Echocardiography
Phone: 919-861-5574
Email: sota@asecho.org

Pacific Rim Otolaryngology: **Head & Neck Surgery** Update
Feb 13 - 16, 2016
*United States / Hawaii / Honolulu*
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-5808
Fax: 415-502-1795
Email: info@ocme.ucsf.edu

57th Annual **Obstetrics & Gynecology** Update
Feb 14 - 17, 2016
*United States / Utah / Park City*
Contact: Natalie Moore, University of Utah School of Medicine
Phone: 801-581-5501; Fax: 801-585-5146
Email: natalie.moore@hsc.utah.edu

2016 RNA **Therapeutics**
Feb 15 - 16, 2016
*United Kingdom / London*
Contact: TERI ARRI, SMI Group
Phone: 011-44-20-7827-6162
Email: tarri@smi-online.co.uk

2016 International **Stroke** Conference
Feb 17 - 19, 2016
*United States / California / Los Angeles*
Contact: American Heart Association
Phone: 888-242-2453 (Us) Or 214-570-5935
Email: sessionsadmin@heart.org
Forthcoming Conferences and Meetings December 2015

7th Asianamerican Multispecialty Summit:
Laparoscopy & Minimally Invasive Surgery
Feb 17 - 20, 2016
United States / Hawaii / Honolulu
Contact: Society of Laparoendoscopic Surgeons
Phone: 305-665-9959
Email: info@sls.org

1st Biennial Congress of the World Association For Infectious Diseases & Immunological Disorders
Feb 18 - 20, 2016
Italy / Milan
Contact: Organizing Secretariat, Aim Group International
Phone: 011-39-2-566-011; Fax: 011-39-2-7004-8578
Email: waidid2016@aimgroup.eu

2016 Multidisciplinary Head & Neck Cancer Symposium
Feb 18 - 20, 2016
United States / Arizona / Scottsdale
Contact: Christina Cleveland, Meetings Manager, American Society For Radiation Oncology
Phone: 703-839-7388

2nd Asia - Australia Congress on Controversies in Ophthalmology
Feb 18 - 21, 2016
Thailand / Bangkok
Contact: Julia, Congress Secretariat, Comtecmed
Phone: 972-3-566-6166
Email: cophya@cacomtecmed.com

2nd Manchester Melanoma Surgery Meeting
Feb 18, 2016
United Kingdom / Manchester
Contact: The Christie NHS Foundation Trust
Phone: 011-44-16-1918-7409
Email: education.events Christie.nhs.uk

2nd Seminar on Tendon Transfers of the Upper Limb
Feb 18 - 20, 2016
Greece / Thessaloniki
Contact: Congress Secretariat, Premium Congress & Social Events Solutions
Phone: 011-30-23-1021-9407; Fax: 011-30-23-1022-6250
Email: premium.conf@gmail.com

4th Systemic Sclerosis World Congress
Feb 18 - 20, 2016
Portugal / Lisbon
Contact: Organizing Secretariat, Aim Group International
Phone: 011-39-55-233881; Fax: 011-39-55-248-0246
Email: ssc2016@aimgroup.eu

Center for International Blood & Marrow Transplant Research / American Society of Blood & Marrow Transplantation Tandem Meeting
Feb 18 - 22, 2016
United States / Hawaii / Honolulu
Contact: Conference Direct
Email: bmttandemregistration@conferencedirect.com

Office Orthopedics & Sports Medicine For Primary Care
Feb 18 - 20, 2016
Dominican Republic / Punta Cana
Contact: Leslie Burk, MCE Conferences
Phone: 888-533-9031; Fax: 858-777-5588
Email: Info@mceconferences.com

45th Critical Care Congress
Feb 20 - 24, 2016
United States / Florida / Orlando
Contact: Society of Critical Care Medicine
Phone: 847-827-6869; Fax: 847-827-6886
Email: info@sccm.org

6th International Workshop on HIV & Women
Feb 20 - 21, 2016
United States / Massachusetts / Boston
Contact: Virology Education B.V.
Phone: 011-31-30-230-7140; Fax: 011-31-30-230-7148
Email: info@virology-education.com

Canadian Comprehensive Review Course for Physical Medicine & Rehabilitation
Feb 20 - 27, 2016
Canada / Ontario / Toronto
Contact: Larissa Cerskus, Course Coordinator, Canadian Association of Physical Medicine & Rehabilitation
Phone: 613-507-0480; Fax: 866-531-0626
Email: info@capmr.ca

Principles of Operative Treatment of CranioMAXillofacial Trauma & Reconstruction
Feb 20 - 21, 2016
United States / Texas / Dallas
Contact: Continuing Medical Education, Ao North America
Phone: 800-769-1391 Or 610-695-2459
Fax: 610-695-2420
Email: customerservice@aona.org

29th American College of Oral & Maxillofacial Surgery (ACOMS) / Faces Winter Meeting
Feb 22 - 27, 2016
United States / Colorado / Snowmass
Contact: ACOMS
Phone: 202-367-1182; Fax: 202-367-2182
Email: info@acoms.org
3rd Annual International Conference on Advances in Cancer Medical Research
Feb 22 - 23, 2016
Singapore / Singapore
Contact: Conference Secretariat, Global Science And Technology Forum
Phone: 011-65-6327-0166; Fax: 011-65-6327-0162
Email: secretariat@cancerresearch-conf.org

3rd Annual International Conference on Cardiology & Cardiovascular Medicine Research
Feb 22 - 23rd
Singapore / Singapore
Contact: Conference Secretariat, Global Science And Technology Forum
Phone: 011-65-6327-0166; Fax: 011-65-6327-0162
Email: secretariat@cardioresearch-conf.org

Virtual Colonography
Feb 22 - 24, 2016
Canada / Ontario / Toronto
Contact: Milla Bond, HONS B.A., CHRP, Advanced Imaging And Education Centre, University of Toronto
Phone: 416-340-4800 Ext. 5108
Email: milla.bond@uhn.ca

Medical CBT: Ten-Minute Techniques For Real Doctors (Cognitive Behaviour Therapy)
Feb 24 - 26, 2016
Canada / British Columbia / Whistler
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

2016 American Academy of Podiatric Practice Management (AAPPM) Midwinter Conference
Feb 25 - 28, 2016
United States / Florida / Tampa
Contact: Aappm Executive Offices
Phone: 517-484-1930; Fax: 517-485-9408

74th All India Ophthalmological Society Annual Conference
Feb 25 - 28, 2016
India / Kolkata
Contact: Ophthalmological Society of West Bengal
Phone: 011-91-33-2237-1679
Email: Aioc2016kolkata@Gmail.Com

2nd Fetal Medicine, Paediatric Gastro, Hepatology & Nutrition International Conference
Feb 25 - 27, 2016
United Arab Emirates / Abu Dhabi
Contact: Maria Estoye, Mena Conference
Phone: 011-971-2-491-9888
Email: maria@menaconf.com

3rd International Conference on Heart & Brain
Feb 25 - 27, 2016
France / Paris
Contact: Ichb Secretariat, Kenes International on Behalf of the International Conference on Heart and Brain
Phone: 011-41-22-908-0488
Email: heart-brain@kenes.com

Airway Workshop
Feb 25, 2016
United Kingdom / London
Contact: Meetings and Events, Royal College of Anaesthetists
Phone: 011-44-42-7092-1670; Fax: 011-44-42-7092-1730
Email: events@rcoa.ac.uk

Glasgow Emergency Surgery & Trauma Symposium
Feb 25 - 26, 2016
United Kingdom / Glasgow
Contact: Valerie Crawford, Event Coordinator, Royal College of Physicians & Surgeons of Glasgow
Phone: 011-44-14-1241-6224; Fax: 011-44-14-1221-1804
Email: valerie.crawford@rcpsg.ac.uk

10th International Congress on Men’s Health
Feb 26 - 28, 2016
India / New Delhi
Contact: Pattama Thuanchaisri, Kenes Group
Phone: 011-66-2748-7881
Email: pthuanchaisri@kenes.com

4th International Congress on Cardiac Problems In Pregnancy
Feb 27 - Mar 1, 2016
United States / Nevada / Las Vegas
Contact: Congress Secretariat, Paragon
Phone: 412-253-3094
Email: secretariat@cppcongress.com

Probiotics Congress: Asia
Feb 29 - Mar 1, 2016
Malaysia / Kuala Lumpur
Contact: Global Engage
Phone: 011-44-18-6584-9841

13th Annual Canadian Critical Care Conference
Mar 1 - 4, 2016
Canada / British Columbia / Whistler
Contact: Zena Davidson
Phone: 604-834-9362
Email: zena.davidson@vch.ca

