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EDITORIAL

REVIEW ARTICLE

ORIGINAL ARTICLES

EXPERIMENTAL MEDICINE

CASE REPORTS

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Continued inside

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C O N T E N T S

Continued from cover

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Book

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Book chapter

Philips SJ, Whisnam JP. Hypertension and stroke, In: Laragh JH, Bremner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd Ed. New York: Raven Press; 1995. p 465-478.

Weblinks

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

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Congratulations and best wishes to all our contributors and collaborators.

Professor Adel Kahader Ayed

Editor

Editorial

Primary Spontaneous Pneumothorax: An Update

Adel Khader Ayed

Kuwait Medical Journal 2009, 41 (1) 1 - 2

Primary spontaneous pneumothorax (PSP) is defined as a pneumothorax occurring spontaneously in a person without (known) underlying lung disease. PSP is common in young, tall, thin people without clinically apparent underlying lung disease. The incidence is estimated at 18 - 28 per 100,000 for males and 1.2 - 6 per 100,000 for females[1]. The cause of PSP is unknown, although it is mostly attributed to the rupture of a subpleural bleb or bulla[2]. The etiology of bulla and bleb formation is obscure. Subpleural blebs or bullae, which are designated as emphysema-like changes (ELCs), are seen in 75-100% of patients with PSP even in non-smoking PSP patients[3]. Macroscopic findings in the PSP group, according to the classification of Vandeschueren are: type I (normal findings); type II (pleuropulmonary adhesions); type III (bullae/blebs less than 2 cm diameter); and type IV (bullae >2 cm diameter) cases[3]. In a study of 94 patients treated with video-assisted thorcoscopic surgery (VATS), 67 patients (71%) had a clear bullae in type III and IV. In 15 (16%) cases, (type II) pleuropulmonary adhesions were identified and in only 12 (13%) patients (type I) did thoracoscopy fail to reveal any abnormality[4]. With the development of VATS, blebs and bulla during thoracoscopy were detected in more than 76% of patients[3].

The actual site of air leakage, however, can be located at the ELCs which may be ruptured in some cases or elsewhere at the lung surface ("Pleural Porosity"). True visible air leaks at the site of the ELCs have been observed in a highly variable percentage of PSP patients undergoing thoracoscopy or thoracotomy[5]. Ayed *et al*[4] observed 94 patients with PSP who underwent VATS; leaking or ruptured blebs were seen in 24 patients (26%) at thoracoscopy. Light microscopy studies have shown that only 25% of the ELCs in PSP are truly ruptured, whereas in rest of the cases other lesions were present, referred to as 'Pleural Porosity'[3, 6]. This porosity consists of mesothelial cell proliferation disrupture and elastofibrosis. Light microscopy has shown the actual site of air leakage at the site of ELCs in 15 patients (16%) and elsewhere on the lung surface in five other patients (5%)[4].

A variety of pathologic changes were seen at the lung apices. These changes include ELCs, airway inflammation, and emphysema. In a recent study, 74 out of 94 patients (79%) who required surgical intervention for persistent or recurrent PSP had a diagnosis of ELCs. Irregular emphysema, which was the most common type of emphysema identified, was seen in 14 patients[4]. The same study showed a pleural inflammatory reaction in patients with PSP, which is characterized by increases in parietal pleural tissue eosinophils and neutrophils and associated with pleural fibrosis. Another interesting observation in patients with PSP is that all patients had microscopic evidence of underlying lung disease in the excised apex of the lung. These results suggest that these lesions are the result of a degenerative process in the lung[4,7]. It seems important to care for the apex of the lung because spontaneous pneumothorax originates from dystrophic areas located in the apices of the lung, and not from any kind of pleural disease. These observations support the presence of underlying lung disease in the etiology of PSP. In addition , the inflammatory changes in the distal airways of smokers suggest that there is some degree of endobronchial obstruction involved in the pathogenesis of PSP. Endobronchial obstruction due to accumulation of inflammatory cells between the pulmonary parenchyma and the bronchial tree can induce overpressure in alveolar tissue which can lead to rupture of pulmonary parenchyma[3]. Light and electron microscopy of tissue obtained during surgery for PSP have revealed obstruction and stenosis of the distal airways due to bronchial wall inflammation and peribronchial fibrosis[3,6]. These findings suggest an obstruction check-valve mechanism, with air trapped in small airways because of the narrowed inflamed small airways, as the cause of PSP. Autofluorescence

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thoracoscopy allowed visualization of extensive lung areas with subpleural fluoreseine accumulation suggesting the presence of substantial areas of lung parenchymal abnormality[8].

The therapeutic challenge in the management of PSP is to prevent recurrence because understanding the exact pathophysiology of PSP in an individual is important. The recurrence prevention treatment may differ accordingly. The recurrence technique focuses on the treatment of lung abnormalities such as ELCs or treatment of pleura. In type III and IV cases, VATS blebectomy / bullectomy plus apical pleurectomy or pleurodesis is effective[4,8]. Persistent air leak and recurrence rate of PSP were higher in type I cases after the excision of the apex and apical pleurectomy. This may indicate that the lung apices are not the actual site of the air leak; or air leakage occurs elsewhere at the visceral pleura. Therefore, simple apical excision and apical pleurectomy in these cases are not sufficient and perhaps additional talc poudrage to induce more pleural symphysis might be indicated. Other maneuvers to create pleurodesis and prevent recurrences include parietal pleural abrasion with dry gauze or any other rubbing material, and chemical, laser or electrocautery pleurodesis[8].

Global recurrence rates ranges from zero to 10%[8]. Many of these recurrences are due to failures of the method of treatment. Clipping, ligation and looping of blebs were associated with a recurrence of 11 - 22%[8]. The procedure of choice is stapling of blebs and bullae, or wedge resection of the tip of the lung when lesions are not identified, and pleural symphysis procedure such as mechanical abrasion, apical pleurectomy or patchy electrocoagulation of the parietal pleura. These procedures result in a recurrence rate of 0 - 5%[3-5,8]. In an uncontrolled series of 94 patients, the recurrence rate was 3.1% with a mean follow-up of 48 months[4].

Pleural procedures alone are associated with higher recurrence rates[8]. One reason for recurrence is failure to recognize the site of the air leak in the absence of blebs. Unrecognized blebs or inadequate resection of the diseased portion of the lung may also contribute. Another factor is inadequate pleurodesis, especially in between the tracer sites. These failures suggest that gauze pleural abrasion is probably less effective than apical pleurectomy. Most recurrences occurred within the first month of the operation. Long-term follow-up did not add to the rate of recurrence[4].

Treatment of recurrences varies according to the size of pneumothorax and the presence of air leaks after insertion of chest tubes. For limited pneumothorax in stable patients, rest and observation are recommended. When reoperation is necessary, both repeat VATS and thoracotomy have been performed. In 50% of cases, residual bullae or air leaks are found; these are usually stapled and pleural symphysis procedure is added. When no blebs are identified, symphysis pleurodesis is performed[8].

In conclusion, in all cases of PSP, pathomorphologic changes were observed.

Even when no apical blebs or bullae are identified, pathology of the resected apex virtually always identifies paraseptal emphysema on such specimens. The actual site of air leakage was seen in some patients at VATS and at microscopic examination. VATS stapling of identified blebs or apex of the upper lobe and apical pleurectomy represent the standard treatment for recurrent or persistent PSP. In the absence of blebs or bullae, additional chemical pleurodesis might be indicated.

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Review Article

Prevention of Obesity Using Low Carbohydrate Ketogenic Diet

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ABSTRACT

This review focuses on the effect of low carbohydrate ketogenic diet on obese subjects presenting with various metabolic syndromes. Here, we provide data from our laboratory and from various other investigators on the therapeutic effectiveness of ketogenic diet on obese subjects. In this review we provide the rationale behind using ketogenic diet as a treatment of obesity and its beneficial role in neurodegenerative / neurological disorders, diabetes, hyperlipidemia, coronary diseases, cancer *etc.* Administering ketogenic diet for a relatively longer period did not produce any significant side effect. Therefore, based on the data presented in this review, it is recommended that it is safe to use ketogenic diet for a longer period of time for obesity and associated disorders.

KEY WORDS: coronary diseases, diabetes, hyperlipidemia, ketogenic diet, obesity

INTRODUCTION

Although, historically obesity has been considered as a sign of a prosperous and wealthy society, today obesity has become a major health problem in both developed and developing countries. Obesity has been described as a disease entity since 1700s. Currently obesity levels are increasing at a remarkable level all over the world. Data from a recent survey by the US Center for Disease Control indicates that 66% of the US population are overweight, with 32.3% having a body mass index (BMI) of more than 30 kg/m^2[1]. It is estimated that about 300,000 people die each year from obesity related diseases[1]. A similar trend is observed in Kuwait and other Middle East countries[2].

CLASSIFICATION OF OBESITY

Obesity has been defined by body mass index (kg/m^2) and waist circumference. According to the current classification of the World Health Organization (WHO), body mass index (BMI) greater than 25 is considered overweight[3]. An adult who has a BMI of 30 or higher is considered obese. Obesity is further classified into Class I (BMI > 30), Class II (BMI > 35) and Class III (BMI > 40) obesity. In addition to BMI, increased risk of obesity associated metabolic disorders is found in men with waist circumferences greater than or equal to 102 cm and in women with 88 cm[1]. This classification of obesity is primarily based on a Western population perspective[4]. Therefore, it is necessary to redefine obesity from an Asian or Middle Eastern viewpoint. In Asians, overweight has been suggested to start at BMI 23 and also lower waist circumference cut-offs for men and women have been recommended[4].

HEALTH CONSEQUENCES OF OBESITY

Problems related to obesity affects almost every aspect of life[5-6]. The rise in obesity and its complications is a threat to global healthcare system. The obesity epidemic of the world is out of control and none of the current measures show any improvement in reversing this global crisis. Early measures to curb obesity and public awareness on

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Table 1: Obesity associated risks

Mild risk	Moderate risk	Severe risk
• Low back pain • Impaired fertility • Increased risk during anesthesia • fetal defects due to maternal obesity • Cancer	• Coronary heart disease • Hyperuricaemia • Gout • Osteoarthritis • Complications of pregnancy	• Diabetes • Dyslipidaemia • Hypertension • Gall bladder disease • Sleep apnoea • Breathlessness

obesity associated diseases are the only way towards achieving a sustainable health service. Along with the appropriate measures taken to prevent obesity, priority should be given to the treatment of obesity related diseases. The health consequences of obesity can be categorized into mild, moderate and severe types depending on the risk involved (Table 1).

CONTRIBUTING FACTORS TOWARDS OVERWEIGHT AND OBESITY

Obesity results from the interplay between genes and environment. Both genes and behavior may be needed for a person to become overweight. Other factors that regulate body weight are the diet preferences and the number of calories consumed. One of the genetic components of obesity is insulin resistance which is the probable common pathway for metabolic syndrome. It has been shown that diet choices and physical activity are the major contributing factors towards overweight and obesity. Caloric intake must be equal to the caloric expenditure to maintain a healthy body weight. Calorie, the unit of energy is defined as the amount of heat needed to raise the temperature of one gram of water by one degree Celsius at sea level. By eating roughly the same number of calories that the body requires, the body weight can be maintained in a stable condition. Obviously, weight gain occurs when more calories are taken than the body requires. The extra calories taken in are stored as fat within the body. However, this fact is true only when eating a lot of carbohydrate along with fat. On a diet with controlled amounts of carbohydrate, the body will switch from using glucose to fat for producing energy. This means that a person on low carbohydrate ketogenic diet (LCKD) can take in as much calories and still loose weight. In other words, a person while consuming 3,000 calories on LCKD will loose weight whereas taking in the same calories on a low-fat high carbohydrate diet will gain weight. So the assumption that the only way to lose weight is to strictly control the intake of calories needs to rewritten based on the type of diet. Furthermore, while on LCKD diet the appetite is usually diminished and a person will eat only fewer calories. Hence persons on LCKD will have to burn more fat for producing energy, which will lead to more weight loss.

Another factor that needs to be mentioned is the outcome of certain diet programs that restrict calorie intake. In such circumstances where diets with restricted calories are taken, so as to conserve energy, the overall metabolism in the body shifts into a slow survival mode. But after certain period, when it becomes inevitable for the person on the low calorie diet to go back to a higher-calorie diet, the body metabolism will still remain in its slow survival mode of burning calories slowly. Hence it becomes quite difficult to continue or maintain weight loss in such situations.

OBESITY IN RELATION TO DIET PREFERENCES

Since obesity is the accumulation of excess of body fat, excessive fat intake has been discouraged. Less fat and exercise had become the slogan against obesity to be fit physically and maintain a healthy body. Well, for generations people have tried this recipe of low fat diet, yet they still get obese. Therefore, what we blindly believe about high carbohydrate diet could be completely baseless.

Various researchers have pointed out the bad effects of a high carbohydrate diet. It is the root cause of various chronic diseases. Several studies[7-18] have shown that a diet with a high glycemic load is independently associated with accelerated aging, development of cardiovascular diseases, type II diabetes and certain forms of cancer[7-9].

The glycemic index is a rating system for foods based on their ability to raise the level of blood glucose within two hours of their consumption[19]. When foods of higher glycemic index are eaten there is a rapid release of glucose into the bloodstream. The glycemic index of pure glucose or white bread is arbitrarily scored as 100[20]. Foods with high glycemic index induce a rapid release of insulin[19]. Thus eating foods with a high glycemic index lead to higher levels of circulating insulin. This rapid surge in insulin release can cause a relative hypoglycemic period within the postprandial period. The reactive hypoglycemia thus developed with foods of lower fat and higher carbohydrate content stimulates the appetite and thus leads to obesity[21]. The hyperinsulinemia developed following the consumption of foods with high glycemic index has been implicated in creating atherosclerotic plaques, that can lead to heart disease[22]. Insulin increases salt and water retention, a mediator of high blood pressure and correlates with high levels of triglycerol and low levels of high density lipoprotein (HDL) cholesterol. Now it is evident that high carbohydrate diets increase fasting

Table 2: Recommended and restricted food in ketogenic diet[66]

Recommended Food			Fully Restricted Food	
Proteins	**Vegetables/fruits**	**Oil**	**Carbohydrates**	**Fruits/drinks**
Fish: Tuna,Sardine Prawns, Shrimps. Lobster **Meat:** Kababs, Sausages, Minced **Poultry:** Chicken, Eggs **Cheese:** Full fat cheese	Spinach, Watercress, Eggplant, Parsley, Mulberry, Coriander, Mint, Artichoke, Okra, Cabbage, Mushroom, Avocado, Leek, Carrot, Radish, Celery, Cauliflower, Green pepper, Lettuce, Cucumber, Tomato, 10-15 olives/day, Lemon, Strawberry -6/day, Avocado, Berries-10/day	Olive oil (5 tablespoon, added to the salad), Flax seed oil	Flour, Potato, Macaroni Spaghetti, Noodles, Bread, Rice, Sugar, Sweets, Honey, Cakes	All fruit juices All soft drinks

plasma triglycerol concentrations[23-27] and decrease HDL cholesterol concentrations[28-30]. These changes are associated with enhanced atherogenesis[31]. However, it is found that short-term ketogenic diets improve the lipid disorders that are characteristic of atherogenic dyslipidemia[32]. Furthermore, high insulin levels lead to increased risk of breast cancer and polycystic ovarian syndrome[6,19,33]. In addition, other evidence indicates that consumption of a high–glycemic-index diet is associated with a higher risk of diabetes.

Excess sugar in the bloodstream also leads to the production of free radicals. Free radicals increase significantly one hour after sugar consumption and more than double after two hours. It has been proven that disrupting the oxidant-antioxidant status of the cell will lead to various diseases of the body[33]. Furthermore, increased sugar decreases the blood levels of vitamin E, which leads to a decrease in the natural ability of the body to fight against free radical damage.

Carbohydrates increase levels of triglycerol, total cholesterol, and low density lipoprotein (LDL) and decreases HDL cholesterol. High ratio of triglycerol to HDL has a 16-fold greater incidence of coronary events than those with the low ratio[10.19,22,32]. In several studies, insulin, insulin-like growth factors and carbohydrates were identified as risk factors for cancer. It is quite reasonable to believe that sugar contributes to the growth and metastasis of cancer since cancer cells utilize sugar as their energy source. In other studies it was found that sugar is a causative factor in kidney disease, liver disease and shortened life span. Although there is cumulative scientific evidence to show that high carbohydrate diets can cause more harm than previously thought, we are still unwilling to accept this fact.

Since the 1980's calories from fat intake dropped from 34 to 8%. However, no change in the trend of obesity has been noticed. Interestingly, even after all this; the negative image of fat is still in our mind. In fact, contrary to the common belief, high fat diet has certain therapeutic values. Since 1921, high fat diet was used as an effective alternative therapy to control intractable seizures[34]. In some cases, high fat diet was found to be far better than modern anticonvulsants. The common argument against the consumption of high-fat diet is that it causes obesity. However, recent studies show that the high fat diet can cure obesity. Since obesity results from genetic and environmental influences, an individualized approach probably is the best solution for tackling the obesity problems. Therefore, a low-carbohydrate diet combined with an exercise program, in our experience, can help selected patients to safely achieve weight loss and overcome several obesity associated diseases. As mentioned earlier, since lower insulin levels and less hunger are the physiologic effects of consuming foods with low–glycemic-index, persons who take in low-carbohydrate diets could successfully lose their weight. Furthermore, there is an increased calorie use *via* ketogenesis. Therefore, LCKD is a reasonable alternative for body weight loss for persons who are willing to adhere to this diet. Table 2 gives a brief list of recommended and restricted food in ketogenic diet.

Low carbohydrate ketogenic diets

LCKD is not new to our society. Even early man's prehistoric diets may have been low carbohydrate ketogenic diets[35]. Prior to its use as a diet for obesity, LCKD have been used in the treatment of diabetes[36] and pediatric epilepsy[34]. Also, studies on the therapeutic role of LCKD in obesity are not new at all. Since 1955, scientists were experimenting on the concept that fat can be eaten *ad libitum* and still induce weight loss in obese subjects. A high-fat diet changes the body's metabolism to a new direction. Incomplete oxidation of fatty acids by the liver, results in the accumulation of ketone bodies in the body. The condition in which ketone bodies are formed in excess of the body's ability to metabolize them is called ketosis. Since high-fat diet causes ketosis, they are generally called as ketogenic diets. Ketosis has a significant influence on suppressing hunger. Thus, a ketogenic diet is a good regulator of the body's calorie intake and it is the body's natural adaptation to starvation. However, this mild ketosis has been always confused by the

general public with the dangerous ketoacidosis which is associated with untreated type 1 diabetes. But these two conditions are quite different and virtually opposite. Diabetic ketoacidosis has high blood sugar while ketosis has a high blood level of ketone bodies. Is ketosis safe? If ketosis was bad for health, why does nature switch on to a situation similar to that of administering a ketogenic diet? Well, everyone approaches ketogenesis during the sleep portion of the diurnal cycle. Above all, who can ignore the fact that mother's milk, which has a high fat content, is the best natural food formula taken in during human development? It is also interesting to note that no species could have survived millions of years, if its members could not tolerate occasional brief periods of natural starvation, which results in ketosis.