11th World Congress on Brain Injury
Mar 2 - 5, 2016
Netherlands / Den Hague
Contact: Secretariat, Mcc Association Mgt.
Phone: 703-960-6500; Fax: 703-960-6603
Email: congress@internationalbrain.org
<table>
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<tr>
<th>Event</th>
<th>Date</th>
<th>Location</th>
<th>Contact Details</th>
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<tr>
<td>17th International Congress on Infectious Diseases</td>
<td>Mar 2 - 5, 2016</td>
<td>India / Hyderabad</td>
<td>Contact: International Society for Infectious Diseases</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: 617-277-0551, Fax: 617-278-9113, Email: <a href="mailto:Info@isid.org">Info@isid.org</a></td>
</tr>
<tr>
<td>2016 Diabetes UK Professional Conference</td>
<td>Mar 2 - 4, 2016</td>
<td>United Kingdom / Glasgow</td>
<td>Contact: Diabetes Uk Events Team, Diabetes UK</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: 011-44-34-5123-2399, Email: <a href="mailto:eventsteam@diabetes.org.uk">eventsteam@diabetes.org.uk</a></td>
</tr>
<tr>
<td>2016 Perinatal Stem Cell Society (PSCS) Annual Conference</td>
<td>Mar 2 - 4, 2016</td>
<td>United States / Colorado / Aspen</td>
<td>Contact: Kyle Cetrulo, PSCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: 617-610-9000, Email: <a href="mailto:kyle.cetrulo@auxocell.com">kyle.cetrulo@auxocell.com</a></td>
</tr>
<tr>
<td>2016 Canadian Retina Society Meeting</td>
<td>Mar 3 - 6, 2016</td>
<td>Canada / Quebec / Mont Tremblant</td>
<td>Contact: Rita Afeltra, Registration &amp; Logistics, Canadian Ophthalmological Society</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: 613-729-6779 Ext. 300, Email: <a href="mailto:rafeltra@cos-sco.ca">rafeltra@cos-sco.ca</a></td>
</tr>
<tr>
<td>26th American Glaucoma Society (AGS) Annual Meeting</td>
<td>Mar 3 - 6, 2016</td>
<td>United States / Florida</td>
<td>Contact: AGS Office, Email: <a href="mailto:ags@aoa.org">ags@aoa.org</a></td>
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<tr>
<td>4th International Conference on Prehypertension,</td>
<td>Mar 3 - 6, 2016</td>
<td>Italy / Venice</td>
<td>Contact: Gail Tito, Conference Secretariat, Paragon Group</td>
</tr>
<tr>
<td>Hypertension &amp; Cardio Metabolic Syndrome</td>
<td></td>
<td></td>
<td>Phone: 011-41-22-533-0948, Email: <a href="mailto:secretariat@prehypertension.org">secretariat@prehypertension.org</a></td>
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<tr>
<td>5th Global Congress for Consensus in Pediatrics &amp; Child Health</td>
<td>Mar 3 - 6, 2016</td>
<td>China / Xian</td>
<td>Contact: Sarah Krein, Paragon Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: 011-972-3-576-7704, Email: <a href="mailto:skrein@paragong.com">skrein@paragong.com</a></td>
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<tr>
<td>2016 Perioperative Leadership Summit</td>
<td>Mar 4 - 6, 2016</td>
<td>United States / Florida / Miami</td>
<td>Contact: Kimberly R. Corey, Association Of Anesthesia Clinical Directors</td>
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<tr>
<td></td>
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<td>Phone: 614-784-9772, Fax: 614-784-9771, Email: <a href="mailto:krc@aacdhq.org">krc@aacdhq.org</a></td>
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<tr>
<td>22nd Annual Cool Topics in Neonatology Conference</td>
<td>Mar 4 - 6, 2016</td>
<td>United States / California / San Diego</td>
<td>Contact: Continuing Medical Education, Uc Los Angeles</td>
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<tr>
<td></td>
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<td></td>
<td>Phone: 310-794-2620, Fax: 310-794-2624</td>
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<tr>
<td>2nd Emirates Endometriosis League Symposium on Endometriosis &amp; Chronic Pelvic Pain</td>
<td>Mar 4 - 5, 2016</td>
<td>United Arab Emirates / Dubai</td>
<td>Contact: Ahmed Hajeer, Project Manager, Infoplus Events Llc</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: 011-971-4-421-8996, Email: <a href="mailto:endometriosis@infoplusevents.com">endometriosis@infoplusevents.com</a></td>
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<tr>
<td>61st Alberta College of Family Physicians (ACFP) Annual Scientific Assembly</td>
<td>Mar 4 - 6, 2016</td>
<td>United States / Alberta / Banff</td>
<td>Contact: Wendy Steele, Coordinator, Communications &amp; Events, ACFP</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Phone: 780-488-2395, Fax: 780-488-2396, Email: <a href="mailto:wendy.steele@acfp.ca">wendy.steele@acfp.ca</a></td>
</tr>
<tr>
<td>Cleveland Clinic Valve Disease &amp; Diastology Summit</td>
<td>Mar 4 - 6, 2016</td>
<td>United States / Florida / Miami</td>
<td>Contact: Cleveland Clinic Foundation</td>
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<tr>
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<td>Phone: 216-444-9990</td>
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<tr>
<td>8th Annual Tulane Symposium on Thyroid &amp; Parathyroid Diseases</td>
<td>Mar 5 - 6, 2016</td>
<td>United States / Louisiana / New Orleans</td>
<td>Contact: Center for Continuing Education, Tulane University School of Medicine</td>
</tr>
<tr>
<td></td>
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<td>Phone: 504-988-5466, Email: <a href="mailto:cme@tulane.edu">cme@tulane.edu</a></td>
</tr>
<tr>
<td>2015 Annual Congress &amp; Medicare Expo on Trauma &amp; Critical Care</td>
<td>Mar 7 - 9, 2016</td>
<td>Spain / Madrid</td>
<td>Contact: OMICS, OMICS International</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Email: <a href="mailto:trauma@conferenceseries.net">trauma@conferenceseries.net</a></td>
</tr>
</tbody>
</table>
2016 British Cardiovascular Society (BCS) / Mayo Clinic Cardiology Review Course
Mar 7 - 11, 2016
United Kingdom / London
Contact: Bcs
Phone: 011-44-20-7380-1914
Email: courses@bcs.com

23rd Annual Echocardiographic Workshop on 2-D & Doppler Echo At Vail
Mar 7 - 10, 2016
United States / Colorado / Vail
Contact: CVCME, Mayo Clinic
Phone: 800-283-6296
Email: cvcme@mayo.edu

Infectious Diseases: Adult Issues in the Outpatient & Inpatient Settings
Mar 7 - 11, 2016
United States / Florida / Sarasota
Contact: Tara Esteves, Live CME Manager, American Medical Seminars
Phone: 866-267-4263 (Toll Free) or, 941-388-1766
Fax: 941-365-7073
Email: testeves@ams4cme.com

35th Annual Chest Convention Pulmoconnect:
Bridging Gaps in Pulmonary Medicine
Mar 8 - 11, 2016
Philippines / Manila
Contact: Andee Santiago, Convention Secretariat, Philippine College of Chest Physicians
Phone: 011-63-2-924-9204
Email: secretariat@philchest.org

10th European Breast Cancer Conference
Mar 9 - 11, 2016
Netherlands / Amsterdam
Contact: Conference Secretariat, European Cancer Organisation
Phone: 011-32-2-775-0201; Fax: 011-32-2-775-0200
Email: ebcc10@ecco-org.eu

14th International Athens / Springfield Symposium on Advances in Alzheimer Therapy
Mar 9 - 12, 2016
Greece / Athens
Contact: Ann Hamilton, Coordinator Usa, Southern Illinois University School of Medicine
Phone: 217-545-7711; Fax: 217-545-4413
Email: Ahamilton@siuomed.edu

6th International Neonatology Conference: Hottest Topics in Neonatal Medicine
Mar 10 - 12, 2016
United Arab Emirates / Abu Dhabi
Contact: Afsal Ahmad, Mena Conference
Phone: 011-971-2-491-9888
Email: afsal.ahmad@menaconf.com

Menopause Special Skills Module
Mar 10 - 11, 2016
United Kingdom / Kenilworth
Contact: Kate Ellis, British Menopause Society
Phone: 011-44-16-2889-0199
Email: kate.ellis@bms-whc.org.uk

St. Gallen International Gastrointestinal Cancer Conference: Primary Therapy of Early GI Cancers
Mar 10 – 12, 2016
Switzerland / St. Gallen
Contact: St. Gallen Oncology Conferences
Phone: 011-41-71-243-0032
Fax: 011-41-71-245-6805

2016 Ambulatory Anesthesia Arosa: Patient Safety in The Ambulatory Operating Theatre
Mar 11 - 12, 2016
Switzerland / Arosa
Contact: Dr. Predescu, M-A-S Mobile Anasthesie Systeme
Phone: 011-41-44-748-2425
Fax: 011-41-44-748-1090
Email: info@aaa2016.com