WHAT ARE KETONE BODIES?

Ketone bodies result from the partial oxidation of free fatty acids and are synthesized only in the mitochondria of liver cells. There are three types of ketone bodies. They are: acetoacetate (AcAc), ß-hydroxybutyrate (BHB), and acetone. Ketone bodies are always being produced under normal dietary conditions but in amounts that are too small to cause any metabolic effects[37]. Triacylglycerol (TAG) stored in fat tissue breaks down into glycerol and three fatty acid molecules. This process is lipolysis and is regulated by hormones like glucagon, epinephrine *etc*. These hormones activate the hormone-sensitive lipase (HSL) that hydrolyzes fatty acid from carbon atom 1 and / or 3 of TAG. The remaining fatty acids are removed by other lipases that are specific for diacylglycerol or monoacylglycerol[38].

Fatty acids are classified into short-medium chain fatty acids consisting of 12 carbons or less and long chain fatty acids. Medium chain fatty acids are found in the maternal milk and in medium chain fatty acid oils. The free fatty acids that diffuse from adipose cells either bind with albumin in the blood or remain as free fatty acids. The albumin bound fatty acids are transported to other tissue to be oxidized and the unbound free fatty acids present in the blood reach the liver[38, 39]. The medium chain fatty acids enter the liver without any transporter whereas the long chain fatty acids, the major precursor for ketone bodies, need a special transporter called carinitine to enter the mitochondrial matrix and become oxidized[40].

The medium chain fatty acids become activated to fatty acyl CoA and undergo ß-oxidation to form fatty acetyl CoA whereas the long chain fatty acids become activated into fatty acyl CoA in the liver cytosol. The carinitine acyltransferase system moves the acyl CoA to the mitochondrial matrix where they undergo ß-oxidation to form acetyl CoA[40]. When there is an excess of acetyl CoA, more than that is required for providing energy through Kerb's cycle, the liver converts the extra acetyl CoA into ketone bodies[41,42].

The formation of ketone bodies occurs as follows. Two molecules of acetyl CoA are condensed to form a molecule of acetoacetyl CoA. Then a third molecule of acetyl CoA is added to acetoacetyl CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG CoA). Formation of HMG CoA is catalyzed by the hepatic enzyme, HMG CoA synthase. HMG CoA is then cleaved into acetyl CoA and acetoacetate by the action of another enzyme, HMG CoA lyase. Acetoacetate is either reduced to ß-hydroxybutyrate (BHB) through the action of BHB dehydrogenase or undergoes spontaneous decarboxylation to acetone which is excreted in the breath and urine[41,42].

Ketone bodies are used as an energy source in the body including the brain. BHB is converted to acetoacetate by the reversal reaction of BHB dehydrogenase, producing nicotinamide adenine dinucleotide phosphate (NADH). The acetoacetate, in turn, will bind to coenzyme A (CoA) provided from succinyl CoA molecules through thiophorase reaction producing acetoacetyl CoA. The acetyl CoA is further converted into two molecules of acetyl CoA, which will enter the Kreb cycle for production of energy[42].

EFFECT OF KETOGENIC DIET IN PREVENTING OBESITY

Recent studies from our laboratory have shown that the ketogenic diet is a natural therapy for obesity even in diabetic subjects. The weight and body mass index of the patients decreased significantly ($p < 0.0001$) from week 1 to 56 (Table 3). A similar significant ($p < 0.0001$) weight loss was observed in diabetic subjects who were on a LCKD diet (Table 4).

Several possible mechanisms on the role of very-low carbohydrate diet in reducing body weight have been suggested[43]. It is thought that major part of the weight loss following the administration of ketogenic diet can be attributed to the loss of water. Each 1 g of glycogen is stored in 3 gms of water. This means that the initial weight loss could be due to glycogen depletion and water excretion in urine. The weight lost in this manner will be gained immediately after stopping the ketogenic diet. Glycogen stores replenishes again with retention of a large amount of water as mentioned above[44,45]. Ketones have a diuretic effect and hence lead to an even greater water loss[44]. Furthermore, there is a

decrease in metabolic efficiency resulting in greater loss of energy in the form of heat[46] and in the form of ketones in urine, sweat, and feces.

In addition to the weight loss observed, very-low-carbohydrate ketogenic diets alter the metabolic rate by preserving more lean body mass[47]. Following the administration of ketogenic diet there is a preferential loss of fat mass and preservation of more lean body mass[47-49]. As mentioned earlier, ketone bodies especially BHB, has an effect on appetite suppression[50]. In addition, the high fat content in LCKD delays the digestion providing a sense of fullness[51]. Above all, the utilization of fat as body fuel, promote fat loss and therefore weight loss[52]. In addition to studies from our laboratory, several other studies have shown that low carbohydrate diets compared to low fat diets have a significant long term effect on the reduction of body weight[53-55].

OTHER BENEFICIAL EFFECTS OF KETOGENIC DIET

Although, the main focus of this review is on the beneficial effects of ketogenic diet on obesity, we know that this review will not be complete, if some of the other beneficial effects of ketogenic diets are not mentioned. Therefore, we give here below, some well known beneficial effects of ketogenic diet on neuronal and cardiac efficiency and its therapeutic role in diabetes, heart diseases, cancer *etc*.

Brain function

In humans, ketone bodies are the only additional brain energy source after glucose[56,57]. Hepatic generation of ketone bodies during fasting is a protective mechanism that spares the destruction of muscle from glucose synthesis. Historically, it is known that ketogenic diet is quite effective in antiepileptic treatments. However, how this diet works is still unclear? Several mechanisms that contribute to the anticonvulsant role of LCKD have been suggested. It is found that ketogenic diet increases the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain, which may be involved in the suppression of the seizure activity[58]. Furthermore, LCKD increases the level of polyunsaturated fatty acids (PUFAs), which functions as modulators of neuronal membrane excitability by inhibiting the sodium and calcium ion channels[59]. It is suggested that free radicals contribute to the development and progression of epilepsy. Thus, the anticonvulsant role of ketogenic diet could also be through the antioxidant mechanisms activated by fatty acids and ketones[60]. It has also been found that a ketogenic diet affects signal transduction in neurons by inducing changes in the basal status of protein phosphorylation[61]. Furthermore, ketogenic diet has beneficial influence on the brain energy metabolism[62].This is quite significant, as cerebral hypometabolism is a characteristic feature of those who suffer from depression or mania[62]. Interestingly, it is shown that a ketogenic diet reduces amyloid ß 40 and 42 in a mouse model of Alzheimer's disease[63].

Cardiovascular Diseases

The common notion is that a ketogenic diet will cause high cholesterol, TAG, and cardiovascular disease because of the high fat it contains. In our previous studies and recent studies using ketogenic diet it is shown that LCKD decreased the level of triglycerol and LDL cholesterol and increased the level of HDL cholesterol[53,64-67]. Furthermore, administering a ketogenic diet for a relatively longer period of time did not show any significant side effects in the patients. A similar situation was found when obese subjects with high cholesterol

Table 3: Statistical significance between week 1 and week 56 observation of various parameters studied in normal subjects[67].

Normal Subjects (n = 33)			
	Week 1	Week 56	p-value
Weight (kg)	105.273 + 15.377	74.923 + 11.384	< 0.0001
Total chol (mmol/l)	5.479 + 1.293	4.650 + 0.495	0.0020
HDL (mmol/l)	1.237 + 0.270	1.621 + 0.177	< 0.0001
LDL (mmol/l)	4.030 + 1.148	2.807 + 0.496	< 0.0001
TG (mmol/l)	1.827 + 0.981	0.861 + 0.179	0.0001
Glucose (mmol/l)	5.127 + 0.440	4.726 + 0.529	0.0069
Urea (μmol/l)	5.563 + 1.299	4.419 + 0.743	< 0.0001

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation.

Table 4: Statistical significance between week 1 and week 56 observation of various parameters studied in diabetic subjects[67].

Diabetic Subjects (n = 31)			
	Week 1	Week 56	p-value
Weight (kg)	108.081 + 21.245	83.536 + 18.030	< 0.0001
Total chol (mmol/l)	6.755 + 1.086	4.878 + 0.533	< 0.0001
HDL (mmol/l)	1.033 + 0.264	1.586 + 0.211	< 0.0001
LDL (mmol/l)	5.160 + 0.892	3.379 + 0.608	< 0.0001
TG (mmol/l)	4.681 + 2.468	1.006 + 0.205	< 0.0001
Glucose (mmol/l)	10.481 + 3.026	4.874 + 0.556	< 0.0001
Urea (μmol/l)	5.778 + 0.905	4.972 + 1.050	< 0.0111

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation.

Table 5: Baseline values of different physical and biochemical parameters monitored in persons (high cholesterol / normal cholesterol) subjected to low carbohydrate diet (ketogenic diet) [66]

	Total	Group I (n = 35) (High cholesterol)	Group II (n = 31) (Normal cholesterol)	p-value
Age (years)	42.9 + 10.8	45.5 + 9.2	39.9 + 11.8	0.0731
Weight (kg)	106.9 + 18.3	112.3 + 19.3	100.7 + 15.3	0.0168
BMI (kg/m^2)	39.1 + 6.1	40.1 + 6.1	38.0 + 6.1	0.1385
Total chol (mmol/l)	6.1 + 1.4	7.0 + 0.9	5.0 + 0.8	< 0.0001
HDL (mmol/l)	1.1 + 0.3	1.1 + 0.3	1.2 + 0.3	0.0076
LDL (mmol/l)	4.6 + 1.2	5.4 + 0.8	3.6 + 0.7	< 0.0001
TG (mmol/l)	3.2 + 2.3	4.3 + 2.6	2.0 + 1.1	< 0.0001
Glucose (mmol/l)	7.7 + 3.4	9.4 + 3.7	5.7 + 1.5	< 0.0001

HDL = high density lipoprotein; LDL = low density lipoprotein; TG =Triglyceride
Data is expressed as mean + standard deviation

level and obese diabetic subjects were treated with LCKD for longer period, suggesting that it is safe to use ketogenic diet in both diabetic subjects (Table 3, 4) and in subjects with high cholesterol level (Table 5, 6). Further studies revealed that despite the increase of cholesterol intake with ketogenic diet, there is no significant increase in the total cholesterol or LDL[53,64-67]. This may be due to the low insulin level which will activate HMG CoA lyase, the enzyme responsible for ketone formation and inhibit HMG CoA reductase, the enzyme responsible for cholesterol formation[68]. In a recent study from our laboratory on experimental rats, we have convincingly shown that LCKD enhances cardiac tolerance to global ischemia as compared to rats fed on a high carbohydrate diet [69]. In addition, ultra structural studies have shown that there was a decrease in the number of mitochondria in rats fed a high carbohydrate diet and an increase in the number of mitochondria in those fed a LCKD as compared to the normal diet group, confirming the physiological observations on cardio-protective function of LCKD[69]. It should be noted that pre-historic diets were high in dietary protein and fat. However, these pre-historic societies were relatively free of several cardiovascular diseases that exist today in our society[35].

Diabetes mellitus and insulin resistance

In the pre-insulin era LCKD has been used for diabetes treatment instead of medications[70]. The results from our laboratory show that LCKD has significant beneficial effects in obese diabetic subjects following its long-term administration (Table 3, 4). The blood glucose level decreased significantly from the start until the 56th week. A similar situation was found when obese subjects with high cholesterol level were treated with LCKD for a longer period. As previously mentioned, these studies suggest that it is safe to use ketogenic diet in both obese diabetic subjects and subjects with high cholesterol level (Table 5, 6). Furthermore, LCKD may be effective for improving glycemia and reducing medications in patients with type 2 diabetes.

Insulin resistance is a characteristic feature of Type 2 diabetes[71]. Insulin resistance is defined as the inability of insulin to produce its usual response at concentrations that are effective in normal individuals. As mentioned earlier, the content of carbohydrate in the diet is the most important factor that influences

Table 6: Percentage changes in the various parameters observed at week 56 in persons (high cholesterol / normal cholesterol) subjected to ketogenic diet[66]

	Total (n = 66)	Group I (n = 35) High cholesterol	Group II (n = 31) Normal cholesterol	p-value
Weight (kg)	-25.9 + 6.3	-25.8 + 6.7	-26.0 + 5.8	0.9065
Total chol (mmol/l)	-19.3 + 17.0	-29.2 + 9.4	-6.2 + 16.2	0.0005
HDL (mmol/l)	52.3 + 43.8	63.7 + 52.7	37.1 + 20.6	0.1778
LDL (mmol/l)	-28.2 + 20.1	-33.5 + 19.5	-21.3 + 19.1	0.1331
TG (mmol/l)	-59.0 + 32.1	-69.8 + 32.6	-44.7 + 25.7	0.0537
Glucose (mmol/l)	-31.0 + 25.0	-44.0 + 22.6	-12.8 + 15.1	0.0004

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation. Statistical significance between Group I and Group II are given.

Table 7: Statistical significance between week 1 and week 56 observation of various parameters studied in group I (high cholesterol) and group II (normal cholesterol) subjects[66].

	Total (n = 66)	Group I (n = 35) High cholesterol	Group II (n = 31) Normal cholesterol)
Weight (kg)	< 0.0001	< 0.0001	< 0.0001
BMI (kg/m^2)	< 0.0001	< 0.0001	< 0.0001
Total chol (mmol/l)	< 0.0001	< 0.0001	0.0170
HDL (mmol/l)	< 0.0001	< 0.0001	< 0.0001
LDL (mmol/l)	< 0.0001	< 0.0001	< 0.0001
TG (mmol/l)	< 0.0001	< 0.0001	0.0002
Glucose (mmol/l)	< 0.0001	< 0.0001	0.0034

BMI = Body mass index, Chol = cholesterol, HDL = high density lipoprotein; LDL = low density lipoprotein; TG =Triglyceride

the glycemic level. LCKD appear to improve glycemic control and le ssen the need for exogenous insulin and hypoglycemic medication[67,72]. Furthermore, LCKD significantly improved the insulin sensitivity by up to 75%[54,73]. In a recent study on experimental rats from our laboratory, we have demonstrated that LCKD ameliorated the diabetic state and helped to stabilize hyperglycemia. In addition to its therapeutic effect, LCKD had a significant protective role against the diabetogenic action of streptozotocin (STZ) [74]. STZ is selectively cytotoxic to the ß-cells of pancreatic islets. Therefore it is commonly used to induce diabetes in experimental animals[74].

Osteoporosis

A link between low fat diet and osteoporosis has been suggested. Very-low-fat diets are considered to be low in calcium content. Women on low-fat diets excrete most of the calcium they consume. Therefore, they are more prone to osteoporosis. On the other hand recent studies indicate that a high fat diet can rectify this situation[75].

Cancer

The relation between high fat diet and cancer is close to reality now. It has been found that altered energy metabolism and substrate requirements of tumor cells can provide a target for cancer therapy. Two major metabolic alterations found in cancer cells are the increase in glucose consumption and aerobic glycolysis, the conversion of glucose to lactic acid *via* the reduction of pyruvate even in the presence of oxygen. In addition, there are defects in ketone body metabolism[71,76]. These metabolic changes in cancer cells may provide a rationale for therapeutic strategies that inhibit tumor growth by LCKD. It has been shown that cancers, specifically brain tumors grow minimally on a LCKD[77]. These studies suggest that treatment with LCKD is a safe and effective alternative therapeutic option for malignant brain cancer. In addition, ketone bodies function as anti-inflammatory agents through the reduction of reactive oxygen species and increase of glutathione peroxidase activity[78].

SIDE EFFECTS OF KETOGENIC DIET

It is noticed that some individuals on ketogenic diet may experience a bad breath. However, vast majority of individuals do not develop medical problems. As in the case of any form of diet with restricted caloric intake, ketogenic diet is also deficient in minerals and water-soluble vitamins [79]. In order to overcome this side effect, subjects on ketogenic diet are given multi vitamin and mineral supplements daily to avoid such deficiencies.

Another criticism of ketogenic diet is the reduction of fruits, vegetables and whole grains, which are considerd to be healthy foods. However, it should be noted that LCKD can include a wide range of healthy vegetable as mentioned in Table 2. It has been suggested that chances of having increased formation of kidney stones could be another side effects of LCKD. Factors that could enhance the stones formation could be the limited fluid intake and increased production and the decreased excretion of uric acid. Also, similar to suppression of food intake, ketone bodies are involved in the suppression of thirst, leading to reduced fluid intake. Thus hyperuricemia gives rise to urate stone formation. It is suggested that with 5% carbohydrates composition in the diet this situation can be prevented[80]. However, it should be noted that, in our studies we have observed a decrease in serum level of urea (Tables 3, 4).

Constipation is also a noted side effect of LCKD. This could be due to the decreased fiber content and as mentioned above the suppression of thirst by ketones leading to dehydration. Also, with increased absorption / digestion of foods, there is a decrease in the stool volume. This situation can be easily avoided by increasing the fiber content by taking in vegetables in the diet, increasing fluid intake and using sugar-free laxatives[34,81]. Apart from these, the data presented in this review from our laboratory and from the studies of various investigators show that chronic ketosis without caloric restriction poses no danger to maintaining a healthy body.

CONCLUSION

The data presented from the various studies conducted at the Faculty of Medicine, Kuwait University, in a population comprising of Kuwaiti and non-Kuwaiti subjects and the results of several investigators mentioned in this review show that a ketogenic diet (consisting of 30 gms carbohydrate,

1 gm/kg body weight protein, 20% polysaturated, 80% polyunsaturated and monounsaturated fat) induces a miraculous weight loss in normal obese subjects as well as obese subjects with diabetes and hyperlipidemia. In addition to weight loss, there was a significant decrease in the level of triglycerols, total cholesterol, LDL-cholesterol and glucose whereas there was an increase in the level of HDL in these patients. Also, recent studies have shown that LCKD may actually be cardio-protective. All these studies clearly indicate that it is safe to administer ketogenic diet for a relatively longer period.

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Original Article

Elastofibroma Dorsi: An Under-Diagnosed Entity - Clinical, Imaging and Pathological Features

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ABSTRACT

Objectives: To report clinical, radiological and histopathological findings of elastofibroma dorsi. The purpose is to increase awareness among radiologists and clinicians of this under-diagnosed and interesting benign lesion.
Design: Retrospective review of 624 consecutive thoracic Computed Tomography (CT), 92 ultrasounds and 130 Magnetic Resonance Image (MRI) scans for detection of elastofibroma dorsi along with review of the clinical and histopathological findings. Three radiologists evaluated the imaging features using previously defined criteria. A histopathologist reviewed the pathological findings.
Setting: A tertiary level hospital and a specialized orthopedic center
Subjects: Patients who were subjected to CT, Ultrasound and MRI scans of the thorax
Interventions: CT, MRI, Ultrasound scans of the thorax and surgical excision
Main Outcome and Measures: Detection of elastofibromas and their clinical, radiological and histopathologic findings
Results: Only 50% of patients with elastofibroma dorsi could be detected by all modalities though, on review, all lesions showed characteristic location, morphology, imaging as well as typical clinical and pathological features. Significant contrast enhancement of all lesions on MRI was an unusual finding in our study.
Conclusions: An awareness of the radiological findings and enhancement patterns on CT and MRI can help in the proper diagnosis of elastofibroma dorsi an entity often misdiagnosed in a high percentage of patients.