7th Annual Snowmass Retina & Eye Conference
Mar 11 - 15, 2016
United States / Colorado / Snowmass
Contact: Eleanor Thom, Meeting Coordinator, Eye Research Foundation
Phone: 772-287-1750
Email: ethom@snowmasscme.com

24th European Congress of Psychiatry
Mar 12 - 15, 2016
Spain / Madrid
Contact: EPA Congress, Secretariat, European Psychiatric Association
Phone: 011-41-2-2908-0488
Email: epa@kemen.com

Profile-Plasty: Esthetic Surgery of the Nose & Chin
Mar 12 - 13, 2016
United States / Louisiana / New Orleans
Contact: American College of Oral & Maxillofacial Surgeons
Phone: 202-367-1182; Fax: 202-367-2182
Email: info@acomss.org

2016 Annual Scandinavian Course in Neurosurgery
Mar 13 - 18, 2016
Norway / Beitostølen
Contact: Grete Furseth, Department of Neurosurgery, Oslo University Hospital Rikshospitalet
Phone: 011-47-2307-4851; Fax: 011-47-2343-1000
Email: beitakurs@rikshospitalet.no
5th World Congress On Neurology & Therapeutics  
Mar 14 - 16, 2016  
United Kingdom / London  
Contact: Narine Johnson, Omics International  
Phone: 650-618-9889  
Email: bipolar-disorder@omicsinc.com

Genetics in Forensics  
Mar 14 - 15, 2016  
United Kingdom / London  
Contact: Guillaume Alonso, Marketing Executive, Oxford Global  
Phone: 011-44-18-6524-8455  
Email: g.alonso@oxfordglobal.co.uk

5th Bergamo Open Rhinoplasty Course  
Mar 15 - 19, 2016  
Italy / Bergamo  
Contact: Organizing Secretariat, MZ Congressi SRL  
Phone: 011-39-2-6680-2323  
Fax: 011-39-2-668-6699  
Email: bergamooplast@mzcongressi.com

10th World Immune Regulation Meeting  
Mar 16 - 19, 2016  
Switzerland / Davos  
Contact: Ms. Hilda Leitner, Congress Coordinator, Davos Congress  
Phone: 011-41-81-415-2165  
Fax: 011-41-81-415-2169  
Email: wirminfo@wirm.ch

9th International Congress on Uremia Research & Toxicity  
Mar 16 - 19, 2016  
Mexico / Guadalajara  
Contact: Ricardo A Wilhelm, PCO Director, Once  
Phone: 011-52-33-1031-0359  
Email: rwilhelm@once.com.mx

10th Anniversary World Congress on Controversies in Neurology  
Mar 17 - 20, 2016  
Portugal / Lisbon  
Contact: Prof. Amos Korczyn, Congress Secretariat, COMTEC Med  
Phone: 011-972-3-566-6166  
Fax: 011-972-3-566-6177  
Email: cony@comtecmed.com

3rd International Conference on Nutrition & Growth  
Mar 17 - 19, 2016  
Austria / Vienna  
Contact: Secretariat, Kenes International  
Phone: 011-41-22-906-9178  
Email: ngc@kenes.com

Diabetes Update & Advances in Endocrinology & Metabolism  
Mar 17 - 1, 2016  
United States / California / San Francisco  
Endocrinology  
Contact: Office of Continuing Medical Education, University of California, San Francisco  
Phone: 415-476-5808; Fax: 415-502-1795  
Email: info@ocme.ucsf.edu

2016 Pulmonary Hypertension Summit  
Mar 18 - 19, 2016  
United States / Ohio / Cleveland  
Contact: Cleveland Clinic Foundation  
Phone: 216-444-9990

20th Annual McGill University Update in Otolaryngology - Head & Neck Surgery  
Mar 18 - 20, 2016  
Canada / Quebec / Mont Tremblant  
Contact: Department of Otolaryngology - Head and Neck Surgery, McGill University School of Medicine  
Phone: 514-934-1934 Ext. 32820  
Fax: 514-843-1403

8th Annual Canadian Conference on Lymphoproliferative Disorders  
Mar 18 - 20, 2016  
United States / Alberta / Lake Louise  
Contact: Island Events  
Phone: 250-714-2591  
Email: info@islandeventsinc.ca

3rd Annual Miami Lung Cancer Conference®  
Mar 19, 2016  
United States / Florida / Miami Beach  
Contact: Physicians’ Education Resource  
Phone: 609-378-3701; Fax: 609-257-0705  
Email: info@gotoper.com

23rd World Congress on Controversies In Obstetrics, Gynecology & Infertility  
Mar 21 - 23, 2016  
Australia / Melbourne  
Contact: Secretariat, Secretariat, Congressmed  
Phone: 011-41-22-339-9985  
Email: cogi@congressmed.com

Autism, Adhd & Developmental Disabilities New Zealand Cruise Conference  
Mar 25 - Apr 8, 2016  
Australia / Sydney  
Contact: Continuing Education, Inc, Continuing Education, Inc  
Phone: 800-422-0711  
Email: registrar@continuieducation.net
3rd World Congress on Controversies in Pediatrics
Mar 31 - Apr 3, 2016
Spain / Barcelona
Contact: Secretariat, Congressmed
Phone: 011-41-22-339-9985
Email: copedia@comtemed.com

7th World Congress on Controversies in Ophthalmology
Mar 31 - Apr 3, 2016
Poland / Warsaw
Contact: Esther/Julia, Congress Secretariat, Comtemed
Phone: 011-972-3-566-6166
Email: cophy@comtemed.com

5th Biennial Schizophrenia International Research Society Conference (SIRS)
Apr 2 - 6, 2016
Italy / Florence
Contact: Sirs Executive Office
Phone: 615-324-2370
Email: info@schizophreniaresearchsociety.org

Anesthesia Update - Vienna
Apr 4 - 8, 2016
Austria / Vienna
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065
Fax: 509-547-1265
Email: coleen@nwas.com

10th International Congress on Autoimmunity
Apr 6 - 10, 2016
Germany / Leipzig
Contact: Anna Varsanyi, Apm, Kenes International
Phone: 011-41-22-908-0488
Fax: 011-41-22-906-9140
Email: autoimmunity@kenes.com

2016 Obesity Medicine
Apr 6 - 10, 2016
United States / California / San Francisco
Contact: American Society Of Bariatric Physicians
Phone: 303-770-2526; Fax: 303-779-4834
Email: info@asbp.org

12th Emirates Critical Care Conference
Apr 7 - 9, 2016
United Arab Emirates / Dubai
Contact: Hachem Farache, Project Manager, Infoplus Events Llc
Phone: 011-971-4-421-8996
Email: eccc@infoplusevents.com

8th Study in Multidisciplinary Pain Research
Apr 8 - 9, 2016
Italy / Rome
Contact: Organizing Secretariat, Fedra Congressi
Phone: 011-39-6-5224-7328; Fax: 011-39-6-520-5625
Email: info@fedracongressi.com

26th European Congress of Clinical Microbiology & Infectious Diseases
Apr 9 - 12th
Turkey / Istanbul
Contact: Ms Sharon Visser, Kenes International
Phone: 011-91-95-2145-9120
Email: info@turkeyichlrs.com

2016 Adventures In Medicine CME Singapore to Dubai Cruise
Apr 12 - May 2, 2016
Singapore / Singapore
Contact: Dr. Martin Gerretsen, Director of Cme, Sea Courses Cruises
Phone: 888-647-7327
Email: cruises@seacourses.com

12th Biennial Canadian Orthopaedic Foot & Ankle Symposium
Apr 14 - 16, 2016
Canada / Ontario / Toronto
Contact: Continuing Professional Development, University of Toronto
Phone: 888-512-8173 Or 416-978-2719
Email: info.cpd@utoronto.ca

2016 World Congress on Osteoporosis, Osteoarthritis & Musculoskeletal Diseases
Apr 14 - 17, 2016
Spain / Malaga
Contact: Congress Secretariat, Humacom
Phone: 011-32-87-852-652; Fax: 011-32-87-315-003
Email: info@humacom.com