KEY WORDS: chest, elastofibroma, neoplasm, pseudotumor, thorax

INTRODUCTION

Elastofibroma dorsi (ED) is a fibroelastic lesion of unknown etiology; most commonly found in the sub or infrascapular regions of the chest wall[1]. It is usually seen in elderly patients and is several times more common in women than in men[2]. The lesions are periscapular in 99% of reported cases, and are often bilateral[3]. The clinico-pathological and imaging features have been documented previously[4] but due to the uncommon occurrence of this lesion and lack of familiarity with its characteristic features it is still misdiagnosed both on radiological assessment and histologically[5]. It is possible to misinterpret this lesion clinically, on imaging and sometimes on pathology[6-10]. The purpose of our article is to increase awareness of the clinical presentation, imaging features and histological findings of ED and to investigate the role of these modalities, especially imaging, in making a correct prospective diagnosis of this condition. We also aimed to study the prevalence of this lesion in asymptomatic individuals on imaging.

SUBJECTS AND METHODS

A retrospective review was conducted of radiological investigations and clinical data of patients with the final diagnosis of elastofibroma in our hospital. For this purpose we reviewed data from the hospital records, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasound examinations over the last four and a half years. A total of 624 chest CT scans, 130 thoracic MRI scans and 92 ultrasound examinations were reviewed. Three musculoskeletal radiologists independently reviewed the radiological data and later also reviewed the cases together.

A pathologist reviewed the histopathology of the cases which had a prior positive histopathological

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Table 1: Clinical and radiological findings in patients with pathologically proven Elastofibroma Dorsi who presented with chest wall symptoms /abnormalities (Group A)

Group A (Diagnosed)	Clinical presentation	Clinical Dx	Location	Radiological Findings			Pathology
				Modalities	Enhancement	Dx / DDx	
Patient 1 71 y Female	Posterolateral chest wall swelling	Lipoma	U/L; near inferior pole of R scapula	CT MRI US	+ + NA	Lipoma Liposarcoma Lipoma	Surgery; Dx as ED on resected specimen
Patient 2 58 y Male	Posterolateral chest wall swelling	Soft tissue sarcoma	U/L; near inferior pole of L scapula	CT MRI US	++ +++ NA	STS STS Hemangioma	Surgery; Dx as ED on resected specimen
Patient 3 81 y Male	Nonspecific Periscapular pain & discomfort; No lump	None specified; Imaging to rule out pathology	U/L; near inferior pole of R scapula	CT MRI	+ +	STS/ fibroma Fibroma;	Core Biopsy; Dx as ED on biopsy specimens
Patient 4 66 y Male	Posterolateral chest wall swellings; Lump seen with arm movement	neurofibromas	B/L; sub-scapular	CT MRI US	++/++ +++/+++ NA/NA	Hemangiomas Atypical Lipomas Hemangiomas	Core Biopsy; & Surgery ; Dx as ED
Patient 5 50 y Female	Periscapular discomfort and clicking; No lump	None specified; Imaging to rule out pathology	B/L; near inferior pole of scapula	CT MRI	++/++ +++/+++	B/L Elastofibroma Dorsi B/L Elastofibroma Dorsi	Core Biopsy; Dx as ED on biopsy specimens

U/L-Unilateral; B/L-Bilateral; STS: Soft tissue sarcoma; ED: Elastofibroma Dorsi, Dx: Diagnosis; DDx: Differential Diagnosis; NA: Not applicable; R- Right, L- Left; Degree of enhancement: – Absent, + Mild enhancement, ++ Moderate enhancement, +++ Marked enhancement, y = year, CT: Computed tomography, MRI: Magnetic resonance imaging, US: Ultrasound

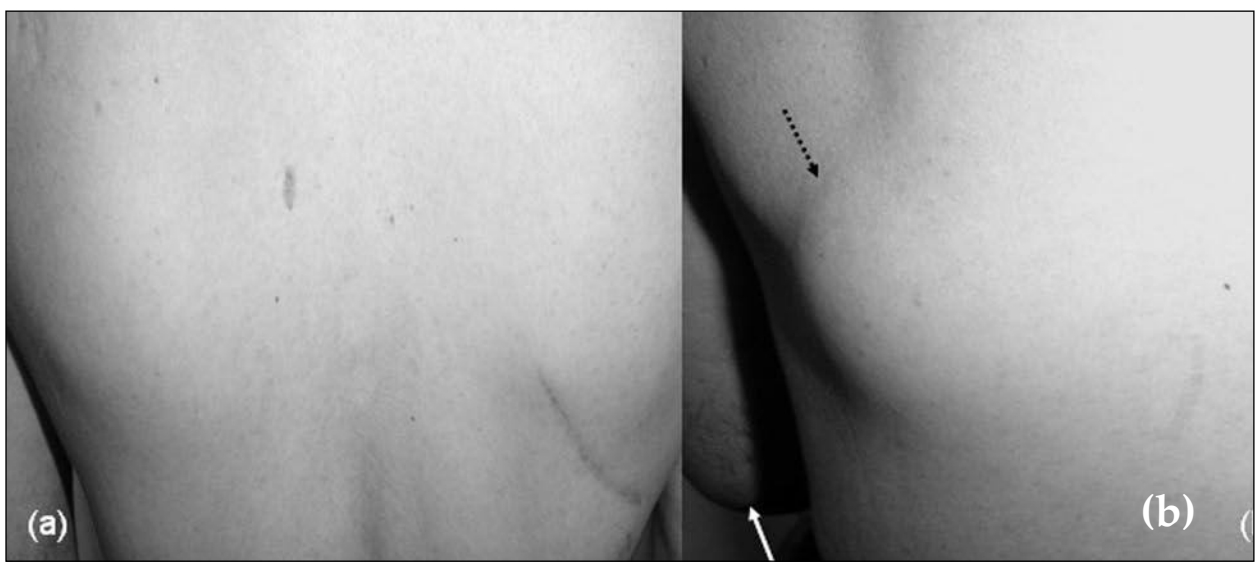

Fig 1: Clinical findings in elastofibroma dorsi; **(a)** Photograph of a patient's back with normal position of the arms showing no apparent lesion on the left side. Note the scar on the right side following removal of a prior elastofibroma, **(b)** With the patient's arms extended (white arrow), note the obvious swelling due to the left sided elastofibroma (dashed black arrow).

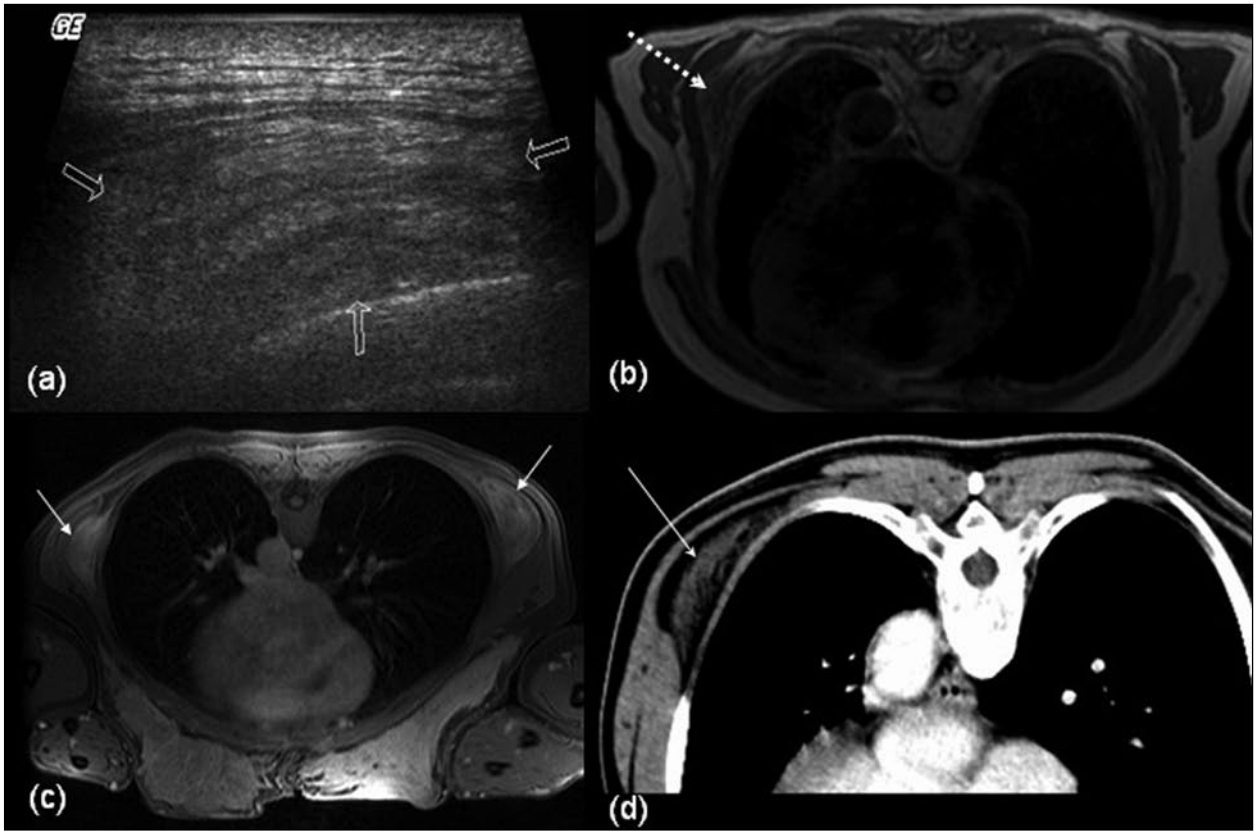

Fig 2: Imaging of elastofibroma; **(a)** Ultrasound scan of a patient with elastofibroma showing the typical layered arrangement of linear or curved hypoechoic strands against an echogenic background (open arrows), **(b)** Axial T1-Weighted MRI scan in a patient with unilateral elastofibroma (dashed arrow) showing typical striated appearance of the lesion. Note the intervening fat seen as hyperintensity within the lesion, **(c)** CE-MRI in a patient with bilateral elastofibromas showing marked enhancement (short arrows). **(d)** CE-CT scan in another patient with elastofibroma showing no appreciable enhancement (long arrow).

diagnosis of ED (n = 5). This included review of the slides (n = 5), additional stains on slides made from the blocks (Hematoxylin & Eosin and Van Gieson elastica in three cases and immunostains for vascular markers, CD 31 and CD 34 in five cases).

The inclusion criteria for the diagnosis of ED were defined for the review of the CT and MRI scans. The posterolateral chest wall was evaluated specifically on either side for the presence of ED, which by definition, is a non-encapsulated, striated / layered soft tissue mass similar to muscle situated deep in relation to the inferior pole of scapula, serratus anterior, latissimus dorsi and levator scapulae muscles but superficial to the ribs and periosteum[5]. Scans with insufficient field of view or artifacts in the region of interest were excluded.

The original reports of the radiologists were also reviewed for each modality and a note was made of the imaging findings, their diagnosis and differential diagnosis. The findings were correlated with the images.

Data regarding the clinical presentation, symptomatology, examination findings, past history, treatment and clinician's impression was also extracted from the hospital records for these cases. A note was made of the presenting complaint, detection of any lump on examination, reasons for radiological referral and the clinician's impression of the case (Tables 1 and 2).

RESULTS

Features of ED were detected in ten patients (14 elastofibromas) across all modalities. Overall, there were six male and four female patients of elastofibroma. The age range was 35 - 81 years with a mean of 58 years. The lesions were bilateral in four cases. In one case there was a history of a similar swelling on the contralateral side few years earlier, for which surgery was done and the lesion turned out to be an elastofibroma (Fig. 1a). These ten patients were divided into two groups for the purpose of analysis.

Group-A consisted of five pathologically proven cases of elastofibroma dorsi who presented with chest wall symptoms or abnormalities and their clinical and radiological findings have been summarized in Table 1. In all group-A patients a final pathological diagnosis of ED was available (Table 1). In two cases the final diagnosis of elastofibroma was made following surgical removal whereas in the other three the diagnosis was made on the basis of radiological findings and histopathology of the biopsy specimen.

Table 2: Clinical and radiological findings in patients with Elastofibroma Dorsi detected during the retrospective review (Group B: not proven pathologically).

Group B (Cases diagnosed during the review)	Clinical Presentation	Location	Radiological Findings			Pathology
			Modality	Enhancement	Dx/DDx	
Patient 1 79 y Male	No chest wall complaints or lump; Evaluation for lung nodule	U/L R sided	CT	+	None; missed on initial scan	-
Patient 2 39 y Male	No chest wall complaints or lump; Non resolving pneumonia	B/L	CT	++/++	None; missed on initial scan	-
Patient 3 45 y Female	No chest wall complaints or lump; breathlessness	B/L	CT	+/+	None; missed on initial scan	-
Patient 4 56 y Male	No chest wall complaints or lump; lung nodule evaluation	U/L L sided	CT	++	None; missed on initial scan	-
Patient 5 35 y Female	No chest wall complaints or lump; Suspected mediastinal mass	U/L R sided	CT	+	None; missed on initial scan	-

U/L-Unilateral; B/L-Bilateral; STS: Soft tissue sarcoma; ED: Elastofibroma Dorsi, Dx: Diagnosis; DDx: Differential Diagnosis; NA: Not applicable; R- Right, L- Left; Degree of enhancement: – Absent, + Mild enhancement, ++ Moderate enhancement, +++ Marked enhancement., y = year, Computed tomography

A correct clinical diagnosis of elastofibroma was not made in any case in this group (Table 1). Three patients presented with the chief complaint related to posterior chest wall swelling. In one patient a lump was detected during the physical examination and it was only visible when the patient moved his arm forward (Fig 1b). However, the clinician did not raise a possibility of elastofibroma in this case. No lump was clinically detected in two patients, but the lesions were detected on CT scans done for related chest complaint which included periscapular pain and clicking sensation.

Imaging of patients in group-A was performed using MRI, CT and Ultrasound scans (Fig 2, Table 1). The lesions were non-encapsulated, poorly circumscribed, predominantly lentiform in shape on imaging and conformed to the typical imaging features of elastofibromas described in the literature[4]. Five out of seven lesions showed considerable enhancement on post Gadolinium enhanced MRI scans (Fig 2c). Enhancement was also noticed on enhanced CT scans but was mild to moderate and was never greater than the enhancement of the adjacent skeletal muscles (Fig 2d).

A correct initial radiological diagnosis of elastofibroma was made in only one case (20%) in patients from group-A although on review of the respective scans the imaging features were considered characteristic of elastofibroma in all cases using the previously described inclusion criteria. The radiological differential diagnosis included malignant lesions in the other three cases in spite of the typical imaging appearances. In the last case of this group the differential diagnosis mentioned by the reporting radiologist included only benign lesions (Table 1).

The gross pathological examination in two cases of elastofibroma showed the tumors as firm masses with gray-white glistening appearance on cut section. The size ranged from one to nine cm in maximal dimension. Microscopically, the tumors were hypocellular masses containing a mixture of eosinophilic collagen and elastic fibers (Fig 3a). The elastic fibers were coarse, fragmented and showed serrated margins. All lesions were mixed with collagen and adipose tissue and were seen blending with the surrounding fat and connective tissue. Van Gieson elastica stain showed deeply staining fragmented branched and unbranched fibers exhibiting a central dense core and serrated margins (Fig 3b). The vascular markers, CD 31 and CD 34, did not reveal strong tumor vascularity.

The three patients on follow up after biopsy and histological diagnosis did not show any significant interval growth of their lesions or development of new symptoms. The two patients in whom surgical excision was performed have not experienced any recurrence of elastofibromas.

The other five patients formed group B (Table 2) which consisted of previously undiagnosed cases detected during the review of the CT images in the current study. Since these lesions were

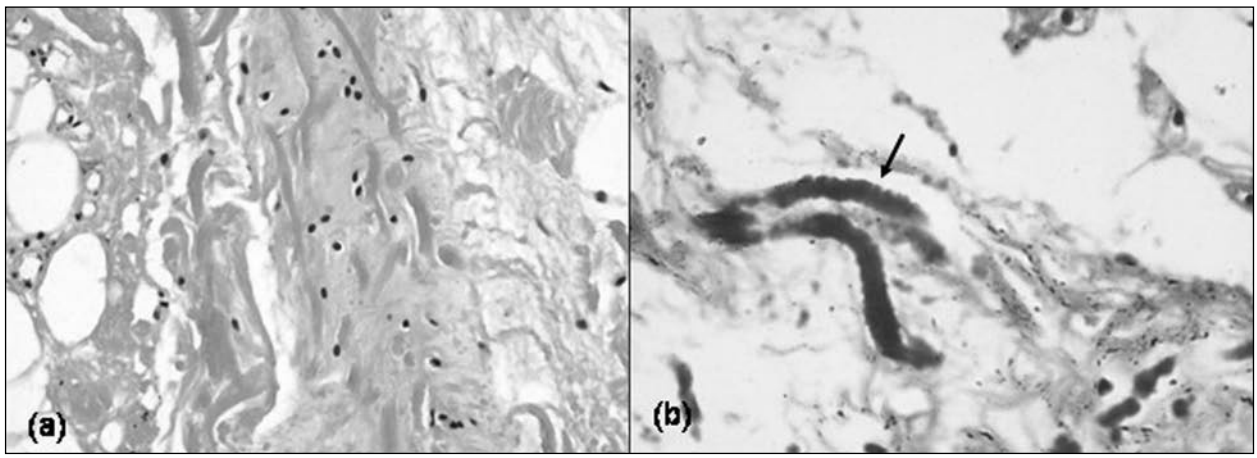

Fig 3: Histology of elastofibroma; **(a)** Coarse fibers admixed with collagen and adipose tissue. Magnification (x 20). Stain: Hematoxylin and Eosin **(b)** Van Gieson Elastica stain showing elastic fibers with serrated edges (arrow). Magnification (x 40).

asymptomatic incidental discoveries, there was no supportive pathology data but these cases were included in the study because of the characteristic location and appearance and based on the fact that all of these lesions conformed to the definition of ED[5]. All five patients in group-B had no complaints related to the chest wall. CT scans were performed for other pulmonary complaints (Table 2). Two out of five patients had bilateral lesions. CT scan showed typical imaging features of elastofibroma described earlier. Contrast enhancement was mild to moderate. The sizes of these asymptomatic, incidentally detected lesions were found to be smaller (less than 4 cm) than that of the lesions in group-A. No follow up data was available in these five patients.

DISCUSSION

ED is a rare benign mesenchymal fibroproliferative lesion, which occurs most commonly in the periscapular region of middle aged to elderly women. It usually occurs in active subjects above the age of 50 with a male:female ratio of 1:5. However, there are reports in literature showing similar incidence in men and women or even a more frequent occurrence in men[9,11]. In our study the overall male:female ratio was 1.5. The ratio was 3:1 in favor of the females in the native population but was 5:1 in favor of the males in the non-native population.

Though the sample was not entirely representative of the native population, it could reflect a true increased prevalence in the native female population.

The etiology of this tumor is uncertain. An increased prevalence in persons who perform manual labor involving the shoulder girdle suggests role of trauma due to mechanical friction of the scapula against the ribs as a causative factor. This theory does explain the right-sided preponderance of the lesion and may explain the increased prevalence of the lesion in non-native males who may be involved in more manual work.

Another possibility is that the lesion may have a genetic basis. In many cases, the patient has a family history of the tumor, suggesting a non-traumatic genetic origin. A study on chromosomal gains suggested that certain chromosomal regions may contain genes which may be involved in the development of these tumors[12]. Cytogenetic chromosomal instability and presence of some clonal chromosomal changes have raised the possibility that the lesion represents a true neoplastic process[13].

Clinically, over 50% of subjects are usually asymptomatic but they may also present with a painless swelling. In our study we encountered five such previously undiagnosed asymptomatic patients on review of CT scans of the chest done for other indications. The asymptomatic prevalence of this lesion based on CT data according to our study is around 1%. A higher prevalence rate on autopsy[1] and CT [5] studies has however been reported in the literature but the reason for this could be selection of only elderly patients for such calculations which may not be true as elastofibromas are consistently seen in the younger population as well. Approximately 25% of cases present with a clicking sensation when the arm is moved the so-called snapping scapula syndrome[14]. Fewer than 10% of patients present with mild pain. Joint stiffness can also be a presenting symptom. Occasionally, ED can also mimic the shoulder impingement syndrome[15].

Plain radiography may be normal or may show a soft tissue density in the periscapular region when the scapula is raised. The sonographic appearance of ED consists of arrays of interspersed linear or curved hypoechoic strands against an echogenic background[7,16] (Fig. 2a). On CT, elastofibroma is typically a poorly defined, non-homogeneous soft

tissue mass with appearance similar to that of skeletal muscle, containing linear streaks of fat attenuation in most of the cases (Fig 2d). However, in some cases, it could be relatively homogenous without the interspersed fat and attenuation similar to that of muscle[17]. MRI is the best non-invasive technique and most useful for diagnosis. Elastofibromas appear as poorly circumscribed soft tissue lesions with similar signal intensity to that of skeletal muscle but interspersed with high signal intensity areas representing fat (Fig 2b). Elastofibromas may show marked enhancement, which is considered atypical[18]. Usually they have been described as mildly enhancing or non-enhancing lesions[17]. But, all the lesions we describe showed moderate to marked enhancement patterns on MRI without any appreciable enhancement on CT scans (Fig 2c and d). Schick *et al*[18] have demonstrated strong tumor vascularity on histological workup in cases with marked contrast enhancement on MRI. Whereas in our cases, the vascular markers, CD 31 and CD 34, did not reveal strong tumor vascularity. Although the basic nature of the contrast enhancement in elastofibroma is not well understood, our cases show that marked MR contrast enhancement could be seen commonly in elastofibromas and this could mimic an inflammatory or malignant mass. This was possibly one of the reasons of radiological misdiagnosis in few of our cases in spite of typical imaging findings on non-contrast images. We, therefore, want to stress on the importance of recognizing the strikingly different contrast enhancement patterns of ED on MRI and CT scan to avoid any diagnostic confusion and unnecessary interventions.

The differential diagnosis of a periscapular lesion with signal intensity similar to skeletal muscle is limited and includes extra abdominal desmoids, neurofibroma, cicatricial fibroma and malignant fibrous histiocytoma[19].

Pathologically, the diagnosis of elastofibroma can be made if the typical features are seen (Fig. 3), but it has been noted that many elastofibromas do not have the typical findings and may even show an intermediate stage, the so called pre-elastofibroma changes which manifest as weakly elastinophilic material without definite elastic tissue formation[9]. It is therefore possible that on pathological examination, especially of a small biopsy specimen, a definite diagnosis may not be reached inspite of other typical clinical and imaging features.

A correct non-operative diagnosis of this lesion therefore requires awareness of the clinical presentation, characteristic location and the typical imaging features of this entity on various modalities. The diagnosis can be easily made on history and physical examination if the patient's symptomatology is correlated with the typical location and the characteristic change in appearance of the lesion on flexion and extension of the patient's arm(s) (Fig. 1). On imaging, the unique features of the lesion are due to the presence of intralesional fat giving its characteristic appearance on cross sectional imaging techniques. If these features are seen, which is the case in vast majority of these lesions, a definite diagnosis of ED is possible preventing unnecessary investigations or surgical intervention.

Another feature of this tumor, which may help in making a correct diagnosis, especially in cases with atypical imaging features, is the bilateral occurrence of the lesion. Of those in the sub scapular region, approximately 10 to 66% elastofibromas are bilateral and this favors the mechanism of repeated mechanical friction in the genesis of this lesion. We encountered bilateral lesions in four patients (40% cases).

The preferred treatment for patients who are clinically symptomatic is complete surgical excision. In asymptomatic individual simple excision of the lesion exceeding 5 cm in diameter has been recommended. The lesion can also be followed up on imaging in an asymptomatic patient.

CONCLUSION

ED has characteristic location and imaging appearances. The knowledge of these unique clinical and imaging features of elastofibroma dorsi will help in avoiding confusion and possible misdiagnosis of malignancy in most cases. The brisk enhancement of these lesions may be a rule rather than an exception, especially on MRI scans, and therefore knowledge of this finding will be helpful in avoiding a diagnostic error. The identification of similar lesion on the contralateral side further supports the diagnosis and prevents unnecessary biopsies and extensive surgical resection.

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Original Article

Prevalence of Substance Use among Iranian High School Students in 2005-2006

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ABSTRACT

Objectives: To determine the prevalence of substance use among high-school students in Guilan province, Iran
Design: Cross-sectional study conducted from September 2004 to June 2005
Settings: Guilan province high-schools, Iran
Subjects: A representative sample of 1927 students
Interventions: A self-report questionnaire that included socio-demographic data, type of substance used, history of lifetime and past month substance use, first motivation, first place and first provider of substance was applied.
Main Outcome Measure(s): Frequency of substance use in high-school students and some associated factors.
Results: About 24% of subjects had substance use during their lifetime. 24% of the sample used tobacco and 10.5%, alcohol. Substance use was significantly higher in males ($p < 0.001$). The highest frequency of substance use was among 3rd and 4th grade students (28.8% and 23.7% respectively). Substance use was related with higher educational grades in boys ($p < 0.001$) and significantly associated with smoker parents ($p < 0.001$). First experience with substances most commonly happened at home (26.6%), friends' parties (26.3%) and park / street (20.4%). 55.68% had obtained drugs, first time, from friends. Curiosity was the most common reason for drug use in 42.61% of the sample. Although substance use was higher in public schools and students with illiterate parents, it was not related with the type of school and parents' educational levels.
Conclusion: A large number of high-school students had the experience of substance use, mostly tobacco and alcohol. Effective solutions and preventive programs should be applied to reduce substance use in Iranian youth population.

KEY WORDS: high-school students, Iran, prevalence, substance use

INTRODUCTION

Substance use in young population has been of scientific, political and public concern[1]. Since adolescents are affected by massive physiological and psychological growth transformation[2], the first experiences with drugs often take place during adolescence[3]. Review of literature specifies that drug use is a combination of special factors such as heredity, personality trait, family and friends influence as well as social conditions[4]. Moreover, several studies have analyzed the role of individual factors in drug use among students and they concluded that male gender[5], age[2,6], profession[7], family breakup[8] and absence of religion[1] are associated with higher rates of drug use in students. Adolescent substance abuse negatively affects well-being of the individual and potentially holds a number of negative consequences for the individual's health status including the elevated risk of injury and death because of violent behavior and motor vehicle accidents[9], increased probability of high-risk sexual behavior[10] and increased risk for suicidal ideation and behaviors[11]. There is an association between drug use in adolescents and co-morbid psychiatric disorders like affective disorders, conduct disorder and antisocial personality disorder, attention-deficit hyperactivity disorder, and anxiety disorders[12]. Furthermore, substance abuse in adolescents results in low levels of academic achievements[13]. Substance use in adolescents is associated with engaging in deviant activities and higher rates of substance use have been found in young offenders[14].

As regards drug abuse among Iranian adolescents, Ayatollahi showed that 2.1% of 10th grade students in Shiraz (located in Southern part of Iran) had experimented with drugs during their lives[15]. In another study carried out by Poorasl *et al*, it was concluded that 12.7% of all 10th grade male students in Tabriz City (a city in north-west of Iran) had used alcohol and 2% had used drugs. Drug use was related with older age, having general risk taking behavior,

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Table 1: Distribution of sample by selected socio-demographic variables

Variables	n (%)
Gender	
Male	1041 (54.02)
Female	886 (45.97)
Age Group	
≤ 14 yrs	347 (18)
15-16 yrs	495 (25.68)
17-18 yrs	507 (26.31)
≥ 19 yrs	190 (9.85)
School Grade	
First	735 (38.14)
Second	495 (25.68)
Third	507 (26.31)
Fourth	190 (9.85)
Type of School	
Public	1630 (84.58)
Private	297 (15.42)

higher smoking stage, having self-injury, higher socio-economic class and ever use of illicit drugs [16].

Our goal was to determine the prevalence of substance use among Guilan province high-school students. In addition, we tried to focus on some associated factors with substance use in students.

SUBJECTS AND METHODS

In a descriptive and cross-sectional study, 1950 students out of a total number of 122,182 high-school students in Guilan province were selected by random proportional cluster sampling from 2004 to 2005. Samples were chosen from 55 high-schools in nine cities in Guilan province. First, the list of students was obtained from Education and Training Office of Guilan. The number of clusters as well as the number of samples in each cluster was chosen according to the total number of students. Based on a random number table, the location of the first cluster was selected and then subsequent clusters were chosen with regard to inter-cluster interval. An anonymous self-administrative questionnaire was distributed among the students aiming to obtain information on drug use (the kind of substance, history of substance use during life and previous 30 days, first motivation, first place and first provider of substance, demographic data (age, sex, type of school (public or private), educational grade), parents' educational levels and tobacco use by the parents. The reliability of both factors (each item and whole of the questionnaire) was examined in a pilot study among 120 students (65 boys and 55 girls). According to the results of pilot study, the questionnaire was adjusted quantitatively and terminologically. Eventually, the final version of questionnaire was distributed to the students. We assessed the use of tobacco, opium, heroin, cannabis, ecstasy and alcohol. Any use of these substances at any time was considered as having the history of life-time drug use in our samples. The frequency of substance use was assessed by dividing it into five different groups: 1. does not use currently, 2. rarely, 3. monthly, 4. weekly, 5. everyday.

In order to measure the first motivation of substance use, respondents were asked to select one of the following choices: curiosity, peer pressure, sense of pleasure, escape from problems and other reasons. The first place of substance use was grouped as follows: home, familial parties, friends' parties, school, park / street and other places.

Subjects were asked to specify the person who had provided them with the substance for the first time from these choices: parents, siblings, friends, drug dealers and others. Respondents were asked to provide data on their demographic characteristics such as age, sex, grade and school type (public or private).

In the end, we assessed the consumption of tobacco by the parents. (Possible answers: yes or no). Students were asked to fill out the questionnaires in their class rooms supervised by principal administrators. The study was approved by the local ethical committe and a verbal consent was obtained from parents/subjects

Statistical analysis was performed using the SPSS Statistical Package for Windows, version 14 using Chi-square test / or Fisher exact test.

RESULTS

From 1950 subjects, 23 were excluded because of incomplete response and a total number of 1927 samples were included. 886 individuals (46%) were female and 1041(54%) were male. It was seen that a higher proportion of our participants were male. The number of public schools is more than private schools

Table 2: Frequency of consumption of each substance among our subjects at the time of survey

Substance Type	Frequence of Substance Use: n (%)				
	Does not use	**Rarely**	**Daily**	**Weekly**	**Monthly**
Tobacco	268 (71.5)	31 (8.3)	24 (6.4)	25 (6.7)	27 (7.2)
Alcohol	116 (60.1)	31 (16.1)	6 (3.1)	17 (8.8)	23 (11.9)
Opium	34 (73.9)	4.(8.7)	3 (6.5)	1 (2.2)	4 (8.7)
Ecstasy	25 (64.1)	7 (17.9)	2 (5.1)	1 (2.6)	4 (10.3)
Cannabis	20 (57.1)	5 (14.3)	2 (5.7)	3 (8.6)	5 (14.3)
Heroin	0 (0)	1 (16.7)	3 (50)	1 (16.7)	1 (16.7)

Table 3:. Distribution of consumption of each substance between samples according to the sex

Substance Type	Sex: n (%)		p -value
	Male	Female	
Tobacco	270 (25.9)	115 (13)	0.001
Alcohol	173 (16.6)	30 (3.4)	0.000
Opium	34 (3.3)	13 (1.5)	0.016
Ecstasy	31 (3)	10 (1.1)	0.008
Cannabis	37 (3.6)	2 (0.2)	0.000
Heroin	5 (0.5)	1 (0.1)	0.301

in Guilan province. Thus, most of the subjects were attending public schools. Demographic data of our samples is shown in Table 1.

Characteristic of substance use: 457 students (23.7%) had substance use including tobacco use at least once during their lives and 246 students (12.8%) had life-time substance use without considering tobacco use.

The relative frequency of substance use was as follows: tobacco 385 (20%), alcohol 203 (10.5%), opium 47 (2.4%), ecstasy 41 (2.1%), cannabis 39 (2%) and heroin 06 (0.3%). The two substances most frequently experimented with were tobacco and alcohol which most students consumed at least once during their lives.

Frequency of substance use: Table 2 shows the frequency of consumption of substances among our respondents at the time of the survey. More than a half of our subjects did not use tobacco, alcohol, opium, ecstasy and cannabis at the time of survey whereas 6.4% and 3.1% were day to day users of tobacco and alcohol respectively.

Substance use and sex: Regarding sex distribution, overall consumption of substances was 326 (31.3%) in boys and 131 (14.8%) in girls and this difference was statistically significant ($p < 0.001$). According to the use of each substance, a significantly higher proportion of boys were tobacco, alcohol, opium, ecstasy and cannabis users ($p < 0.001$) while the frequency of heroin use was not high enough to permit such an analysis. (Table 3).

Substance use and school grade: The number of male and female students who had ever experienced drugs according to their school grades is summarized in Table 4. The highest frequency corresponded to grade 3 (28.8%) and grade 4 (23.7%). Furthermore, It was shown that substance use in male students was significantly related with higher school grade ($p < 0.001$).

Table 4: Relative frequency of substance use according to school grade

Gender	School Grade				p - value
	First	Second	Third	Fourth	
Male	116 (28)	70 (26.4)	107 (40.4)	33 (34)	0.001
Female	51 (18.9)	29 (12.6)	39 (16.1)	12 (12.9)	0.620

Substance availability: Regarding Substance availability, the three places most commonly reported for the first experience of substances were home (26.6%), friends' parties (26.3%) and park / street (20.4%). Other places less involved with substance availability were familial parties (14.8%), and school (4.03%); however, 53 (7.6%) students could not localize the first place of substance use (Table 5).

As regards the first person who had provided students with drugs, more than half of them (55.68%) obtained drugs from their friends for the first time. Other ways were parents (12.64%), siblings (2.55%) and drug dealers (16.47%). 89 (12.64%) students could not remember their first source of obtaining substances.

Motivations for substance use: When substance users were asked about their motivations, 300 out of 704 (42.61%) reported curiosity to be the main reason. Other reasons were search for sense of pleasure (19.88%), escaping problems by using drugs (14.48%) and peer pressure (13.77%). 65 students (9.23%) could not specify their reasons (Table 6).

Substance use and age groups: Substance use in different age groups was assessed. The highest prevalence of substance use was in age group 19 years and above (35.5%). Substance use in male students was significantly related with higher age groups while in female students this difference was not considerable (Table 7).

Substance use and type of school: 396 (24.3%) out of 1630 students who were studying in public schools

Table 5: Number of students who have been offered a drug for the first time by different locations in each class of substance

Substance Type	Location: n (%)					
	Home Party	Friend's Party	Familial	School	Park/ Stret	Other / not localized
Tobacco	112 (29.9)	68 (18.1)	30 (8)	12 (3.2)	117 (31.2)	36 (9.6)
Alcohol	37 (19)	70 (35.9)	65 (33.3)	3 (1.5)	11 (5.6)	9 (4.6)
Opium	31 (68.9)	4 (8.9)	2 (4.4)	3 (6.7)	1 (2.2)	4 (8.9)
Ecstasy	3 (7.7)	24 (61.5)	5 (12.8)	3 (7.7)	4 (10.3)	0 (0)
Cannabis	0 (0)	2 (40)	0 (0)	2 (40)	1 (20)	0 (0)
Heroin	185 (26.6)	183 (26.3)	103 (14.8)	28 (4.03)	142 (20.4)	53 (7.6)

Table 6: Motivations of first time substance use in Guilan high-school students

Substance Type	Motivation (s) of First Time Substance Use: n (%)				
	Curiosity	Sense of pleasure	Escape problems	Peer pressure	Other
Tobacco	206 (53.9)	52 (13.8)	47 (12.3)	52 (13.6)	25 (6.5)
Alcohol	71 (36.4)	56 (28.7)	18 (9.2)	20 (10.2)	30 (15.3)
Opium	3 (6.4)	10 (21.3)	27 (57.4)	0 (0)	7 (14.9)
Ecstasy	11 (27.5)	11 (27.5)	3 (7.5)	15 (37.5)	0 (0)
Cannabis	9 (25.7)	9 (25.7)	6 (17.1)	9 (25.7)	2 (5.7)
Heroin	0 (0)	2 (40)	1 (20)	1 (20)	1 (20)
Total	300 (42.61)	110 (19.88)	102 (14.48)	97 (13.77)	65 (9.23)

Table 7: Frequency of substance use according to the age group

Age Group	Substance Use: n (%)		
	Male	Female	Total
≤14 yrs	54 (26.6)	14 (9.7)	68 (19.6)
15-16 yrs	188 (30.2)	76 (15.6)	264 (23.8)
17-18 yrs	76 (36.9)	32 (14.7)	108 (25.5)
≥ 19 yrs	8 (88.9)	9 (23.1)	17 (35.5)

and 61 (20.5%) of 297 private school students reported consumption of substances during life. This difference was not statistically significant.

Parents consumption of tobacco and substance use by students: more than a half (252 out of 457) the students who were substance users, had smoker parents while in 1470 non-user students, 508 students had smoker parents. Cigarette smoking was significantly higher in substance users' parents ($p < 0.001$, Table 8).