9th International Update on Neuro-Anaesthesia & Neuro-Intensive Care Meeting
Apr 14 - 16, 2016
Spain / Barcelona
Contact: Organization Secretary, Pacific World
Phone: 011-34-902-090-561
Email: euroneuro2016@pacificworld.com
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<tr>
<td>Congenital Hypoglycemia Disorders: Hyperinsulinism &amp; GSD</td>
<td>Apr 14 - 15, 2016</td>
<td>United States / Pennsylvania / Philadelphia</td>
<td>Ms. Micah Holliday, Continuing Medical Education Department, Children’s Hospital of Philadelphia. Phone: 215-590-5263; Fax: 215-590-4342</td>
</tr>
<tr>
<td>Older People, Cancer &amp; Dementia</td>
<td>Apr 14, 2016</td>
<td>United Kingdom / Manchester</td>
<td>Education Events, the Christie Nhs Foundation Trust. Phone: 011-44-16-1918-7409 Email: <a href="mailto:education.events@chrside.co.uk">education.events@chrside.co.uk</a></td>
</tr>
<tr>
<td>36th International Society of Hematology World Congress</td>
<td>Apr 18 - 21, 2016</td>
<td>United Kingdom / Glasgow</td>
<td>Sharon Forster, BSH Conference Secretariat, BSH. Phone: 011-44-132-350-3019 Fax: 011-44-132-350-9753 Email: <a href="mailto:sharon.forster@bshconferences.co.uk">sharon.forster@bshconferences.co.uk</a></td>
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<tr>
<td>2016 Canadian Blood &amp; Marrow Transplant Group Annual Conference</td>
<td>Apr 24 - 27, 2016</td>
<td>Canada / British Columbia / Vancouver</td>
<td>Malachite Management Inc. Phone: 604-874-4944; Fax: 604-874-4378 Email: <a href="mailto:cbmtg@malachite-mgmt.com">cbmtg@malachite-mgmt.com</a></td>
</tr>
<tr>
<td>3rd International Conference &amp; Exhibition on Rhinology &amp; Otology</td>
<td>Apr 25 - 27, 2016</td>
<td>United Arab Emirates / Dubai</td>
<td>Mr. Abhishek, Omics International. Phone: 872-886-0790 Email: <a href="mailto:editor.jor@scitechnol.org">editor.jor@scitechnol.org</a></td>
</tr>
<tr>
<td>13th International Conference on Obesity</td>
<td>May 1 - 4, 2016</td>
<td>Canada / British Columbia / Vancouver</td>
<td>World Obesity Federation. Phone: 011-44-20-7685-2580; Fax: 011-44-20-7685-2581 Email: <a href="mailto:ico@worldobesity.org">ico@worldobesity.org</a></td>
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<tr>
<td>2016 International Surgical Pathology Symposium</td>
<td>May 3 - 6, 2016</td>
<td>Spain / Madrid</td>
<td>Mayo Medical Laboratories. Phone: 800-533-1710 Email: <a href="mailto:mmleducation@mayo.edu">mmleducation@mayo.edu</a></td>
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<tr>
<td>14th Congress - 2nd Global Conference of European Society of Contraception &amp; Reproductive Health (ESC)</td>
<td>May 4 - 7, 2016</td>
<td>Switzerland / Basel</td>
<td>Nancy Habils, Orga-Med Congress Office, Esc Central Office. Phone: 011-32-2-582-0852; Fax: 011-32-2-582-5515 Email: <a href="mailto:nancy.habils@escrh.eu">nancy.habils@escrh.eu</a></td>
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<tr>
<td>3rd International Congress on Treatment of Dystonia</td>
<td>May 4 - 7, 2016</td>
<td>Germany / Hannover</td>
<td>Interplan Congress, Meeting &amp; Event Management Ag. Phone: 011-49-40-3250-9257; Fax: 011-49-40-3250-9244 Email: <a href="mailto:dystonia2016@interplan.de">dystonia2016@interplan.de</a></td>
</tr>
<tr>
<td>19th Senologic International Society World Congress on Breast Healthcare</td>
<td>May 5 - 8, 2016</td>
<td>Poland / Warsaw</td>
<td>Sarah Krein, Paragon Group. Phone: 011-41-2-2580-2953 Email: <a href="mailto:skrein@paragong.com">skrein@paragong.com</a></td>
</tr>
<tr>
<td>3rd International Congress on Medical Writing</td>
<td>May 5 - 7, 2016</td>
<td>Turkey / Istanbul</td>
<td>Official Congress Organizer, Pure Spot Congress &amp; Event Organizers. Phone: 011-20-2-2672-1944; Fax: 011-20-2-2671-8421 Email: <a href="mailto:info@egypure.org">info@egypure.org</a></td>
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<tr>
<td>2016 Indian Society of Ultrasound In Obstetrics &amp; Gynecology</td>
<td>May 6 - 8, 2016</td>
<td>India / Hyderabad</td>
<td>Dr Geeta, Fernandez Hospital, Hyderabad. Phone: 011-98-4-801-8064 Email: <a href="mailto:insuog2016@gmail.com">insuog2016@gmail.com</a></td>
</tr>
<tr>
<td>2016 Canadian Society for Transfusion Medicine (CSTM) Conference</td>
<td>May 11 - 15, 2016</td>
<td>Canada / British Columbia / Vancouver</td>
<td>CSTM. Phone: 855-415-3917 or 905-415-3917 Fax: 866-882-7093 or 905-415-0071 Email: <a href="mailto:2016info@transfusion.ca">2016info@transfusion.ca</a></td>
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<tr>
<td>32nd Annual Cervical Spine Research Society European Section Meeting</td>
<td>May 11 - 13, 2016</td>
<td>Czech Republic / Prague</td>
<td>Secretariat, Guarant International. Phone: 011-420-284-001-444 Email: <a href="mailto:csrsprague2016@guarant.cz">csrsprague2016@guarant.cz</a></td>
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2016 Australasian College of Dermatologists (ACD) Annual Scientific Meeting
May 14 - 17, 2016
Australia / Perth
Contact: ACD
Phone: 011-61-2-8765-0242; Fax: 011-61-2-9736-2194
Email: admin@dermcoll.asn.au

23rd Annual International Stress & Behavior Neuroscience & Biopsychiatry Conference
May 16 - 19, 2016
Russia / St. Petersburg
Contact: Na Nutsa, Conference Secretary, International Stress & Behavior Society
Phone: 240-899-9571
Email: isbs.congress@gmail.com

1st Asia Pacific Aids & Co-Infections Conference
May 17 - 19, 2016
China / Hong Kong
Contact: Virology Education B.V.
Phone: 011-31-30-230-7140; Fax: 011-31-30-230-7148
Email: info@virology-education.com

2016 Association of Psychology & Psychiatry for Adults & Children (APPAC) Annual International Conference
May 17 - 20, 2016
Greece / Athens
Contact: Dr J. Kouros, Appac Secretariat
Phone: 011-30-210-620-3710; Fax: 011-30-210-684-2079
Email: congress@appac.gr

13th International Congress on Shoulder & Elbow Surgery
May 18 - 21, 2016
South Korea / Jeju
Contact: Icses 2016 Secretariat, COEX
Phone: 011-82-2-6000-8136; Fax: 011-82-2-6000-8190
Email: secretariat@icses2016.org

Care of the Critically Ill Surgical Patient
May 18 - 20, 2016
United Kingdom / Cambridge
Contact: Angela Gray, Course Administrator, Addenbrooke’s Hospital
Phone: 011-44-12-2327-4452
Email: jpn33@medschl.cam.ac.uk

Relevant Topics in Anesthesia - Amsterdam
May 23 - 27, 2016
Netherlands / Amsterdam
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065; Fax: 509-547-1265
Email: coleen@nwas.com

2016 International Society of Physical & Rehabilitation Medicine World Congress
May 29 - Jun 2, 2016
Malaysia / Kuala Lumpur
Contact: Linda Friedman, Kenes International
Phone: 011-41-22-908-0488
Email: isprm@kenes.com

84th European Atherosclerosis Society Congress
May 29 - Jun 1, 2016
Austria / Innsbruck
Contact: Yoav Shlezinger, Kenes Group
Phone: 011-41-22-908-0488
Email: yshlezinger@kenes.com

Current Topics in Anesthesia - Greek Isles & Mediterranean Cruise
May 31 - Jun 12, 2016
Italy / Rome
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065; Fax: 509-547-1265
Email: coleen@nwas.com

2016 World Congress of Cardiology & Cardiovascular Health
Jun 4 - 7, 2016
Mexico / Mexico City
Contact: MCI Suisse Sa
Phone: 011-41-22-339-9585; Fax: 011-41-22-339-9631
Email: wcc2016reg@mci-group.com

10th International Conference on Cholesteatoma & Middle Ear Surgery
Jun 5 - 8, 2016
United Kingdom / Edinburgh
Contact: Matthew Yang, British Society of Otology
Phone: 011-44-20-7808-5621
Email: chole2016@tfigroup.com

8th World Congress on Pediatric Intensive & Critical Care
Jun 5 - 8, 2016
Canada / Ontario / Toronto
Contact: Rebecca Johnstone, Kenes International
Phone: 011-41-22-908-0488
Email: picc@kenes.com

Global Cancer: Occurrence, Causes & Avenues to Prevention
Jun 7 - 10, 2016
France / Lyon
Contact: Conference Administrator, International Agency for Research on Cancer
Phone: 011-33-4-7273-8485
Email: iarc-conference2016@iarc.fr
1. DISABILITY AND HEALTH

Overview
The International Classification of Functioning, Disability and Health (ICF) defines disability as an umbrella term for impairments, activity limitations and participation restrictions. Disability is the interaction between individuals with a health condition (e.g., cerebral palsy, Down syndrome and depression) and personal and environmental factors (e.g., negative attitudes, inaccessible transportation and public buildings, and limited social supports).