Parents' educational levels and substance use: The highest prevalence of substance use was in children of illiterate parents (26.9% & 27.2% respectively); however, the relationship between parents' educational levels and substance use was not statistically different (Table 9).

DISCUSSION

Our results demonstrate a noticeable degree of substance abuse among high-school students in Guilan province (in northern part of Iran). Regarding the frequency of substance abuse, the rate of lifetime drug use in the present study was 23.7% which was different from that of pervious studies, showing lower rates (2.0% & 2.1%)[15,16]. It is possible that this difference is partly due to differences in methodology, especially sampling. In this study, frequency of tobacco use was high and it was counted toward the final assessment of the frequency of substance use. However, tobacco use was not included in afore-mentioned studies in Iran. Therefore, it may account for the difference between the frequency of substance use in our study and previous studies. Furthermore, these studies were carried out in different regions of Iran with different cultures and different lifestyles and this might affect the results. By contrast, in a study which was performed in the same region as ours, (Rasht City - the capital of Guilan province) the overall frequency of substance use (23%) was almost the same as in our study[17]. The prevalence of substance use in adolescents in other countries was close to our study in some cases. In a research in Croatia, the lifetime prevalence of substance use was 26%[18]. In the US, more than 57% of all high-school seniors reported using illicit drugs at least once in 2000[19].

The two substances most frequently experimented with were tobacco and alcohol (20 & 10.5% respectively). In the same study in Shiraz (a city located in southern part of Iran), tobacco (25.4%) and alcohol (9.6%) were the most prevalent substances[20]. Ljubotina *et al* showed that tobacco and alcohol were the most frequent substances used by elementary and high-school Croatian students[21]. Soldera *et al* demonstrated that alcohol (11.9%) and tobacco (11.7%) were the most utilized drugs in Brazilian high-school students[22]. An interesting finding in our study is that considering religious and legal prohibition for alcohol use in Iran, the alcohol consumption prevalence of around 11% indicates that such use is considerable and must be taken into account in educational, preventative and therapeutic programs in Iranian adolescents. Opium (2.4%), ecstasy (2.1%), cannabis (2%) and heroin (0.3%) were other drugs used by our samples. These frequencies are consistent with other studies in Iran[17, 20].

We found that boys were more likely than girls to consume substances. In review of literature, there was a considerable similarity between Iran and Western countries in this respect[1,17,21,23-28]. Our results indicate a dramatic increase in drug use in older age

Table 8: Parents tobacco consumption and substance use in their children Substance Use

Substance Use	Parents' Cigarette Smoking n (%)	p -value
Male	169 (40.9)	0.000
Female	83 (23.9)	

groups since 35.5% of substance users belonged to the age group 19 and above and being in higher age groups was statistically related with substance use in male students while it was not significant in females. Ehabrol *et al* concluded that the frequency of substance use increases in higher ages[29]. Hotujac *et al* showed that drug use in older Croatian high-school students increased dramatically[18].

According to substance availability, we concluded that substances were readily available for our students and they had easy access to them. Home and friends' parties appeared to be places most commonly involved in drug use. We determined the first place of substance use stratified by each class of drugs. Park / street was the most common place for tobacco use for the first time and opium was most commonly used at homes while alcohol, cannabis, ecstasy and heroin were mostly offered to the students at friends' parties. There are few studies focusing on the availability of drugs in Iran. In the same study in Croatia, private parties, café bars and parks were the most common places for drug use[18]. On the whole, there is very little information about the first place of substance use and more studies in this field would be necessary and valuable.

The data from the present research showed that substances were offered to more than a half of substance users (55.68%) by their friends. It was surprising that although all of the drug classes were mostly offered to students by their friends, opium was most commonly offered to the students by their parents. In a 20-year research in England, it was revealed that most of the young drug users were introduced to drugs by their friends[30]. Hotujac *et al* demonstrated that 42.5% of students know someone from the same school who uses drug[18].

The main reason for substance use was curiosity in our samples. Search for sense of pleasure, escape from problems and peer pressure were other reasons for drug use. According to Hotujac's research, curiosity was the most common reason for adolescent substance use[18]. On the other hand, it seems that peers play a major role in the initiation and maintenance of drug use[31] and friends are an important source of information regarding drug use[30].

The use of drugs in public schools was higher than private schools (24.3% Vs 20.5%). In addition, there was not any significant difference between the type of school and substance use. However, in a similar study in Rasht city, studying in private schools was related to higher substance use[17]. Moreover, Ogle *et al* showed that substance use in private schools is higher than public schools [32]. The larger sample size in present study and absence of obvious incongruous socio-economic classes in Guilan province as compared to a capital like Rasht city may account for this difference.

Table 9: Parents educational levels and substance use in their children

Parents	Educational Level	Substance use n (%)	p - value
Father	Illiterate	45 (26.9)	0.613
	Elementary school	90 (23.8)	
	Guidance school	79 (22.4)	
	High-school	105 (26.4)	
	Higher	138 (21.8)	
Mother	Illiterate	79 (27.2)	0.689
	Elementary school	116 (22.2)	
	Guidance school	86 (22.2)	
	High-school	83 (24.3)	
	Higher	93 (24.2)	

More than half of substance users had smoker parents and tobacco use was significantly higher in the parents' of substance users. Wagner *et al* concluded that 69.4% of smoker students' parents and 41.6% of non-smoker students' parents were smokers and the relationship between tobacco use in parents and smoking in children was significant[33]. In similar studies carried out in Iran, tobacco use was significantly higher in substance users' parents[17,34]. It may define the role of family in the adolescent's drug use and children of smoker parents should be considered as an important target in preventive and educational programs.

Care should be taken in interpreting the results of this study due to some limitations with the data:

1. The study relied on self-report data. Although we made our efforts to ensure confidentiality and anonymity, the possibility of under-reporting of illegal substance use still remains.

2. The survey did not include adolescents who did not attend regular schooling systems. Considering the fact that most of the adolescents with serious substance use do not attend school, performing a school-based research was another limitation to this study.

CONCLUSION

High prevalence of substance use among high-school students indicates failure of preventive measures. Drug use seems to be a serious problem in this population. In addition, it is logical to focus the preventative programs to reduce smoking and alcohol consumption among young male students in the higher age groups. Moreover, the role of parents in reducing drug use in their children should be taken into special consideration. Eventually, more studies about substance use in Iranian adolescent population

such as assessing students' knowledge and attitudes toward substance use seem necessary.

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Original Article

Increased Oxygen Free Radical Production from Isolated Human PMNLs and Whole Blood by Luminol-Enhanced Chemiluminescence in Autistic Children

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ABSTRACT

Objective: To investigate the estimated capacity of polymorphonuclear leucocytes (PMNLs) and whole blood to produce reactive oxygen species (ROS) in children with autism and mental retardation, and compare it with normal children

Design: Cohort study conducted between January and April 2007

Setting: Chemiluminescence laboratory (CL), Department of Physiology, Faculty of Medicine, King Khaled University Hospital, Riyadh, Saudi Arabia

Subjects: Forty autistic and eight mentally retarded children

Interventions: Oxygen free radical production (O_2-, H_2O_2, OH-) was detected by luminol-enhanced chemiluminescence, from isolated PMNLs and whole blood, stimulated by phorbol myristate acetate (PMA) and opsinized zymazan (OPZ).

Main Outcome Measures: Oxygen free radical production from whole blood and PMNLs

Results: Forty autistic (35 male and five female), and eight mentally retarded children (study group) were compared with forty six normal Saudi children (control group). The mean age was 7.4 ± 0.5 years. The CL peak response of whole blood and PMNLs stimulated with PMA and OPZ, in autistic children was significantly higher ($p < 0.05$) compared to control children. However, the CL peak response in children with mental retardation did not show any significant differences when compared to the control group.

Conclusion: There is an increase in oxygen free radicals production from whole blood and from PMNLs in autistic children. Therefore, an increase the antioxidant consumption in autistic children is strongly recommended.

KEY WORDS: autism, chemiluminescence, neutrophils, whole blood

INTRODUCTION

Autism is a neurodevelopmental disorder, usually diagnosed around the age of 36 months, and it is characterized by deficits in social interaction, language skills and repetitive behaviors[1]. It affects as many as one out of 166 children in the United States. Similar incidence of autism is found worldwide including Saudi Arabia. The male to female ratio is 4:1. Although there is growing research in the field of autism, there is still no known etiology as yet. Numerous studies have revealed evidence of cerebral hypoperfusion[2], neuroinflammation and gastrointestinal inflammation[3], immune dysregulation[3], oxidative stress[4], relative mitochondrial dysfunction, neurotransmitter abnormalities and impaired detoxification of toxins[5-10]. Many of those finding have been correlated with repetitive, self stimulatory and stereotypical behaviors and impairment of communication, sensory perception, and social interaction[3,4]. A significant role for genetics in the etiology of the autistic disorder is supported by a high concordance of autism between monozygotic twins and increased risks among siblings of affected children and of autistic symptoms associated with several inheritable genetic diseases. This association of autism with genetic deficits in specific enzymes might suggest the possibility that the genetic component of primary autism could be expressed as a chronic metabolic imbalance that impairs normal neurodevelopment and immunologic function[5- 7].

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There is some evidence that oxygen free radicals play an important role in the pathophysiology of many neuropsychiatric disorders[8]. An impaired antioxidant mechanism leads to increase in free radicals production, which might lead to cell injury. Several recent studies proposed that nitric oxide and other parameters related to oxidative stress have a pathophysiological role in autism[4,9]. Scientist, found an increase in red blood cells nitric oxide levels and increase in plasma glutathione peroxidase (GSH) activity in autistic children when compared to controls[9]. Others found the activity of super oxide dismutase (SOD), and erythrocyte and plasma glutathione peroxidase were significantly lower in autistic children compared to control[10]. This indicates a low antioxidant enzyme level activity in autistic children, and consequently an accumulation of free radicals leading to tissues damage.

The aim of this work was to investigate the estimated capacity of Polymorphonuclear leukocytes (PMNLs) and whole blood to produce reactive oxygen species (ROS) in autistic and children with mental retardation, and compare it to normal children in the control group. It is worth mentioning that no single work has been conducted on autistic children measuring the oxygen free radical production directly from neutrohpils and whole blood through CL technique, both locally in Saudi Arabia and in rest of the world.

SUBJECTS AND METHODS

This study was conducted in the department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia between January 2007 and April 2007. Forty autistic children (age up to 10 years old), with confirmed professional diagnoses were selected. The diagnosis was carried out either by a qualified psychologist, psychiatrist or neurologist, according to diagnostic criteria DSM-IV. In addition, eight children with mental retardation were included in the study. A written consent was obtained from their parents in the beginning. Healthy age and sex matched control volunteers were also recruited. Blood samples were collected by venepuncture in sodium heparin tubes, followed by measurement of oxygen free radicals directly from the fresh blood [11].

PMNLs separation

PMNLs were separated by using PMN isolation medium (Robbins Scientific Corporation, Sunnyvale, CA). Five to seven milliliters of heparinized blood was layered over 4 ml of PMNLs in a 15 ml tube and then centrifuged at 400 x g for 30 min at room temperature. The leukocyte-rich plasma was carefully removed with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube, filled with phosphate buffered saline (PBS) and centrifuged at 350 x g for 10 min (Jouan centrifuge Model B4i, France). Two milliliters of lysing buffer (0.87% NH4Cl) was added to lyse the residual erythrocytes, vortex to re-suspend the pellets and centrifuged at 250 x g for 10 min. The supernatant was discarded and the sediment suspended in 1 ml of 5% FCS. The cells were then counted and adjusted to the desired final concentration [11, 12].

PMNLs viability

The percentage of viable PMNLs was estimated by trypan blue exclusion test carried out by a microscopic count of cells not stained by 0.2% trypan blue and was expressed as percent of unstained cells to total cell numbers [13].

Chemiluminescence assay

Luminol-enhanced chemiluminescence: A Berthold (AutoLumatPlus LB 953) luminometer with a constant temperature (37 °C) controller (Bethold Technologies GmbH & Co. KG, Calmbacher Straße 22, D-75323 Bad Wildbad-Germany) connected to a computer was used. The reaction mixture consist of 100μl of whole blood or PMNLs suspension and 900 μl medium containing 10-5M luminol (5-amino-2,3-dihydro,1,4-phthalazinedione Sigma Chemical Co., St. Louis, MO, USA) , 2 ng/ml phorbol myristate acetate (PMA) (Sigma Chemical Co., St. Louis, MO, USA) , 1.25 mg/ml opsonized zymosan (OPZ) (Sigma Chemical Co., St. Louis, MO, USA) and phosphate buffered saline (PBS). Light emission was recorded in millivolts (mV) and the readings were recorded at one minute intervals for 30 minutes. CL emission was quantified as the peak height in mV[12, 13].

Statistical analysis

Metabolic data are presented as mean ± SDs. Statistical differences were ascertained by using the Student's t test with significance set at 0.05.

RESULTS

Forty-eight Saudi child participated in the study, with the following confirmed diagnosis: 40 autistic (35 males and five females), and eight with mental retardation. Forty six age and sex matched normal Saudi children who participated in the study as controls. All children who participated in the study were not on medication during sample collection. The mean age for the all children in the study was 7.4 ± 0.5 years. The results of the respiratory burst of whole blood and PMNLs from autistic and children with mental retardation compared with the control subjects are shown in Table 1, 2, 3 and 4. The respiratory burst of whole blood stimulated with PMA and OPZ, in autistic (male and female) children were all significantly higher ($p < 0.05$) compared to

Table 1: Respiratory burst of whole blood stimulated by PMA, as measured by chemiluminescence (CL), in control, autistic and children with mental retardation

Children (n)	(CL) Measurement (mv)		
	Basal	Maximum peak (mV)	Time to peak (min)
Control			
Male (28)	0.97 ± 0.6	11 ± 4	1850 ± 53
Female (18)	0.99 ± 0.7	13 ± 6	1770 ± 65
Autistic			
Male (35)	1.70 ± 0.5	25.33 ± 2*	1646 ± 43
Female (5)	1.5 ± 0.3	27.4 ± 6*	1540 ± 53
Mental retardation (8)	0.87 ± 0.2	15 ± 5**	1653 ± 36

PMA concentration = 2μg/cuvete; Luminol concentration = 2 M4/cuvete; Values are expressed as mean ± SD *p < 0.05 (as compared to control group); **p < 0.05 (as compared to autistic group)

Table 2: Respiratory burst of whole blood stimulated by OPZ, as measured by chemiluminescence (CL), in control, autistic and children with mental retardation

Children (n)	(CL) Measurement (mv)		
	Basal	Maximum peak (mV)	Time to peak (min)
Control			
Male (28)	0.97 ± 0.6	33 ± 5	2216 ± 65
Female (18)	0.8 ± 0.7	29 ± 4	2310 ± 54
Autistic			
Male (35)	1.60 ± 0.4	51± 7*	3068 ± 76
Female (5)	1.49 ± 0.3	67 ± 6*	3214 ± 62
Mental retardation (8)	0.97 ± 0.2	29 ± 5**	2234 ± 73

PMA concentration = 2 μg/cuvete; Luminol concentration = 2 M4/cuvete; Values are expressed as mean ± SD *p < 0.05 (as compared to control group); **p < 0.05 (as compared to autistic group)

control children (Table 1 and 2). The respiratory burst of children with mental retardation did not show any significant difference when compared to the control children (Table 1 and 2). Similar findings were also seen in the respiratory burst of PMA from autistic and children with mental retardation as compared to the control group (Table 3 and 4).

DISCUSSION

The current study demonstrated an increase in free radicals production (superoxide anion (O_2^-) hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH)), from whole blood and isolated human PMNLs in autistic children when compared to control. However, children with mental retardation showed no significant changes in oxygen free radicals production from whole blood and neutrophils.

Oxidative stress is a process caused by exposure to reactive oxygen intermediates, such as superoxide anion (O_2^-) hydrogen peroxide (H_2O_2), hydroxyl radicals (OH) and nitric oxide (NO) which can damage proteins, nucleic acids and cell membranes. At the same time the cell expresses enzymes that detoxify the reactive oxygen species or repairs the damage caused by them[4,5,14]. The presence of an efficient antioxidant system such as, the presence of SOD which converts O_2^- into (H_2O_2), which is rapidly reduced by catalase and glutathione peroxides[15,16] is very important to detoxify these reactive species before they can cause damage to cellular structures. Under pathological conditions an increase in free radical formation or a reduction of antioxidant defense system takes place resulting in excessive cell damage.

Under normal conditions, a dynamic equilibrium exists between the production of reactive oxygen species (ROS) and the antioxidant capacity of the cell[17,18]. The ROS within the cells are neutralized by antioxidant defense mechanisms. SOD, catalase,

Table 3: Respiratory burst of polymorphoneuclear leukocytes (PMNLs), stimulated by PMA, as measured by chemiluminescence (CL) in control, autistic and children with mental retardation

Children (n)	(CL) Measurement (mv)		
	Basal	Maximum peak (mV)	Time to peak (min)
Control			
Male (28)	20.9 ± 6	303 ± 34	728 ± 35
Female (18)	19.7 ± 1.5	298 ± 26	875 ± 42
Autistic			
Male (35)	29.8 ± 3	491± 51*	593 ± 54
Female (5)	22.7 ± 4	398 ± 41*	643 ± 75
Mental retardation (8)	20 ± 1.9	209 ± 32**	653 ± 56

PMA concentration = 2μg/cuvete; Luminol concentration = 2 M4/cuvete; Values are expressed as mean ± SD *P<0.05 (as compared to control group); **p < 0.05 (as compared to autistic group)

Table 4: Respiratory burst of polymorphoneuclear leukocytes (PMNLs), stimulated by OPZ, as measured by chemiluminescence (CL) in control, autistic and children with mental retardation

Children (n)	(CL) Measurement (mv)		
	Basal	Maximum peak (mV)	Time to peak (min)
Control			
Male (28)	21.9 ± 6	1113 ± 39	2107 ± 45
Female (18)	19.7 ± 1.5	1200 ± 37	2234 ± 54
Autistic			
Male (35)	28.8 ± 3	1717± 61*	1600 ± 64
Female (5)	23.7 ± 4	1698 ± 43*	1700 ± 54
Mental retardation (8)	18 ± 1.9	1198 ± 38**	2317 ± 53

PMA concentration = 2μg/cuvete; Luminol concentration = 2 M4/cuvete; Values are expressed as mean ± SD *p < 0.05 (as compared to control group); **p < 0.05 (as compared to autistic group

and glutathione peroxidase (GPx) are the primary enzymes involved in direct elimination of ROS, whereas glutathione reductase and glucose-6-phosphate dehydrogenase are secondary antioxidant enzymes, which help in maintaining a steady concentration of glutathione and NADPH necessary for optimal functioning of the primary antioxidant enzymes[14-17]. These enzymes require micronutrients such as selenium, iron, copper, zinc, and manganese as co-factors for optimal catalytic activity and effective antioxidative defense mechanism[17]. Additionally, glutathione (GSH), iron-binding transferrin, copper-binding ceruloplasmin, *a*-tocopherol (Vitamin E), carotenoids, and ascorbic acid (Vitamin C) are also involved in the anti-ROS defense system[17,18]. GSH is the most important antioxidant for detoxification and elimination of environmental toxins. Oxidative stress occurs when ROS levels exceed the antioxidant capacity of a cell. These ROS are highly toxic and react with lipids, proteins and nucleic acids, and lead to cell death *via* apoptosis or necrosis[18].

The brain is highly vulnerable to oxidative stress due to its limited antioxidant capacity, higher energy requirement, and higher amounts of lipids and iron[18]. The brain makes up about 2% of body mass but consumes 20% of metabolic oxygen. The vast majority of energy is used by the neurons[19,20]. Due to the lack of glutathione-producing capacity by neurons, the brain has a limited capacity to detoxify ROS. Therefore, neurons are the first cells to be affected by the increase in ROS and shortage of antioxidants and, as a result, are most susceptible to oxidative stress. Antioxidants are required for neuronal survival during the early critical period[10,21-23]. Children are more vulnerable than adults to oxidative stress because of their naturally low glutathione levels from conception through infancy[21,22]. Several studies have shown decreased levels of antioxidants such as SOD, transferrin and cereluplasmin in blood or serum of patients with autism spectrum disorders[10,22,23]. Furthermore, significant elevation in oxidative stress biomarker profile was documented in autistics, indicating increased oxidative stress[23,24]. The risk created by this natural deficit in detoxification capacity in infants is increased by the fact that some environmental factors that induce oxidative stress are found at higher concentrations in developing infants than in their mothers, and these accumulate in the placenta. Taken together, these studies suggest that the brain is highly vulnerable to oxidative stress, particularly during the early part of development that may result in neurodevelopmental disorders such as autism. In fact, recent evidence points towards increased oxidative stress in autism, including the current study.

Increased oxygen free radical production can lead to increased apoptosis. This might contribute to Purkinje cell hypoplasia observed in a some autistic cases, which in turn, contributes to the stereotypic behavior observed in autism[10,22,25,26]. The reduction in Purkinje cell number is likely to affect the neuronal communication and could contribute to autistic behavior such as planning, learning, cognitive flexibility, sensory processing, exploratory activity and other cognitive[27] and emotional processes[28]. Sajdel-Sulkowska *et al* suggested a tentative oxidative-stress-mediated model of autistic pathology based on possible interaction between environmental and genetic factors, leading together to an increase production of free radical both centrally (in the brain) and peripherally (in the plasma). This may result in apoptosis, and reduction in the Purkinje cell number leading to autistic pathology[29].

CONCLUSION

Results from the current study demonstrated an increase in oxygen free radicals production from whole blood and from PMNLs in autistic children. Increased oxidative stress may lead to membrane lipid abnormalities, mitochondrial dysfunction, excitotoxicity, inflammation, and immune dysregulation in autism[30,31]. These defects might contribute to behavioral abnormalities, sleep disorder, and gastrointestinal disturbances in autism. Thus, increased antioxidant consumption in autistic children is strongly recommended. This can be achieved either by increasing the intake of food with high antioxidant contents such as strawberries, tomato, spinach, broccoli and nuts or, through antioxidant supplementation, such as vitamin E, co-enzyme Q10, glutathione and vitamin C. This preliminary data suggest a need for more extensive studies of oxidative stress in autism, its relationship to the environmental factors and the possibility of prevention of its negative effect by antioxidants therapy. Our finding of increased oxygen free radical production from neutrophils and whole blood in autistics, further supports the hypothesis of oxidative stress involvement in autism pathology.

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Original Article

Surveillance of Healthcare-Associated Infections in Adult Patients with Leukemia in Kuwait Cancer Control Center

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ABSTRACT

Objective: To study the incidence, types and microbial etiology of healthcare-associated infections affecting adult patients with leukemia and the antimicrobial susceptibility of Gram-negative bacteria to ciprofloxacin
Design: Prospective study
Setting: Kuwait Cancer Control Center (KCCC), Kuwait
Subjects: All adult patients suffering from different types of leukemia, managed in the Hematology-Oncology unit over a period of 15 months (January 2006 - March 2007)
Methods: Prospective surveillance of healthcare-associated infections
Results: Overall incidence density rate of healthcare-associated infections was 13.4/1000 patient days. Patients suffering from acute myeloid leukemia (AML) had the highest infection rate (16.2/1000 patient days). The rates were significantly higher in acute types of leukemia than chronic ones ($p = 0.001$). Infections develop significantly more in female patients ($p < 0.001$). The most frequently reported infections were blood stream infections (BSI, 46.9%) followed by skin and soft tissue infections (SST, 25.7%). Eighty-three percent of BSI was central line-associated. Gram-negative bacteria, Gram-positive bacteria and fungi were isolated from 69.9, 18.6 and 4.4% of all infections respectively. *Escherichia coli (E. coli)* were isolated from 35.2% of all microbiologically-documented infections followed by *Pseudomonas aeruginosa* (15.2%). Majority of the isolated Gram-negative bacteria were ciprofloxacin resistant including *E. coli*, with 97.3% resistance to ciprofloxacin. Majority of the infections (80.5%) were associated with a neutrophil count of < 500 cell/mm^3 in patients receiving ciprofloxacin prophylaxis.
Conclusion: Infections remain a major complication in adults with acute leukemia. Continuous monitoring of the rate of Gram-negative bacteremia is recommended for timely detection of the loss of efficacy of fluoroquinolone prophylaxis.

KEY WORDS: healthcare-associated infections, leukemia, neutropenia, surveillance

INTRODUCTION

Healthcare improvement has allowed increasingly aggressive management in diagnostic and therapeutic procedures for hematology-oncology patients. These intensified treatments have been associated with severe neutropenia which has been identified as the most important risk factor for infectious complications in patients with neoplastic diseases[1-3]. As a result, infections become an important cause of morbidity and mortality and are associated with prolonged hospital stay and increased healthcare costs[4,5]. Therefore, the present study was undertaken to study the incidence of healthcare associated infections affecting adult patients with leukemia during their admission to Kuwait Caner Control Center (KCCC). The study also aimed to identify types and microbial etiology of such infections as a step towards improving infection control policies. In addition, testing of antimicrobial susceptibility of isolated Gram-negative bacteria to ciprofloxacin (which is used as oral prophylaxis for gut decontamination during the neutropenia period) was another objective.

SUBJECTS AND METHODS

All adult patients suffering from different types of leukemia who were managed in the Hematology-Oncology unit of Hussein Makki Al-Jumaa Center for Specialized Surgeries (Kuwait Cancer Control Center) over a period of 15 months from January 2006 to March 2007 were enrolled in the present study.

Prospective surveillance of healthcare-associated infections was performed based on the Center for Disease Control and Prevention (CDC) standard definitions for nosocomial infections[6]. Healthcare-associated infections were diagnosed by collecting information from clinical data (symptoms and signs),

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Table 1: Distribution of adult patients with leukemia according to the disease type and incidence rate of healthcare- associated infections

Type of leukemia	Patients n (%)	Number of infections	Number of patient days	Incidence density rate of health care- associated infections /1000 patient days
Acute myelocytic leukemia (AML)	132 (53.9)	70	4315	16.2
Acute lymphocytic leukemia (ALL)	58 (23.7)	41	3122	13.1
Chronic myelocytic leukemia (CML)	35 (14.3)	2	680	2.9
Chronic lymphocytic leukemia(CLL)	20 (8.1)	0	328	0
Total	**245 (100)**	**113**	**8445**	**13.4**

investigations (laboratory, radiological, *etc*) and microbiological culture and sensitivity results[6].

The study was approved by the Ethical Committee of the Ministry of Health. Patients' clinical data were obtained from charts, doctors' notes, nurses' notes, and additional information provided from the attending physicians.

The findings were recorded in a preformed format that included demographic data, specific medical devices used (peripheral or central venous catheters, urinary catheters, nasogastric tubes and endotracheal tubes), WBCs and neutrophil counts and antibiotics used including ciprofloxacin oral prophylaxis. Data about the details of healthcare-associated infection episodes such as date and site of onset, clinical findings, investigation done and microbiologic culture and sensitivity results were included. Antimicrobial susceptibility of the isolated Gram-negative bacteria to ciprofloxacin was performed in Ibn Sina Hospital Laboratory Department.

In cases of blood stream infections (BSI), urinary tract infections (UTI) and pneumonia (PNEU), the infections were specified as device-associated (central line, indwelling urinary catheter and ventilator respectively) or not device-associated. This was in accordance with the CDC / National Healthcare Safety Network (NHSN) patient safety component protocol[7].

Neutropenic fever of unknown origin that was without evidence of a specific infection at any site and without an identifiable pathogen from body specimens (lacks a direct microbiological or clinical confirmation and may thus be of limited specificity) was excluded from the present study.

Incidence density rate of healthcare-associated infections (nosocomial infections) was calculated by the following formula[8]:

$$\frac{\text{Number of new nosocomial infections acquired in the study period x 1000}}{\text{Total of patient-days for the study period}}$$

Statistical methodology

Data were collected and then entered into the computer using the SPSS version 12 for Windows. Entered data were checked for accuracy and then for normality. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean (*X*) and standard deviation (S).

The following statistical tests were used:

1. Independent samples t-test was used as a parametric test of significance for comparison between two sample means.
2. The X^2 test was used as a test of significance for comparison between the incidence density rates.
3. The Fisher's exact test was used whenever the X^2-test was not appropriate.

A 5% level was chosen as a level of significance in all statistical significance tests used.

RESULTS

The study included 245 adult patients with different types of leukemia. Their ages ranged from 18-78 years with mean of 42.19 ± 14.51 years. There were 163 (66.5%) male and 82 (33.5%) female patients. The patients stayed 8445 days in KCCC during the study period. The majority of patients (53.9%) were suffering from acute myelocytic leukemia (AML) (Table 1)

The study revealed that a total of 113 healthcare-associated infections developed in 73 patients. Their ages ranged from 18-74 years with a mean of 40.01 ± 12.59 years. Forty-two (57.5%) were female whereas 31 (42.5%) were male.

The age difference between the patients who developed infections and patients who did not was not statistically significant ($t = 1.535$, $p = 0.126$). However, the sex difference was significant ($X^2 = 27.043$, $p < 0.001$) and female patients were more prone to infections.

The overall incidence density rate of healthcare-associated infections was 13.4 / 1000 patient days. The rates were significantly higher in acute types of leukemia than chronic ones ($X^2 = 11.261$, $p = 0.001$). AML had the highest infection rate (16.2 / 1000 patient days).

The most frequently reported infections were blood stream infections (BSI, 46.9 %) followed by skin and soft tissue infections (SST, 25.7%). Pneumonia (PNEU) represented 11.5% while urinary tract infections (UTI) represented 7.1% of the total infections. Oral candida mucositis was reported in 2.7% of cases. *Clostridium difficile (C. difficile)* accounted for 1.7 % and 4.4% constituted other infections.

Seventy nine infections (69.9%) were due to Gram-negative bacteria while 21 (18.6%) and five (4.4%) infections were due to Gram-positive organisms and fungi respectively. Eight infections clinically diagnosed without microbiological documentation represented 7.1% of all infections; half of them were pneumonia cases. *Escherichia coli (E. coli)* were isolated from the majority of microbiologically documented infections (35.2%). *Pseudomonas aeruginosa (P.aeruginosa)* was the second commonest encountered pathogen causing 16 (15.2%) of microbiologically proven infections. The distribution of the different pathogens among the different types of healthcare-associated infections is shown in Table 2. Only 22 infections (19.5 %) were associated with a neutrophil count > 1000 cell/mm^3 while 91 infections (80.5 %) were associated with neutrophil count of < 500 cell / mm^3 in patients receiving ciprofloxacin prophylaxis.

The majority of isolated Gram-negative bacteria were ciprofloxacin resistant. All *E. coli* isolates from different types of infections were ciprofloxacin resistant except one strain (overall resistance 97.3%)

Table 2: Pathogens causing healthcare-associated infections in adult leukemia patients from January 2006 -March 2007 at KCCC

Organism	Site of Infection							
	UTI	PENU	GI	ORAL	BSI	SST	others	Total
Staphylococcus aureus					1	1	1$	3
Methicillin -resistant Staphylococcus aureus					2			2
Coagulase -negative staphylococci					7			7
Enterococcus faecalis	1					1		2
Enterococcus faecium					2	1		3
Enterococcus gallinarum						1		1
Streptococcus mitis					1			1
Clostridium difficile			2					2
Escherichia coli	4	1			22	10		37
Enterobacter cloacae						1		1
Proteus mirabilis	1					1		2
Klebsiella pneumoniae					6	1		7
Pseudomonas aeruginosa	1	2			2	10	1	16
Citrobacter freundii					1			1
Stenotrophomonas maltophilia		3			5	1	1	10
Acinetobacter baumannii		1			1			2
Chryseobacterium. meningosepticum					2			2
Burkholderia cepacia					1			1
Candida albicans		1		1				2
Candida krusei	1	1						2
Aspergillus flavus							1+	1
Culture not done				2			1+	3
No pathogen isolated		4				1		5
Total	8	13	2	3	53	29	5	113

UTI = urinary tract infection; PNEU=pneumonia; GI = gastrointestinal system infection; BSI = blood stream infection; SST = skin and soft tissue infection; Others: $surgical site infection (SSI), *Hickman exit site infection, +sinusitis

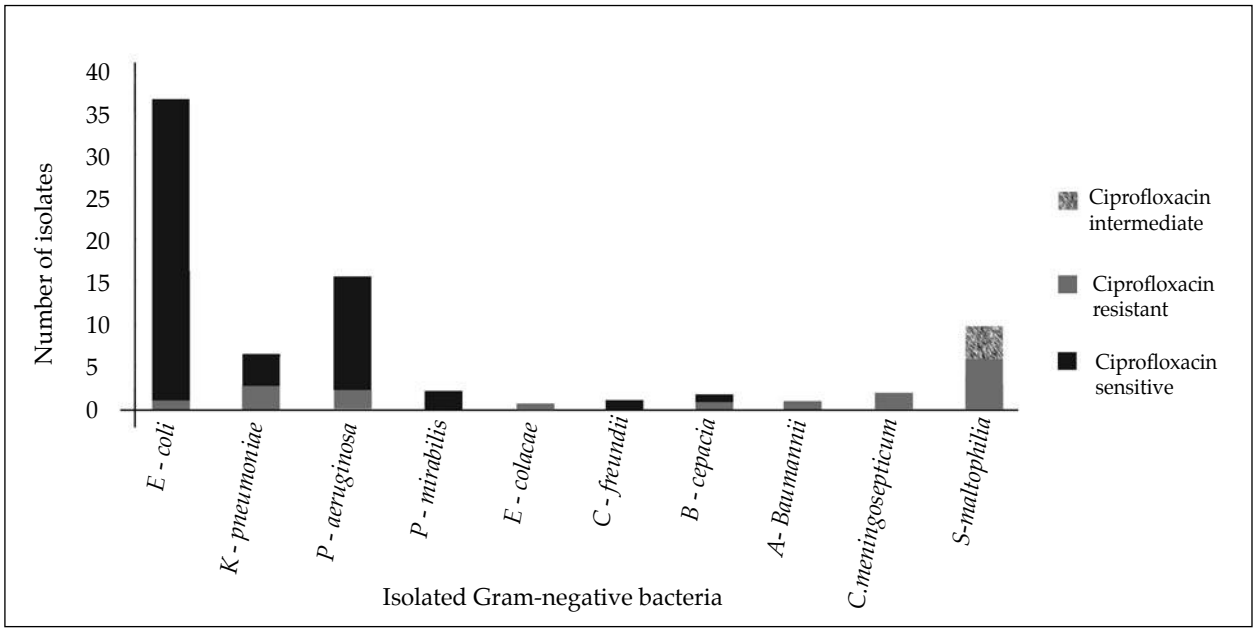

Fig. 1: Susceptibility of the isolated Gram-negative bacteria to ciprofloxacin.The only sensitive strain of *E.coli* was isolated from SST infection

which was isolated from SST infection. Four isolates (57.1%) of *Klebsiella pneumoniae (K. pneumoniae)* were resistant to ciprofloxacin. *E.coli* were significantly more resistant to ciprofloxacin than *K. pneumoniae* ($p = 0.01$). The susceptibilities of the isolated Gram-negative bacteria to ciprofloxacin are shown in Fig. 1.

Out of BSI, 44 infections (83%) were central line-associated. Regarding UTI, four infections (50%) were associated with indwelling urinary catheter while no case was diagnosed as ventilator associated pneumonia (VAP).

DISCUSSION

The increasingly intensified chemotherapy in hematology-oncology population have led to higher hematologic toxicity with more severe and prolonged neutropenia, as well as other types of immunosuppresion, making these patients more vulnerable to nosocomial infections[9]. Our results revealed that the overall incidence of healthcare-associated infections in adult patients with leukemia was 13.4 / 1000 patient days. Higher incidence (17.7 / 1000 patient days) was reported by Urrea *et al*[9] in pediatrics with different hemato-oncology diseases and not only confined to leukemia as in our study. Moreover, in their study, they did not perform intestinal decontamination in neutropenic patients. On the other hand, our patients received ciprofloxacin (for gut decontamination) with or without antifungal prophylaxis during the neutropenia period (ANC < 1000 c/mm^3). Engelhart *et al*[10] reported a lower incidence (11 / 1000 patient days) of nosocomial infections among adults with different hematology-oncology diseases and not only leukemia.

In the present study, the incidence density rates were significantly higher in acute types of leukemia than in chronic ones. Several studies reported that patients with acute leukemias are more prone to infection complications. This marked susceptibility generally results from both chemotherapy-induced neutropenia, which is typically prolonged and profound, and mucositis affecting the oropharynx and gastrointestinal tract[10-14].

Female patients significantly developed more infections in the present study; however, we could not find any reports in the literature regarding sex difference in the susceptibility of adult leukemia patients to infections.

Several studies indicate that at least half of neutropenic patients who have a fever of unknown origin have an established or occult infection[10,11]. However, fever can also be a manifestation of many non-infectious causes such as the underlying leukemia, transfusion reactions, thrombo-embolism, drugs, allergic reactions, hematomas and radiation injury[10,11]. The proportion of non-infectious causes of fever of unknown origin can be reduced further by a thorough clinical assessment[12].

The appearance of fever in a neutropenic patient is considered a medical emergency and requires immediate attention[13]. Due to the severity and high mortality of infections in this patient population, prompt empiric therapy is mandatory. Therefore, for many febrile episodes, the infectious etiology cannot be established before antimicrobial therapy is initiated[14]. Diagnosis of infections in neutropenic patients is often impeded, because a marked decrease in the number of neutrophils is associated with a diminished

inflammatory response and often muted clinical signs[12]. Drug fever can occur after the administration of virtually any medication, even one administered for long periods without problems[15]. Based on the previous facts and due to lack of microbiological or clinical confirmation and limited specificity of fever of unknown origin, we excluded this clinical entity from the present study.