Disability is extremely diverse. While some health conditions associated with disability result in poor health and extensive health care needs, others do not. However, all people with disabilities have the same general health care needs as everyone else, and therefore, need access to mainstream health care services. Article 25 of the UN Convention on the Rights of Persons with Disabilities (CRPD) reinforces the right of persons with disabilities to attain the highest standard of health care, without discrimination.

KEY FACTS
- Over a billion people, about 15% of the world’s population, have some form of disability.
- Between 110 million and 190 million adults have significant difficulties in functioning.
- Rates of disability are increasing due to population ageing and increases in chronic health conditions, among other causes.
- People with disabilities have less access to health care services and therefore experience unmet health care needs.

Unmet needs for health care
People with disabilities report seeking more health care than people without disabilities and have greater unmet needs. For example, a recent survey of people with serious mental disorders, showed that between 35% and 50% of people in developed countries, and between 76% and 85% in developing countries, received no treatment in the year prior to the study.

Health promotion and prevention activities seldom target people with disabilities. For example women with disabilities receive less screening for breast and cervical cancer than women without disabilities. People with intellectual impairments and diabetes are less likely to have their weight checked. Adolescents and adults with disabilities are more likely to be excluded from sex education programs.

How are the lives of people with disabilities affected?
People with disabilities are particularly vulnerable to deficiencies in health care services. Depending on the group and setting, persons with disabilities may experience greater vulnerability to secondary conditions, co-morbid conditions, age-related conditions, engaging in health risk behaviors and higher rates of premature death.

Secondary conditions
Secondary conditions occur in addition to (and are related to) a primary health condition, and are both predictable and therefore preventable. Examples include pressure ulcers, urinary tract infections, osteoporosis and pain.

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: info@who.int; Web site: http://www.who.int/
Co-morbid conditions
Co-morbid conditions occur in addition to (and are unrelated to) a primary health condition associated with disability. For example, the prevalence of diabetes in people with schizophrenia is around 15% compared to a rate of 2 - 3% for the general population.

Age-related conditions
The ageing process for some groups of people with disabilities begins earlier than usual. For example, some people with developmental disabilities show signs of premature ageing in their 40s and 50s.

Engaging in health risk behaviours
Some studies have indicated that people with disabilities have higher rates of risky behaviours such as smoking, poor diet and physical inactivity.

Higher rates of premature death
Mortality rates for people with disabilities vary depending on the health condition. However, an investigation in the United Kingdom found that people with mental health disorders and intellectual impairments had a lower life expectancy.

Barriers to health care
People with disabilities encounter a range of barriers when they attempt to access health care including the following.

Prohibitive costs: Affordability of health services and transportation are two main reasons why people with disabilities do not receive needed health care in low-income countries – 32 - 33% of non-disabled people are unable to afford health care compared to 51 - 53% of people with disabilities.

Limited availability of services: The lack of appropriate services for people with disabilities is a significant barrier to health care. For example, research in Uttar Pradesh and Tamil Nadu states of India found that after the cost, the lack of services in the area was the second most significant barrier to using health facilities.

Physical barriers: Uneven access to buildings (hospitals, health centres), inaccessible medical equipment, poor signage, narrow doorways, internal steps, inadequate bathroom facilities, and inaccessible parking areas create barriers to health care facilities. For example, women with mobility difficulties are often unable to access breast and cervical cancer screening because examination tables are not height-adjustable and mammography equipment only accommodates women who are able to stand.

Inadequate skills and knowledge of health workers: People with disabilities were more than twice as likely to report finding health care provider skills inadequate to meet their needs, four times more likely to report being treated badly and nearly three times more likely to report being denied care.

Addressing barriers to health care
Governments can improve health outcomes for people with disabilities by improving access to quality, affordable health care services, which make the best use of available resources. As several factors interact to inhibit access to health care, reforms in all the interacting components of the health care system are required.

Policy and legislation: Assess existing policies and services, identify priorities to reduce health inequalities and plan improvements for access and inclusion. Make changes to comply with the CRPD. Establish health care standards related to care of persons with disabilities with enforcement mechanisms.

Financing: Where private health insurance dominates health care financing, ensure that people with disabilities are covered and consider measures to make the premiums affordable. Ensure that people with disabilities benefit equally from public health care programs. Use financial incentives to encourage health-care providers to make services accessible and provide comprehensive assessments, treatment, and follow-ups. Consider options for reducing or removing out-of-pocket payments for people with disabilities who do not have other means of financing health care services.

Service delivery: Provide a broad range of modifications and adjustments (reasonable accommodation) to facilitate access to health care services. For example changing the physical layout of clinics to provide access for people with mobility difficulties or communicating health information in accessible formats such as Braille. Empower people with disabilities to maximize their health by providing information, training, and peer support. Promote community-based rehabilitation (CBR) to facilitate access for disabled people to existing services. Identify groups that require alternative service delivery models, for example, targeted services or care coordination to improve access to health care.

Human resources: Integrate disability education into undergraduate and continuing education for all health-care professionals. Train community workers so that they can play a role in preventive health care services. Provide evidence-based guidelines for assessment and treatment.

Data and research: Include people with disabilities in health care surveillance. Conduct more research on the needs, barriers, and health outcomes for people with disabilities.
WHO response
In order to improve access to health services for people with disabilities, WHO:
• guides and supports Member States to increase awareness of disability issues, and promotes the inclusion of disability as a component in national health policies and programs;
• facilitates data collection and dissemination of disability-related data and information;
• develops normative tools, including guidelines to strengthen health care;
• builds capacity among health policy-makers and service providers;
• promotes scaling up of CBR; promotes strategies to ensure that people with disabilities are knowledgeable about their own health conditions, and that health-care personnel support and protect the rights and dignity of persons with disabilities.

2. CONGENITAL ANOMALIES

Overview
Congenital anomalies are important causes of childhood death, chronic illness and disability in many countries. In 2010, the World Health Assembly adopted a resolution on birth defects calling all Member States to promote primary prevention and improve the health of children with congenital anomalies by:
• developing and strengthening registration and surveillance systems;
• developing expertise and building capacity;
• strengthening research and studies on etiology, diagnosis and prevention;
• promoting international cooperation.

KEY FACTS
• An estimated 276,000 babies die within four weeks of birth every year, worldwide, from congenital anomalies.
• Congenital anomalies can result in long-term disability, which may have significant impacts on individuals, families, health-care systems and societies.
• The most common severe congenital anomalies are heart defects, neural tube defects and Down syndrome.
• Although congenital anomalies may be genetic, infectious, nutritional or environmental in origin, most often it is difficult to identify the exact causes.
• Some congenital anomalies can be prevented. For example, vaccination, adequate intake of folic acid or iodine through fortification of staple foods or provision of supplements, and adequate antenatal care are keys for prevention.

Fig. 1. Causes of 2.761 million deaths during the neonatal period in 2013, worldwide
Source adapted from WHO 2000-2013 child causes of death

Definition
Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations. Congenital anomalies can be defined as structural or functional anomalies (e.g., metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life.

Causes and risk factors
Although approximately 50% of all congenital anomalies cannot be linked to a specific cause, there are some known causes or risk factors.

Socioeconomic and demographic factors
Although low income may be an indirect determinant, congenital anomalies are more frequent among resource-constrained families and countries. It is estimated that about 94% of severe congenital anomalies occur in low- and middle-income countries, where women often lack access to sufficient, nutritious food and may have increased exposure to agents or factors such as infection and alcohol that induce or increase the incidence of abnormal prenatal development. Further, advanced maternal age increases the risk of chromosomal abnormalities, including Down syndrome, while young maternal age increases the risk of some congenital anomalies.
Genetic factors
Consanguinity (when parents are related by blood) increases the prevalence of rare genetic congenital anomalies and nearly doubles the risk for neonatal and childhood death, intellectual disability and other anomalies in first-cousin unions. Some ethnic communities (e.g., Ashkenazi Jews or Finns) have a comparatively high prevalence of rare genetic mutations, leading to a higher risk of congenital anomalies.

Infections
Maternal infections such as syphilis and rubella are a significant cause of congenital anomalies in low- and middle-income countries.

Maternal nutritional status
Iodine deficiency, folate insufficiency, obesity and diabetes mellitus are linked to some congenital anomalies. For example, folate insufficiency increases the risk of having a baby with a neural tube defect. Also, excessive vitamin A intake may affect the normal development of an embryo or fetus.

Environmental factors
Maternal exposure to certain pesticides and other chemicals, as well as certain medications, alcohol, tobacco, psychoactive drugs and radiation during pregnancy, may increase the risk of having a fetus or neonate affected by congenital anomalies. Working or living near, or in, waste sites, smelters or mines may also be a risk factor, especially if the mother is exposed to other environmental risk factors or nutritional deficiencies.