In the present investigation, 80.5% of infections developed during the period of severe neutropenia (neutrophil count of < 500 cell/mm^3). Several studies stated that, patients with severe neutropenia are at high risk for bacterial and fungal infections[8-10,15,16]. The organisms responsible for infections associated with neutropenia are most often the patient's own bacteria[13]. The primary source of pathogens is the alimentary tract, where cancer chemotherapy-induced mucosal damage allows invasion of endogenous organisms. Similarly, skin damaged by invasive procedures, *e.g.*, with vascular access devices, is another portal of entry for infectious organisms[13].

In addition to exogenous routes of infection, the endogenous intestinal bacterial flora is a potential source of life-threatening bacteremia caused by Gram-negative microorganisms, with intestinal colonization being the antecedent to bacterial translocation across the gut and systemic dissemination. To reduce the incidence of bacteremia, such patients often receive antibiotic prophylaxis, called selective decontamination of the gut. This prophylaxis is intended to eliminate potentially pathogenic bacterial species while maintaining native anaerobic flora. The fluoroquinolones such as ciprofloxacin show excellent activity, good bioavailability, and high concentrations in the gut, and thus provide an important component of the standard selective decontamination in many centers including our center[17-20]. As a result of this practice, during the past two decades, the microbial etiology of BSI in patients with febrile neutropenia has shifted from Gram- negative to Gram-positive organisms in many centers[9-11,13].

In the present study, despite the use of ciprofloxacin prophylaxis for acute leukemia patients during neutropenic period (ANC < 1000 c/mm^3), the most frequently reported infections were primary BSI caused by Gram- negative bacteria, predominantly *E.coli*, which were all resistant to ciprofloxacin. Similarly, Comez *et al*[21] reported higher rate of Gram- negative bacteremia in the ciprofloxacin receiving group than in the control group not receiving prophylaxis. Their study was carried out among adult patients with acute leukemia who developed episodes of febrile neutropenia. Cattaneo *et al*[22] in their study on infections in patients with hematological malignancy used levofloxacin prophylaxis in patients with more than seven days expected neutropenia. They reported that Gram-negative (49.4%) outweighed Gram-positive bacteria (40.9%), *E. coli* being most frequent (23.2%) and 86.8% of *E. coli* were quinolone resistant. Uqarte -Torres *et al*[23] reported that bacteremia was most frequently caused by Gram- negative organisms (18 / 29), E. coli being the most commonly isolated pathogen in their study on leukemia patients.

Central venous catheters (CVCs) are necessary to facilitate treatment of hematologic disorders, but catheter-related bloodstream infections (CR-BSIs) are important causes of morbidity and mortality, and may lead to interruptions in planned therapy for malignancy or increases in length of hospital stay[24]. In the present study, 83% BSIs were associated with a central line. Inorder to determine that central venous catheters were the source of bloodstream infections (central line related BSI), specific criteria including the requirement of peripheral blood cultures and catheter-tip cultures to be positive, together with other methods of confirmation. Confirmatory microbiological methods include a differential time to positivity of > 2 hours (blood culture drawn from the catheter becomes positive at least two hours earlier than a simultaneously drawn peripheral blood culture) and a > 5:1 ratio of simultaneously drawn quantitative central blood culture compared with peripheral blood culture[24, 25]. These criteria were not implemented in our center.

Skin and soft tissue infections represented about one quarter of infections in leukemic patients in the present study. They are mainly caused by *E.coli* and *P.aeruginosa.* SST represented 13% of infections in patients with acute leukemia reported by Jagarlamudi *et al*[26]. Lopez and Sanders[27] stated that *P. aeruginosa* has an important role in SST infections in febrile neutropenic patients with cancer. Prevention in immuno-compromised patients is important and demands careful attention to measures that protect the skin from unnecessary trauma, maceration, or alterations in the normal microbial flora[28].

In the present investigation, culture of specimens from the respiratory tract of patients with clinical and radiological evidence of pneumonia was unrevealing in 30.8% of cases. Madani[11] stated that the majority of pneumonia cases in his study on acute AML patients were culture negative. Engelhart *et al*[10] isolated pathogens from only one third of pneumonia cases. Negative cultures may be due to either early antibiotic administration or inadequate specimens submitted for microbiologic evaluation[29].

CONCLUSION

Despite the use of prophylactic antibiotics, infections remain a major complication in adults with acute leukemia. Infection is directly proportional to the degree of neutropenia. Continuous monitoring of the rate of Gram-negative bacteremia is recommended for timely detection of the loss of efficacy of fluoroquinolone prophylaxis.

We expect that these data will guide local prevention strategies and could help to design control guidelines aimed at reducing infection rates, morbidity and mortality associated with infections in leukemic patients.

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Original Article

Effect of Anterior Nasal Packing on Middle Ear Pressure and Hearing Threshold

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ABSTRACT

Objective: To evaluate the effect of anterior nasal packing on middle ear pressure and hearing threshold
Design: Prospective study conducted between June and December 2007
Setting: Department of Otolaryngology, Al-Adan Hospital, Ministry of Health, Kuwait
Subjects: Twenty patients of either sex in the age group 18 - 45 years admitted for septoplasty
Interventions: Pure Tone Audiometry (PTA) and impedance audiometry (IA) were done in all patients preoperatively, 48 hours after surgery with nasal packs in position and seven days after removal of packs.
Main Outcome Measures: PTA and IA before and after nasal packing
Results: Normal middle ear pressure was observed preoperatively in most of the ears. Forty eight hours after septal surgery with nasal packs in position, 14 ears had abnormal negative middle ear pressure of 100 to 300 mm H_2O. Seven days after pack removal, there was marked improvement in middle ear pressure. Hearing threshold remained normal before and after surgery. Nasal packing following septal surgery is a frequent cause of short-term eustachian tube dysfunction but rarely severe enough to cause symptoms of middle ear effusion. Tubal dysfunction is most likely due to peritubal inflammation or stasis of peritubal lymphatics and reduced swallowing in the post operative period due to pain.
Conclusion: Changes in middle ear pressure following nasal packing associated with most nasal surgeries were transient and not severe.

KEY WORDS: hearing threshold, impedance audiometry, middle ear pressure, nasal pack, pure tone audiometry

INTRODUCTION

Eustachian tube maintains middle ear pressure equal to that of atmosphere. Its function may be deranged due to variety of factors like adenoids, cleft palate, nasogastric tubes, allergy, and nasopharyngeal intubation. It has been suggested that nasal packing following septal surgery is a frequent cause of short-term Eustachian tube dysfunction[1-6]. As nasal packing is frequently required following nasal surgery, the present study was undertaken to evaluate the effect of nasal packing on middle ear pressure and hearing threshold.

SUBJECTS AND METHODS

Twenty patients (40 ears) of either sex in the age group of 18 to 45 years admitted for septal surgery to department of otolaryngology, Al-Adan Hospital, Kuwait, were included in the study. Pure Tone Audiometry (PTA) and impedance audiometry (IA) were done in all cases before surgery, 48 hours after surgery with nasal packs in position and seven days after removal of packs. The hearing threshold and middle ear pressure were compared.

The study was approved by the Hospital Ethical Committee.

RESULTS

1. Preoperatively: PTA revealed normal hearing threshold in 37 ears (up to 20 dB is normal) while three ears had hearing threshold of 20 to 40 dB. Impedance audiometry (IA) revealed normal middle ear pressure in all the ears (Table 1 and 2).
2. Forty-eight hours after septoplasty with nasal packs in position,14 ears had abnormal negative middle ear pressure of 100 to 300 mm

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Table 1: Comparison of hearing threshold. (N = 40)

Hearing threshold (in dB)	Pre-operative Ears (N = 40)	48 hours postoperative with nasal pack Ears (N=40)	7 days After pack removal Ears (N = 40)
0-10	26	22	26
11-20	11	14	10
21-30	2	3	3
31-40	1	1	1

Table 2: Comparison of middle ear pressure. (N = 40)

Middle ear pressure (mm of H_2O)	Pre-operative Ears (N=40)	48 hours postoperative with nasal pack Ears (N = 40)	7 days after pack removal Ears (N = 40)
+100 to +1	12	11	16
0 to -99	28	15	24
-100 to -199	0	9	0
-200 to -300	0	5	0

H_2O while four ears had hearing threshold of 20 to 40 dB (Table 1 and 2).

3. Seven days after pack removal, there was marked improvement in middle ear pressure in all the ears. Hearing threshold remained the same (Table 1 and 2).

DISCUSSION

Nasal packing following septal surgery is a frequent cause of short-term Eustachian tube dysfunction but rarely severe enough to cause symptoms of middle ear effusion. Tubal dysfunction is most likely due to a combination of surgical edema and a direct effect of the nasal packing[2].

In the present series, there was no significant change in hearing threshold after 48 hours of nasal packing and seven days after pack removal. IA after 48 hours of nasal packing revealed abnormal middle ear pressure in 14 out of the 40 ears tested. Seven days after nasal pack removal there was improvement in middle ear pressure in all ears. Similar findings were observed by other workers also[1,2,4,5]. The possible mechanisms for this transient eustachian tube dysfunction could be:

1. Inflammatory edema of nasopharyngeal mucosa as a result of packing may lead to Eustachian tube dysfunction possibly by causing peritubal inflammation or stasis of peritubal lymphatics[1].

2. There may be deficiency of surfactant which facilitates opening of the Eustachian tubes. This material is inactivated by inflammation which occurs following nasal packing.

3. Reduced swallowing in the postoperative period due to pain leads to restrictive opening of eustachian tube.

This transient change in middle ear pressure is unlikely due to anesthesia as middle ear pressure studies prior to general anesthesia were not statistically different from middle ear status under anesthesia[7].

CONCLUSION

Changes in middle ear pressure following nasal packing associated with most nasal surgeries were transient but not severe.

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Original Article

Congenital Pouch Colon from Al-Ahsa Region of Saudi Arabia – A Changing Demography?

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ABSTRACT

Objective: To study the demography, anatomy and management of congenital pouch colon (CPC) in the Al - Ahsa region of the Kingdom of Saudi Arabia (KSA)
Design: Retrospective descriptive analysis of CPCs was made with regard to patient demography, pre- and intra-operative diagnostic features and initial neonatal management.
Setting: Maternity and Children Hospital, Al-Ahsa region, KSA
Subjects and Methods: Records of all children with anorectal malformations (ARM) treated between August 2004 and August 2007 were reviewed. Out of the 37cases of ARMs, seven were diagnosed as CPCs.
Interventions: Records were analysed for perineal findings, X-ray abdomen and invertogram (when indicated), abdominal ultrasound, type of pouch, division of any urinary fistula, and surgical management.
Results: Six out of seven CPCs were among Saudi nationals belonging to Al-Ahsa region. The male to female ratio was 4:3. Six were type IV and one was type III pouch. Preoperative diagnoses were made in two cases by radiology and all cases showed classic anatomical features of CPC intra-operatively. 71% had associated anomalies. Excision of pouch and end colostomy was done in three, loop stoma was done in two and excision of pouch with neonatal pull-through was done in two cases.
Conclusion: CPCs are recently being increasingly reported in Saudi nationals. Adequate awareness about radiological, anatomical and histological features would lead to correct diagnosis and reporting. Appropriate neonatal management would prevent pouch related morbidity. Collective data from multiple centers across the Arab peninsula will help define the demographic pattern of this entity in the region.

KEY WORDS: anatomy, congenital pouch colon, demography, etiology, Saudi Arabia

INTRODUCTION

The condition of Congenital Pouch Colon (CPC) has been associated with ano-rectal agenesis, particularly seen in Asia and is defined as an anomaly in which whole or part of the colon is replaced by a pouch like dilatation, which mostly communicates distally with the urogenital tract by a fistula[1]. Recently the Krickenbeck classification for anorectal malformations (ARM) has classified this entity as a rare anomaly[2]. This condition is seen much more frequently in the northern, northwestern and central part of India and neighboring nations like Pakistan, Bangladesh and Nepal, accounting for more than 90% of the reported cases. Only a few reports have originated from China, Japan, Sweden, United Kingdom and other parts of world[1,3,4] but none from the Arab peninsula.

The cause of this unique geographical distribution has not yet been ascertained. We report a series of seven cases of CPCs from Al Ahsa region of Eastern Province of Kingdom of Saudi Arabia (KSA) treated at the Maternity and Children's Hospital (MCH). To our knowledge, this is the first reported series of CPCs from KSA and the Arab world.

SUBJECTS AND METHODS

Between August 2004 and August 2007, 37 cases of ARMs were treated at MCH, Al Ahsa region of the Eastern Province of KSA. Seven of these were detected to have CPC. The patient demographics are given in Table 1. We have made a descriptive analysis of the patient characteristics, anatomical features, and initial management at presentation and discussed the etiology of this rare anomaly.

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Table 1: Patient demographics

Patient No.	Sex	Type of pouch and ARM	Associated anomalies	Surgical procedure
1	M	Type IV with pouch-vesical fistula	Lumbo sacral hemivertebrae	Excision of pouch, division of fistula and end colostomy
2	M	Type IV without urinary fistula	Cleft palate and facial dysmorphism	Excision of pouch and end colostomy
3	M	Type III with pouch urethral fistula	Esophageal atresia and tracheo-esophageal fistula(TEF), VSD (VACTREL association)	Loop colostomy and repair of TEF by right thoracotomy
4	F	Type IV and rectovestibular fistula	None	Excision of pouch and neonatal pull-through
5	F	Type IV and rectovaginal fistula	Tetralogy of Fallot	Loop colostomy
6	F	Type IV and rectovestibular fistula	None	Excision of pouch and neonatal pull-through
7	M	Type IV and pouch vesical fistula	Sacral agenesis	Excision of pouch, division of fistula and end colostomy

This study was approved by the ethical committee of the hospital.

RESULTS

Out of 37 cases of ARM, seven cases were diagnosed to have CPC. There were four male and three female babies. Six out of seven cases were Saudi nationals and one was an Indian expatriate. In two of the male babies a large air fluid level occupying more than half of the width of the abdomen on plain skiagram helped in the preoperative diagnosis of CPC (Fig. 1). In rest of five cases CPC was diagnosed intra-operatively. The anatomical features of pouches in our series included thick walled abrupt change of tubular caliber of distal colon into spherical pouch without any transition zone (Fig. 2). There were absent or ill defined taenia coli, absent haustrations and appendices epiploicae. The mesentery was somewhat short and vessels were arising from superior mesenteric artery or hypoplastic inferior mesenteric artery forming a leash of blood vessels around the pouch. The wall of the pouch was thick, muscular, lined with hypertrophied mucosa. Histopathologically there was thickening of the submucosal layer and criss-cross pattern of decussating fibres in the muscle coat. The normal longitudinal and circular pattern was lost.

We categorized our CPCs according to the popular classification by Rao *et al* [5], as shown in

Table 2: Types of pouch colon (Rao *et al*)[5]

Pouch colon	Diagnosis of CPC
Type I	Absent normal colon, ileum opens directly into colonic pouch
Type II	Cecum and short segment of ascending colon opens into colonic pouch
Type III	Cecum, ascending colon and part of transverse colon opens into colonic pouch
Type IV	Most of the colon is normal, part of sigmoid and rectum are pouch like

CPC = Congenital pouch colon

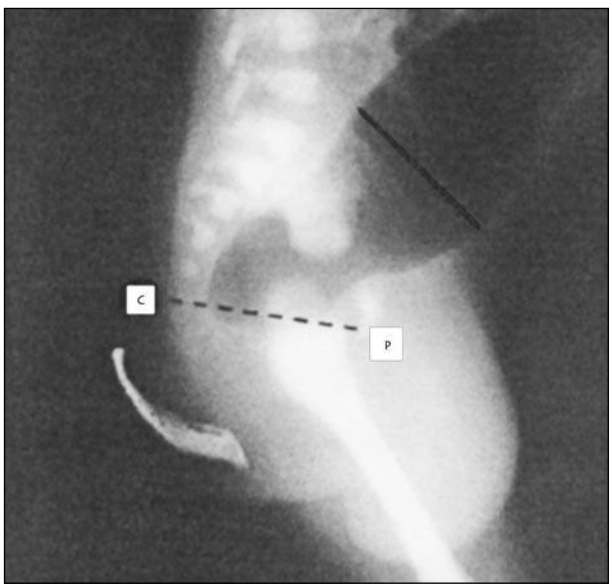

Fig. 1: Invertogram showing colonic air shadow greater than 50% of abdominal width (solid line) and intermediate ARM (dotted line denotes pubo-coccygeal line).

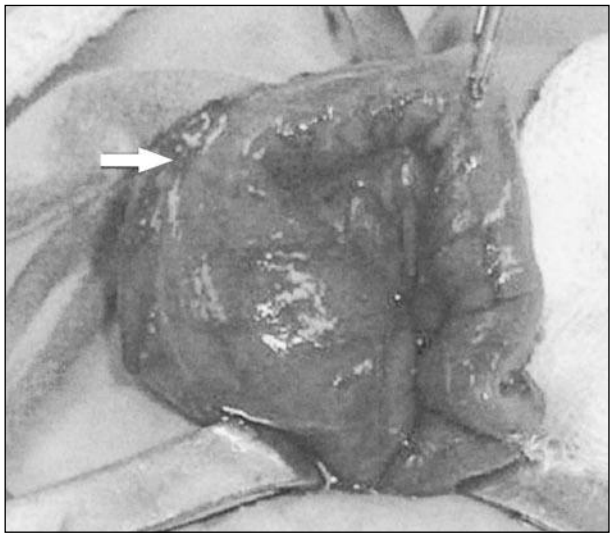

Fig. 2: Intraoperative feature of pouch colon. Block arrow shows sudden transition of tubular colon into a spherical pouch.

Table 3: Working classification of congenital pouch colon (Gupta *et al*)[1]

1. Complete Congenital pouch colon – If there is no or little normal colon left that is not enough for performing the pull-through. A coloplasty procedure would be required to retain only 15 cm length of pouch colon in the form of a tube and this is brought out as an end colostomy. A pull-through procedure at the time of performing coloplasty should not be preferred in the newborn stage as it is associated with high morbidity and mortality.

2. Incomplete Congenital pouch colon – Where the length of colon is adequate for performing the pull through, without the need for doing a coloplasty. The procedure would involve excision of pouch with an end colostomy at birth and a definite pull-through later. A single stage neonatal pull-through can also be undertaken if the condition of the baby permits.

Table 2 and it included six type IV and one type III pouch. Our initial management of these babies with ARM was based on recent recommendations similar to those by Gupta *et al*[1] as shown in Table 3. We performed excision of pouch with end colostomy in three of these and complete neonatal pull-through in two cases (with vestibular fistulae). Out of two remaining cases, loop stoma was constructed in a male child due to multiple congenital anomalies requiring simultaneous thoracotomy and repair of tracheo-esophageal fistula in order to minimize the operating time. Also in another female child with recto-vaginal fistula, type IV pouch and associated tetralogy of Fallot a proximal loop colostomy was constructed as a quick initial procedure due to anesthetic issues (baby developed hemodynamic instability due to Tetralogy of Fallot). The five neonates with stoma underwent definitive pull-through (abdomino - sagittal anorectoplasty) between 3 - 6 months of age. Five out of seven cases had associated congenital anomalies (2 vertebral, 2 cardiac anomalies including one VACTREL, one cleft palate and facial dysmorphism). Two out of four males had pouch vesical fistulae, one male baby had pouch prostatic urethra fistula and one female had a pouch genital fistula (recto-vaginal fistula).