Prevention
Preventive public health measures delivered through health services decrease the frequency of certain congenital anomalies. Primary prevention of congenital anomalies includes:
• improving the diet of women throughout their reproductive years, ensuring an adequate dietary intake of vitamins and minerals, and particularly folic acid, through daily oral supplements or fortification of staple foods such as wheat or maize flours;
• ensuring mothers abstain from, or restrict, their intake of harmful substances, particularly alcohol;
• controlling preconceptional and gestational diabetes, through counseling, weight management, diet and administration of insulin when needed;
• avoiding environmental exposure to hazardous substances (e.g., heavy metals, pesticides) during pregnancy;
• ensuring that any exposure of pregnant women to medications or medical radiation (e.g., imaging rays) is justified, based on careful health risk–benefit analysis;
• improving vaccination coverage, especially against the rubella virus, for children and women. Rubella can be prevented through childhood vaccination. The rubella vaccine can also be given at least one month prior to pregnancy to women who have not been vaccinated and do not have a history of rubella in childhood;
• increasing and strengthening education of health staff and others involved in promoting prevention of congenital anomalies.

Detection
Health care before (preconception) and around the time of conception (peri-conception) includes basic reproductive health practices, as well as medical genetic screening and counseling. Screening can be conducted during the three periods listed next.
• Preconception screening can be useful to identify people at risk for specific disorders or at risk for passing a disorder onto their children. Screening includes obtaining family histories and carrier screening, and is particularly valuable in countries where consanguineous marriage is common.
• Peri-conception screening: maternal characteristics may increase risk, and screening results should be used to offer appropriate care, according to risk. This may include screening for young or advanced maternal age, as well as screening for use of alcohol, tobacco or other psychoactive drugs. Ultrasound can be used to screen for Down syndrome during the first trimester, and for severe fetal anomalies during the second trimester. Additional tests, and amniocentesis may help in the detection of neural tube defects and chromosomal abnormalities during the first and second trimesters.
• Neonatal screening includes clinical examination and screening for disorders of the blood, metabolism and hormone production. Screening for deafness and heart defects, as well as early detection of congenital anomalies, can facilitate life-saving treatments and prevent progression towards some physical, intellectual, visual or auditory disabilities. In some countries, babies are routinely screened for abnormalities of the thyroid or adrenal glands before discharge from the maternity unit.

Treatment and care
Many structural congenital anomalies can be corrected with paediatric surgery and early treatment can be administered to children with functional problems such as thalassaemia (inherited recessive blood disorders), sickle cell disorders and congenital hypothyroidism (reduced function of the thyroid).
WHO response
In 2010, the World Health Assembly considered a report and adopted a resolution on birth defects. The report describes the basic components for creating a national program for the surveillance, prevention and care of congenital anomalies before and after birth. It also recommends priorities for the international community to assist in establishing and strengthening these national programs.

The WHO Department of Public Health and Environment focuses on a number of activities, and defines interventions, to address the environmental and social determinants of child development. These include children’s unique vulnerabilities to polluted indoor and outdoor air, contaminated water, lack of sanitation, toxicants, heavy metals, waste components and radiation; combined exposures with social, occupational and nutrition factors; and the settings in which children dwell (home, school).

3. OBESITY AND OVERWEIGHT

Overview
Obesity and overweight are defined as abnormal or excessive fat accumulation that presents a risk to health. A crude population measure of obesity is the body mass index (BMI), a person’s weight (in kilograms) divided by the square of his or her height (in metres). A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight.

Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings.

KEY FACTS
• Worldwide obesity has more than doubled since 1980.
• In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.
• 39% of adults aged 18 years and over were overweight in 2014, and 13% were obese.
• Most of the world’s population live in countries where overweight and obesity kills more people than underweight.
• 42 million children under the age of five were overweight or obese in 2013.
• Obesity is preventable.

What are overweight and obesity?
Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person’s weight in kilograms divided by the square of his height in meters (kg/m²).

The WHO definition is:
• a BMI greater than or equal to 25 is overweight
• a BMI greater than or equal to 30 is obesity.

BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals.

Facts about overweight and obesity
Some recent WHO global estimates follow.
• In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.
• Overall, about 13% of the world’s adult population (11% of men and 15% of women) were obese in 2014.
• In 2014, 39% of adults aged 18 years and over (38% of men and 40% of women) were overweight.
• The worldwide prevalence of obesity more than doubled between 1980 and 2014.
• In 2013, 42 million children under the age of five were overweight or obese. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. In developing countries with emerging economies (classified by the World Bank as lower- and middle-income countries) the rate of increase of childhood overweight and obesity has been more than 30% higher than that of developed countries.

Overweight and obesity are linked to more deaths worldwide than underweight. Most of the world’s population live in countries where overweight and obesity kill more people than underweight (this includes all high-income and most middle-income countries).

What causes obesity and overweight?
The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there has been:
• an increased intake of energy-dense foods that are high in fat; and
• an increase in physical inactivity due to the increasingly sedentary nature of many forms of
work, changing modes of transportation, and increasing urbanization.

Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing and education.

**What are common health consequences of overweight and obesity?**

Raised BMI is a major risk factor for noncommunicable diseases such as:

- cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2012;
- diabetes;
- musculoskeletal disorders (especially osteoarthritis - a highly disabling degenerative disease of the joints);
- some cancers (endometrial, breast, and colon).

The risk for these noncommunicable diseases increases, with an increase in BMI. Childhood obesity is associated with a higher chance of obesity, premature death and disability in adulthood. But in addition to increased future risks, obese children experience breathing difficulties, increased risk of fractures, hypertension, early markers of cardiovascular disease, insulin resistance and psychological effects.

**Facing a double burden of disease**

Many low- and middle-income countries are now facing a “double burden” of disease.

- While they continue to deal with the problems of infectious disease and under-nutrition, they are experiencing a rapid upsurge in noncommunicable disease risk factors such as obesity and overweight, particularly in urban settings.
- It is not uncommon to find under-nutrition and obesity existing side-by-side within the same country, the same community and the same household.

Children in low- and middle-income countries are more vulnerable to inadequate pre-natal, infant and young child nutrition. At the same time, they are exposed to high-fat, high-sugar, high-salt, energy-dense, micronutrient-poor foods, which tend to be lower in cost but also lower in nutrient quality. These dietary patterns in conjunction with lower levels of physical activity, result in sharp increases in childhood obesity while undernutrition issues remain unsolved.

**How can overweight and obesity be reduced?**

Overweight and obesity, as well as their related noncommunicable diseases, are largely preventable. Supportive environments and communities are fundamental in shaping people’s choices, making the healthier choice of foods and regular physical activity the easiest choice (accessible, available and affordable), and therefore preventing obesity.

At the individual level, people can:

- limit energy intake from total fats and sugars;
- increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts;
- engage in regular physical activity (60 minutes a day for children and 150 minutes per week for adults).

Individual responsibility can only have its full effect where people have access to a healthy lifestyle. Therefore, at the societal level it is important to:

- support individuals in following the recommendations above, through sustained political commitment and the collaboration of many public and private stakeholders;
- make regular physical activity and healthier dietary choices available, affordable and easily accessible to all - especially the poorest individuals.
- The food industry can play a significant role in promoting healthy diets by:
  - reducing the fat, sugar and salt content of processed foods;
  - ensuring that healthy and nutritious choices are available and affordable to all consumers;
  - practicing responsible marketing especially those aimed at children and teenagers;
- ensuring the availability of healthy food choices and supporting regular physical activity practice in the workplace.

**WHO response**

Adopted by the World Health Assembly in 2004, the WHO Global Strategy on Diet, Physical Activity and Health describes the actions needed to support healthy diets and regular physical activity. The Strategy calls upon all stakeholders to take action at global, regional and local levels to improve diets and physical activity patterns at the population level.

**4. INFANT AND YOUNG CHILD FEEDING**

**Overview**

Undernutrition is estimated to cause 3.1 million child deaths annually or 45% of all child deaths. Infant and young child feeding is a key area to improve child survival and promote healthy growth and
development. The first two years of a child’s life are particularly important, as optimal nutrition during this period lowers morbidity and mortality, reduces the risk of chronic disease, and fosters better development overall.

Optimal breastfeeding is so critical that it could save about 800,000 under-five child lives every year. WHO and UNICEF recommend:
• early initiation of breastfeeding within one hour of birth;
• exclusive breastfeeding for the first six months of life; and
• the introduction of nutritionally-adequate and safe complementary (solid) foods at six months together with continued breastfeeding up to two years of age or beyond.

However, many infants and children do not receive optimal feeding. For example, only about 36% of infants aged 0 - 6 months worldwide are exclusively breastfed over the period of 2007 - 2014.

**KEY FACTS**
- Every infant and child has the right to good nutrition according to the Convention on the Rights of the Child.
- Undernutrition is associated with 45% of child deaths.
- Globally in 2013, 161.5 million children under five were estimated to be stunted, 50.8 million were estimated to have low weight-for-height, and 41.7 million were overweight or obese.
- About 36% of infants 0 - 6 months old are exclusively breastfed.
- Few children receive nutritionally adequate and safe complementary foods; in many countries less than a fourth of infants 6 - 23 months of age meet the criteria of dietary diversity and feeding frequency that are appropriate for their age.
- About 800,000 children’s lives could be saved every year among children under five, if all children 0 - 23 months were optimally breastfed.

Recommendations have been refined to also address the needs for infants born to HIV-infected mothers. Antiretroviral drugs now allow these children to exclusively breastfeed until they are six months old and continue breastfeeding until at least 12 months of age with a significantly reduced risk of HIV transmission.

**Breastfeeding**

Exclusive breastfeeding for six months has many benefits for the infant and mother. Chief among these is protection against gastrointestinal infections which is observed not only in developing but also industrialized countries. Early initiation of breastfeeding, within one hour of birth, protects the newborn from acquiring infections and reduces newborn mortality. The risk of mortality due to diarrhea and other infections can increase in infants who are either partially breastfed or not breastfed at all.

Breast milk is also an important source of energy and nutrients in children aged 6 - 23 months. It can provide half or more of a child’s energy needs between the ages of six and 12 months, and one third of energy needs between 12 and 24 months. Breast milk is also a critical source of energy and nutrients during illness, and reduces mortality among children who are malnourished.

Adults who were breastfed as babies are less likely to be overweight/obese. Children and adolescents that have been breastfed perform better on intelligence tests. Breastfeeding also contributes to the health and well-being of mothers; it reduces the risk of ovarian and breast cancer and helps space pregnancies—exclusive breastfeeding of babies under six months has a hormonal effect which often induces a lack of menstruation. This is a natural (though not failsafe) method of birth control known as the Lactation Amenorrhea Method.

Mothers and families need to be supported for their children to be optimally breastfed. Actions that help protect, promote and support breastfeeding include:
• adoption of policies such as the International Labour Organization’s Maternity Protection Convention 183 and Recommendation No. 191, which complements Convention No. 183 by suggesting a longer duration of leave and higher benefits;
• the International Code of Marketing of Breast-milk Substitutes and subsequent relevant World Health Assembly resolutions;
• implementation of the Ten Steps to Successful Breastfeeding specified in the Baby-Friendly Hospital Initiative, including:
  • skin-to-skin contact between mother and baby immediately after birth and initiation of breastfeeding within the first hour of life;
  • breastfeeding on demand (that is, as often as the child wants, day and night);
  • rooming-in (allowing mothers and infants to remain together 24 hours a day);
  • not giving babies additional food or drink, even water, unless medically necessary;
• provision of supportive health services with infant and young child feeding counseling during all contacts with caregivers and young children, such as during antenatal and postnatal care, well-child and sick child visits, and immunization; and
• community support, including mother support groups and community-based health promotion and education activities.
Complementary feeding

Around the age of six months, an infant’s need for energy and nutrients starts to exceed what is provided by breast milk, and complementary foods are necessary to meet those needs. An infant of this age is also developmentally ready for other foods. If complementary foods are not introduced around the age of six months, or if they are given inappropriately, an infant’s growth may falter. Guiding principles for appropriate complementary feeding are:

• continue frequent, on-demand breastfeeding until two years of age or beyond;
• practise responsive feeding (e.g., feed infants directly and assist older children. Feed slowly and patiently, encourage them to eat but do not force them, talk to the child and maintain eye contact);
• practise good hygiene and proper food handling;
• start at six months with small amounts of food and increase gradually as the child gets older;
• gradually increase food consistency and variety;
• increase the number of times that the child is fed: 2 - 3 meals per day for infants 6 - 8 months of age and 3 - 4 meals per day for infants 9 - 23 months of age, with 1 - 2 additional snacks as required;
• use fortified complementary foods or vitamin-mineral supplements as needed; and
• during illness, increase fluid intake including more breastfeeding, and offer soft, favourite foods.

Feeding in exceptionally difficult circumstances

Families and children in difficult circumstances require special attention and practical support. Wherever possible, mothers and babies should remain together and get the support they need to exercise the most appropriate feeding option available. Breastfeeding remains the preferred mode of infant feeding in almost all difficult situations, for instance:

• low-birth-weight or premature infants;
• HIV-infected mothers;
• adolescent mothers;
• infants and young children who are malnourished; and
• families suffering the consequences of complex emergencies.

HIV and infant feeding

Breastfeeding, and especially early and exclusive breastfeeding, is one of the most significant ways to improve infant survival rates. However, HIV can pass from mother to child during pregnancy, labour or delivery, and also through breast milk. In the past, the challenge was to balance the risk of infants acquiring HIV through breastfeeding versus the higher risk of death from causes other than HIV, in particular malnutrition and serious illnesses such as diarrhea and pneumonia, among HIV-exposed but still uninfected infants who were not breastfed.

The evidence on HIV and infant feeding shows that giving antiretroviral drugs (ARVs) to HIV-infected mothers can significantly reduce the risk of transmission through breastfeeding and also improve her health. This enables infants of HIV-infected mothers to be breastfed with a low risk of transmission (1 - 2%). HIV-infected mothers and their infants living in countries where diarrhea, pneumonia and malnutrition are still common causes of infant and child deaths can therefore gain the benefits of breastfeeding with minimal risk of HIV transmission.

Since 2010, WHO has recommended that mothers who are HIV-infected take ARVs and exclusively breastfeed their babies for 6 months, then introduce appropriate complementary foods and continue breastfeeding up to the child’s first birthday. Breastfeeding should only stop once a nutritionally adequate and safe diet without breast milk can be provided.

Even when ARVs are not available, mothers should be counselled to exclusively breastfeed for six months and continue breastfeeding thereafter unless environmental and social circumstances are safe for, and supportive of, feeding with infant formula.

WHO’s response

WHO is committed to supporting countries with implementation and monitoring of the “Comprehensive implementation plan on maternal, infant and young child nutrition”, endorsed by Member States in May 2012. The plan includes 6 targets, one of which is to increase, by 2025, the rate of exclusive breastfeeding for the first 6 months up to at least 50%. Activities that will help to achieve this include those outlined in the “Global Strategy for Infant and Young Child Feeding”, which aims to protect, promote and support appropriate infant and young child feeding.

WHO has formed a Network for Global Monitoring and Support for Implementation of the International Code of Marketing of Breast-milk Substitutes and subsequent relevant WHA resolutions called NetCode. The goal of NetCode is to protect and promote breastfeeding by ensuring that breastmilk substitutes are not marketed inappropriately. Specifically, NetCode is building the capacity of Member States and civil society to strengthen national Code legislation, continuously monitor adherence to the Code, and take action to stop all violations. In addition, WHO and UNICEF have developed courses for training health workers to provide skilled support to breastfeeding mothers, help them overcome problems, and monitor the
growth of children, so they can identify early the risk of undernutrition or overweight/obesity.

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WHO provides simple, coherent and feasible guidance to countries for promoting and supporting improved infant feeding by HIV-infected mothers to prevent mother-to-child transmission, good nutrition of the baby, and protect the health of the mother.

¹Black RE, Victora CG, Walker SP, and the Maternal and Child Undernutrition and Overweight in low-income and middle-income countries. Lancet 2013; published online.

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

5. FOUR WAYS TO REDUCE HEALTH RISKS FROM CLIMATE POLLUTANTS

Overview
A new WHO report highlights the urgent need to reduce emissions of black carbon, ozone and methane - as well as carbon dioxide - which all contribute to climate change. Black carbon, ozone and methane - frequently described as short-lived climate pollutants (SLCPs) - not only produce a strong global warming effect, they contribute significantly to the more than seven million premature deaths annually linked to air pollution.

The report, Reducing global health risks through mitigation of short-lived climate pollutants, produced in collaboration with the Climate and Clean Air Coalition to Reduce Short-Lived Climate Pollutants, reveals that interventions to cut SLCPs can reduce disease and death and contribute to food security, improve diets and increase physical activity.

Reducing emissions of short-lived climate pollutants (SLCPs), which produce strong warming effects, but only persist in the atmosphere for periods ranging from days to about a decade, can provide health benefits in three key ways:

- directly from reduced air pollution and related ill-health;
- indirectly from reduced ozone and black carbon effects on extreme weather and agricultural production (affecting food security);
- and from other types of health benefits that are not associated with air pollution but may accrue as a result of certain SLCP mitigation actions, such as improved diets or more opportunities for safe active travel and physical activity.

This report reviews a range of strategies and policies for action covering sectors such as urban planning, transport, household energy and building design, food production and consumption, power generation, industry, and waste management. Reducing SLCP emissions can yield near-term benefits to health making measures particularly attractive to policy-makers, as well as slowing the pace of climate change over the next few decades.

“For the first time, this report recommends actions that countries, health and environment ministries, and cities can take right now to reduce emissions, protect health and avoid illness and premature deaths, which often take the greatest toll on the most vulnerable.”

The report builds on a 2011 assessment by the UN Environment Program and World Meteorological Organization that estimated that a global deployment of 16 SLCP reduction measures would prevent an average of 2.4 million premature deaths annually by 2030. New estimates could raise that to 3.5 million lives saved annually by 2030, and between 3 - 5 million lives per year by 2050. These latest projections take into account, WHO’s latest data on deaths linked to air pollution as well as some new SLCP measures.

“Quick action to reduce black carbon, methane and other ozone precursors are much needed now,” says Helena Molin Valdés, head of the UNEP-hosted CCAC.

“We know that the sooner we start reducing these pollutants the sooner we will relieve the pressures on climate and human health.”

Top actions for health and climate benefits
WHO rated more than 20 available and affordable measures to mitigate short-lived climate pollutants, including vehicle emissions standards, capturing landfill gas, switching from fossil fuels to renewables, reducing food waste and improving household cooking fuels, to see which have the greatest potential to improve health, reduce SLCP emissions and prevent climate change.

Four interventions rated medium to high in all three categories.

- Reducing vehicle emissions by implementing higher emissions and efficiency standards could reduce black carbon and other co-pollutants from fossil fuels, improve air quality and reduce the disease burden attributable to outdoor air pollution.
- Policies and investments that prioritize dedicated rapid transit such as buses and trains and foster safe pedestrian and cycle networks can promote
multiple benefits, including: safer active travel and reduced health risks from air and noise pollution, physical inactivity, and road traffic injuries.

- Providing cleaner and more efficient stove and fuel alternatives to the approximately 2.8 billion low-income households worldwide dependent on primarily wood, dung and other solid fuels for heating and cooking, could reduce air pollution-related diseases and reduce the health risks and time invested in fuel-gathering.

- Encouraging high and middle-income populations to increase their consumption of nutritious plant-based foods could reduce heart disease and some cancers, and slow methane emissions associated with some animal-sourced foods.

“The health benefits that may be obtained from these strategies are far larger than previously understood, and they can be enjoyed immediately and locally,” says Maria Neira, WHO Director, Department of Public Health, Environmental and Social Determinants of Health. “The environment and health sectors can now prioritize interventions to meet both of their goals—preventing climate change and ensuring good health.”

**What are SLCPs?**

Short-lived climate pollutants (SLCPs), found in ambient (outdoor) and household air pollution, produce strong climate change effects but only remain in the atmosphere briefly; for a few days to about a decade. The short life span of SLCP’s means that assertive action now to reduce emissions can rapidly improve both air quality as well as slowing the rate of near-term climate change.

The main SLCPs of direct concern to health include black carbon (or ‘soot’), methane and ozone, which all contribute to both health-harmful air pollution and global warming. Black carbon (BC) makes up a significant portion of fine particulate matter, the air pollutant most associated with premature death and morbidity. Ozone has significant adverse impacts on respiratory health, and methane contributes to ozone formation.

**Where do these pollutants come from?**

Open fires, (including wildfires, deliberate forest/brush burning, and burning of urban and crop waste), comprise the largest single source of black carbon emissions. Fuel combustion in residential and commercial buildings, as well as transport, account for approximately 80% of black carbon emissions from human activities related to energy production and use. Emissions from diesel, biomass and kerosene combustion are among the sources with the heaviest black carbon concentrations, and accordingly have been identified as priority sources for reducing emissions that contribute to near-term climate change. Particulate emissions from other sources, such as coal-fired power plants, are also a source of black carbon emissions, but here BC is co-emitted with other pollutants that have a climate “cooling” effect so that mitigation in this sector would have less of an impact on near-term climate change. In health terms, however, mitigation efforts that reduce fine particulates from other sources can, of course, be beneficial, and may also may reduce CO₂ and thus longer term climate change.

**What is the impact of SCLPs on health?**

Since SLCPs contribute to ambient levels of ozone and PM2.5, SCLP emissions are directly associated with cardiovascular and respiratory diseases, including heart disease, pulmonary disease, respiratory infections and lung cancer. SCLP emissions thus contribute significantly to the more than 7 million premature deaths annually linked to air pollution.

Indirectly, the SLCP’s ozone and black carbon reduce plant photosynthesis and growth, thus decreasing agricultural yields, which in turn threatens food security. They also affect weather patterns and the melting of snow and ice, which may harm and endanger health through extreme weather events such as floods.

**Can SLCP emissions be reduced?**

Yes, SLCPs are emitted from a variety of sources in the transport, agriculture, waste management, residential and industrial sectors, so there a range of mitigation opportunities that exist that can be highly beneficial for health. In fact, addressing SLCP’s has distinct advantages insofar as health benefits from many measures can be enjoyed in the near term, and along with slowing the rate of near-term climate change.

**What are the mitigation actions?**

Four strategies were identified which appear to have the largest aggregate potential for health and SLCP mitigation benefits as well as reducing CO₂.

- Policies and investments that prioritize dedicated rapid transit and walking and cycling networks in compact cities can promote health in multiple ways, including reduced air pollution exposures, reduced injury risks and greater opportunities for safe active travel.

- Encouraging healthier diets rich in plant-based foods and low in red and processed meats among affluent populations at risk of a range of diet-related noncommunicable diseases will have a positive effect on health and will also reduce emissions.

- Provide and promote the use of clean and efficient cook-stoves and fuels, and cleaner energy sources, to the approximately 2.8 billion low-income
households that currently rely on solid fuels for heating and cooking.

- Reducing vehicle emissions of both particulate matter as well as ozone precursors (e.g., NOₓ) by implementing stricter vehicle and fuel emissions and efficiency standards.

Along with these four, improved waste management strategies, more energy efficient homes and buildings, phasing out kerosene lamps and greater reliance on clean light and power sources, using including renewable energy, for homes and health clinics, cleaner brick industries and coke ovens, etc., are also identified to contribute better health conditions.

**In what ways will reducing emissions be beneficial for health?**

In summary, there are three key ways in which reducing emissions of SLCPs can provide health benefits:

1. directly, it will reduce air pollution exposures and related diseases;
2. indirectly, the negative effects that ozone and black carbon have on weather and food production, which affect food security, will be reduced;
3. As a result of certain SLCP mitigation actions, such as improved transport systems, healthier diets, or better waste management, other health benefits may also be obtained, such as improved chances for physical activity, less risk of traffic injury, reduced risks of diet-related chronic diseases, or reduced exposure to waste and sanitation-related health risks.

**Why should we act now?**

There is increasing evidence that direct exposure to certain SLCPs is associated with ill-health. Controlling emissions of the SLCPs or their precursors could save lives through improved air quality, reduce expected warming by 0.5 °C or more over the next few decades and contribute to food security.

**Why is it important for policymakers?**

Mitigation measures are highly compatible with the immediate development priorities of local and national policymakers since they reduce harmful air pollution, make cities healthier and more attractive to live and work, and also provide greater opportunities for healthier lifestyles.

**What can I do?**

Some simple lifestyle choices coming from individuals can have potential benefits for reducing emissions and contributing to better health. The choices we make on what we eat, how we travel, and the energy sources we use, for example, choosing to take public transport over private cars and being active by walking or cycling will contribute to the reduction of emissions and noise pollution while increasing health and well-being.

**What else is being addressed?**

Aside from the large benefits for public health, many of the health-enhancing strategies for reducing SLCP emissions can also lead to substantial co-reductions in CO₂ emissions and therefore, help mitigate both near- and long-term climate change.

**The way forward**

Release of the WHO report on 22 October 2015 is a significant step in its ongoing work to prevent diseases and deaths related to air pollution – and towards achieving the new global health goal. Target 3.9 aims to “By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination.”

Evidence from previous WHO studies on healthy transport already suggest that shifts to mass transport and the introduction of safe walking and cycling networks are relatively inexpensive when compared with the loss of life and costs of treating people for air-pollution related illnesses, traffic injuries and diseases related to physical inactivity.

**For more information contact:** Christian Lindmeier,
Communications Officer, WHO,
Telephone: +41 22 791 1948, Mobile: +41 79 500 6552,
E-mail: lindmeierc@who.int

Nada Osseiran, WHO Department of Public Health,
Environmental and Social Determinants of Health,
Mobile: +41 79 445 1624, Telephone: +41 22 791 4475,
E-mail: osseirann@who.int

Dr Margaret Harris, Communications Officer,
WHO. Tel: +41 227 911 646; Mobile: +41 796 036 224.
E-mail: harrism@who.int
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