DISCUSSION

Ever since its first description in 1912 by Spriggs in a London hospital museum specimen with absence of the left half of the colon and rectum[6], various terms have been used to describe congenital pouch colon including pouch colon syndrome[5], extrophia splanchnica[7], congenital absence of colon and rectum[8], colonic reservoir[9] and association of imperforate anus with short colon (AIASC)[10,11].

Interestingly, the sex ratio reported by authors outside Indian subcontinent has been almost equal (M:F = 1.27:1), while the reported incidence in India favors male preponderance (M:F = 3 - 4.3:1)[1] .We had an M:F sex ratio of 1.3:1 in our series. Similar to the recent trend, we had encountered mostly incomplete type of CPCs (six type IV and one type I). Associated anomalies were seen in 71% (5 out of 7) cases, higher than those reported in the literature[1,3,4]. Most of these cases (5 out of 7) were operated in a staged manner; *i.e.* excision of pouch, division of any urogenital fistula in the neonatal period and definitive pull-through at 3-6 months age. In two female babies with type IV pouch colon and pouch vestibular fistula, single stage neonatal repair was done.

The incidence of CPC among all cases of ARM in northern India has been reported to be between five to 10%, in Bangladesh 1.07% and in Pakistan 8-10 %[1]. Only sporadic case reports are from other parts of the world. Recently Donkol *et al*[12] have reported this anomaly in a Saudi Arabian neonate from Western province (Al-Abha region). Our report is the first case series from Saudi Arabia and the whole of Arab peninsula. In another recent series published from Al-Khobar region of KSA, the author has described 17 cases of CPCs. However, all are from northern part of India (none in Saudi nationals)[13].

Since Saudi Arabia has been harboring a significant expatriate population from India, Pakistan, Bangladesh, Nepal and Srilanka, few cases of CPCs could be expected among them. However, we have found six of our seven cases to be Saudi nationals. We believe the lack of awareness among the physicians about this entity would have led to under-reporting among Saudi nationals and expatriates. Many high ARMs, especially those without fistula, have associated dilatation of blind rectal pouch. It is important for the surgeons to

distinguish these dilatations from pouch by the features mentioned above (see results section) which otherwise prompts tapering colorectoplasty during postero saggital anorectoplasty (PSARP) instead of excision of pouch. Retained pouch tissues lead to postoperative constipation and secondary pouch dilatation with suboptimal outcome.

Various authors have tried to explain the embryological basis of this anomaly including preferential hindgut stimulation[10], vascular insult[11], faulty rotation and fixation of gut theory[9]. Recently, Gupta *et al*[1] have incriminated iodine and vitamin B deficiency, use of pesticides and low socio-economic status as possible environmental factors affecting or precipitating the anomaly at a window time after conception when hindgut is developing and differentiating into urinary and intestinal tracts.

Occurrence of CPC among Saudi neonates points towards a possibility of changing demography of this entity that is not simply explainable by population migration from high prevalence areas. The role of genetic predisposition and interplay of multiple environmental factors in the causation of this entity (mentioned above) needs to be explored in the community. Eastern province in particular has a high rate of consanguinity and interplay of above mentioned environmental factors.

CONCLUSIONS

CPC is a rare variety of ano-rectal malformation known to cluster in specific geographical areas. This is recently being increasingly and disproportionately reported in the Saudi Arabian population. Whether this is reflected by under-reporting or under-diagnosing of CPCs elsewhere, or represent a changing demography needs to be confirmed by collective multi-centeric data from the Arab peninsula. More importantly, it is necessary to identify these cases by the characteristic radiological, anatomical and histological features and to differentiate it from simple dilatation of blind rectal pouch. It is extremely important to employ correct initial management in the newborn period to decrease subsequent pouch related morbidity.

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Experimental Medicine

Effect of Phenytoin Sodium on Reproductive Parameters in Adult Male Wistar Rats

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ABSTRACT

Objective: To assess the effects of phenytoin sodium on rat sperm morphology, sperm count, motility and histopathological changes in testis
Design: Experimental study
Setting: Kasturba Medical College, Manipal, Karnataka State, India
Materials and Methods: Male Wistar rats (13-14 weeks old) were treated with phenytoin sodium and sacrificed at the end of 2nd, 4th, 5th, 7th, 10th and 15th week after the last exposure to phenytoin sodium. Epididymal sperm count, sperm motility, sperm morphology and histopathology of testes were analysed.
Results: Sperm count and sperm motility were decreased significantly by phenytoin sodium. The percentage of abnormal sperms increased significantly in a time dependent manner. Histopathological study revealed that phenytoin sodium caused sloughing of epithelial cells in the testis.
Conclusion: Phenytoin sodium caused reversible change in sperm motility, count, morphology and cytoarchitecture of testes.

KEY WORDS: histopathology, phenytoin sodium, sperm count, sperm morphology, sperm motility

INTRODUCTION

Mainly three factors contribute to sterility in the modern world; the trend for couples to delay having children after marriage, the rise in sexually transmitted diseases and a puzzling drop in sperm production in males. Federal agencies, such as the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) and international bodies like Organization for Economic Co-operation and Development (OECD) provide a number of test protocols and guidelines for identifying the adverse reproductive effects[1]. These protocols and guidelines are used by the industry to test pesticides, industrial chemicals, pharmaceuticals and food additives for potential reproductive toxicity in laboratory animals.

All of this information is critical for performing a risk assessment of the chemical and ultimately, for making regulatory decision about the allowable uses of the substance as well as the labeling requirements. For many years, clinicians have searched for the best end point in semen that could be used to predict the fertility in individual men[2].

Spermatogenesis is a cyclic, well-organized, highly co-ordinated process that encompasses different cell associations called stages. The maintenance of adult mammalian spermatogenesis is dependent upon the steroid hormone testosterone, which is produced by testicular leydig cells in response to the secretion of pituitary luteinizing hormone[3]. Previous studies of spermatogenesis in the rat have shown that the experimental reduction of intratesticular testosterone to low enough levels results in germ cell loss[4-6] and that the re-administration of testosterone restores spermatogenesis[7,8]. Sperm count is one of the most sensitive tests for spermatogenesis, since, it gives the cumulative result of all stages in sperm production, and it is highly correlated with fertility[9]. It is absolutely necessary that epileptic patients receive long-term therapy with antiepileptic drugs. Some antiepileptic drugs such as phenytoin, sodium valproate, primidone and phenobarbitol have been suspected to be gonadotoxic, mutagenic and teratogenic[10-14]. Antiepileptics diminish sexual potency and fertility in young male epileptics[15]. The mutagenic changes

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have proportional relation with carcinogenesis[16]. This is alarmingly problematic especially in children, since these effects last longer affecting fertility and / or forming basis for carcinogenesis. Phenytoin is excreted in human semen in small quantities and this may possibly affect the testosterone levels. Reduced plasma concentrations of free testosterone have been detected in male epileptic patients receiving phenytoin.

Meng *et al* [17] observed possible mutagenic effect of phenytoin on human sperm cells. According to Russel and Russel[18], male germ cells are very ideal and easy for the study of the genotoxicity of drugs since they exist in different phases of cell development and differentiation. Genotoxic effects of the drug would result in morphologically abnormal sperms and therefore the counting and classification of the types of abnormal sperm can determine the presence and extent of genotoxicity[19]. The architectural makeup of stages within seminiferous tubules and atypical cell types within stages varies with the level of efficiency of spermatogenesis, and this variation may reflect differences in yield of early spermatogonial divisions that are responsible for generating the different stages. Increase in tubular length along with diameter seems to be a continuous process until puberty. Testis tubule diameter is directly correlated with testicular weight[20]. Histopathology on reproductive tissues is valuable for male reproductive toxicity assessment. Histological evaluations can be especially useful because they are a relatively sensitive indicators of damage and they provide information on toxicity from a variety of protocols. In addition, histological data can provide information on site (including target cells) and extent of toxicity after short-term testing and can also indicate the potential for recovery. The quality of histological analyses of spermatogenesis is improved by proper fixation and embedding of testicular tissue[21-23].

In view of the above findings, the present study was designed to investigate the effects of phenytoin sodium on rat testis.

MATERIALS AND METHODS

Animals

In the present study, adult male Wistar rats (13 - 14 weeks old) weighing 150-200 g were used. Breeding and maintenance of animals were done according to the guidelines of Committee for the purpose of Control and Supervision of Experiments on Animals; and Animal Welfare Division, Government of India, for the use of laboratory animals. The Institutional Animal Ethical Committee approval was obtained before starting the study. All animals were housed in polypropylene cages using paddy husk bedding at 28 ± 1°C temperature and 50 ± 5% humidity. Animals were fed on laboratory chow and tap water *ad libitum*. All experimental activities are carried out between 8 - 10 AM.

One hundred and forty-four rats were segregated into 24 groups of six animals each. Six groups each were treated with 0.1 ml of distilled water, gum acacia control, phenytoin sodium 50 mg and phenytoin sodium 100 mg for 60 days. Animals were sacrificed by terminal anesthesia (Pentobarbital sodium, 45 mg/kg, Sigma Chemicals Co.) at the end of 2nd, 4th, 5th, 7th, 10th and 15th week after the last exposure to phenytoin sodium. The animals were weighed before sacrificing. The sacrifice time points – weeks 2, 4, 5, 7, 10 and 15 represent the sampling of spermatozoa in the epididymis and testis, spermatids, secondary spermatocytes, primary spermatocytes, spermatogonia and stem cells during treatment, respectively[24, 25].

This study was approved by the ethical committee of the hospital.

Chemicals

The powdered form of phenytoin sodium was obtained from Cadila Health Care Ltd. The dose and route of administration was based on earlier studies[26,27]. The required quantity of phenytoin was weighed just before treatment and dissolved in 10 ml of gum acacia (0.2 g gum acacia dissolved in 10 ml of distilled water) and administered orally for 60 days.

Epididymal sperm count and motility

The rats were sacrificed and laprotomy was conducted to expose the reproductive system. The latter was removed and placed in phosphate buffered saline, and the epididymis was separated. Both the testes from each animal were removed and weighed on an electronic balance. The sperm suspension was prepared by mincing the cauda epididymis in 1 ml of phosphate buffered saline (pH 7.2). Then the suspension was filtered through 80 μm nylon mesh to remove the tissue fragments. An aliquot (0.05 ml) from the sperm suspension (1 ml) was diluted with 1:40 phosphate buffered saline and mixed thoroughly. After discharging a few drops, a sample of the diluted sperm suspension was introduced into a Neuberger's improved counting chamber (ROHEM India, depth 0.1 mm). The sperms present in 8 squares except in the erythrocyte area were counted, and then the total count was multiplied by 5×10^4 to obtain the number of sperms per epididymis[28,29]. A minimum of 100 sperms were observed for motility and percentage of motile sperms was recorded for each animal.

Sperm morphology assay

A fine suspension was made and stained with 0.2 ml of 1% aqueous eosin. About one drop of stained suspension was placed on the clean slide. It was dried, cleaned and mounted in DPX. Slides were examined

Table 1. Effect of phenytoin sodium on sperm count (x 10^6)

Dose	Sampling Time					
	2 weeks	4 weeks	5 weeks	7 weeks	10 weeks	15 weeks
Normal control	53.5 ± 1.85	54.33 ± 1.36	55.5 ± 1.04	56.66 ± 1.36	55.66 ± 2.87	55.5 ± 1.04
Gum acacia control	53.16 ± 0.98	54.5 ± 1.63	54.66 ± 1.63	51.5 ± 1.87	53.16 ± 2.31	54.83 ± 1.16
50 mg/kg	45.66 ± 3.72***	38.33 ± 2.42***	32.3 ± 1.5***	37 ± 1.09***	50.6 ± 2.94	54.66 ± 1.21
100 mg/kg	40.16 ± 6***a	33.5 ± 1.04*** aa	25 ± 0.89*** aaa	34.16 ± 1.32*** a	50 ± 2.89	53 ± 2.36

Each dose from particular time represents mean ± SD from six animals. Significant values are, normal control Vs. treated *** $p < 0.001$; 50 mg/kg Vs. 100 mg/kg ap < 0.05, aap < 0.01, aaap < 0.001.

Table 2. Effect of phenytoin sodium on sperm motility

Dose	Sampling Time					
	2 weeks	4 weeks	5 weeks	7 weeks	10 weeks	15 weeks
Normal control	44.16 ± 1.32	44.16 ± 1.16	44.5 ± 1.76	44 ± 1.41	42.5 ± 1.04	42.66 ± 1.36
Gum acacia control	43.66 ± 1.75	43.33 ± 2.33	42.83 ± 1.16	43.5 ± 1.22	42.83 ± 0.75	43.16 ± 1.72
50 mg/kg	41 ± 1.67*	36 ± 1.41***	32 ± 1.67***	38.66 ± 1.03***	40.33 ± 1.63	43.33 ± 0.81
100 mg/kg	38.33 ± 1.21***	33.83 ± 1.47***	29.16 ± 1.32***a	34.16 ± 1.32*** a	39.66 ± 1.27*	42 ± 1.09

Each dose from a particular time represents mean ± SD from six animals. Significant values are; normal control vs. treated, *$p < 0.05$, ***$p < 0.001$; 50 mg/kg vs. 100 mg/kg, ap < 0.05, aap < 0.01.

for sperm shape abnormality. 1000 sperms /animal were scored. Sperms were classified into normal and abnormal sperms. The abnormal sperms were classified under head abnormalities and tail abnormalities. The head abnormalities were classified as amorphous, hookless, banana shaped, double headed, and bent. The tail abnormalities were classified as coiled / folded and double tailed[9,30].

Histopathology of testis

The testes / epididymis were removed and fixed in Bouin's fluid for 24 hrs. After excessive washing in 70% alcohol, the tissue was processed for paraffin embedding and 5μ thick paraffin sections were stained with haematoxylin and eosin (Culling *et al*, Cellular pathology technique)[28].

The sections were analyzed for the presence or absence of vacuoles, gaps and abnormal cells.

Seminiferous tubular diameter (STD) and epithelial height (SEH): The diameters of 20 transversely cut tubules were measured using ocular micrometer calibrated with the stage micrometer (Erna Opticals, Japan). In each tubule, two measurements were made, one perpendicular to the other and their average is taken. The epithelial height was measured in 10 tubules for each animal. In each tubule, the SEH was measured from the basement membrane to the surface of the epithelium at two different regions and the mean was taken.

Statistical analysis

For each group six animals were used and mean ± SD (standard deviation) was calculated. Results obtained from the present study were correlated and analyzed by Analysis of Variance (ANOVA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Effect on body weight

There was no significant difference between the control group and phenytoin treated group on body weight of rats.

Effect of on sperm count

There was a significant decrease in sperm count during the 2nd, 4th, 5th and 7th week sampling time. The recovery was almost the same in both the doses and complete recovery was observed by the 15th week. The least number of sperm count was observed during the 5th week sampling time for both the doses. The time response graph shows a significant decrease in the sperm count in a linear manner up to the 5th week and during the 7th week sampling time it shows a marginal increase in sperm count which reaches the control values by the 15th week sample time (Table 1).

Effect on sperm motility

On the second week of sampling time there was a significant reduction in the motility of sperms in rats treated with 100 mg/kg of phenytoin sodium. Even though reduction of sperm motility was seen

Table 3: Effect of phenytoin sodium on incidence of abnormal sperms in seven week sampling time

Drug/ Dose	Sample time (weeks)	Normal sperm	Abnormal Sperms						
			Amorphous	Hookless	Banana	Coiled/ folded	Double head	Double tailed	% Sperm abnormalities
Normal Control	7	980.16 ± 5.60	6.16 ± 2.31	3.83 ± 0.75	2.66 ± 0.81	7.16 ± 3.5	0.00 ± 0.0	0.00 ± 0.0	1.98 ± 0.74
Gum acacia control	7	983.16 ± 6.43	4.33 ± 2.06	3.83 ± 1.47	2.33 ± 0.81	6.33 ± 3.20	0.00 ± 0.0	0.00 ± 0.0	1.68 ± 0.75
50 mg/kg	7	940.00 ± 6.45	16.66 ± 2.73	19.16 ± 2.48	9.16 ± 1.47	16.33 ± 1.5	0.00 ± 0.0	0.33 ± 0.51	6*** ± 0.86
100 mg/kg	7	926.33 ± 7.55	20.83 ± 1.47	18.83 ± 2.92	8.83 ± 2.13	24.16 ± 2.63	0.00 ± 0.0	1 ± 0.89	7.36*** ± 1.0

Data represented as mean ± SD from six animals. Significant values are; normal control Vs. treated, ***$p < 0.001$. No significant differences were found between 50 mg Vs. 100 mg groups.

in the rats treated with 50 mg/kg during the 2nd week sampling time it was not as significant as the decrease in sperm motility observed in rats treated with the higher dose. The sperm motility was least during the 5th week sampling time in both the doses of the drug. The recovery period was slightly faster for the rats treated with the 50 mg/kg and complete recovery was seen by the 10th week sampling time (Table 2). However, the recovery period for the rats treated with 100 mg/kg took longer time and reached complete recovery by the 15th week sampling time. Even though there was reduced motility in the 100 mg/kg treated rats when compared to the 50 mg/kg treated rats, significance was observed only during the 5th and 7th week sampling time.

Effect on sperm morphology

No significant difference in the percentage of abnormal sperms was found between the drug treated and control groups during the 2nd week sampling time. The incidence of abnormal sperms progressively increased from the 4th week sampling time to the 7th week sampling time (Table 3). Coiled or folded sperms were the most commonly seen abnormality in all the sampling times studied. However, the number of abnormal sperms with amorphous head and hookless heads was also common during all the sampling weeks. Phenytoin sodium seems to affect the morphology of sperm in a time dependent manner. The percentage of abnormal sperm was highest during the 7th week sampling time in rats treated with 100 mg/kg as well as with rats treated with 50 mg/kg (Table 3). The recovery period was similar for both 100 mg/kg and 50 mg/kg treated rats. The percentage of abnormal sperms reached closer to the control values in both the doses of the drug during the 10th week sampling time. Complete recovery was observed in the 15th week sampling time (Table 4).

Effect on the microscopic architecture of testes

Sloughing was observed in the treated groups. A phenomenal increase in sloughing was observed in rats treated with 100 mg/kg during the 5th week. The presence of vacuoles was also observed in the 5th and 7th week at both the doses (Figs. 1, 2 and 3). At the

Table 4: Effect of phenytoin sodium on incidence of abnormal sperms in fifteen week sampling time

Drug/ Dose	Sample time (weeks)	Normal sperm	Abnormal Sperms						
			Amorphous	Hookless	Banana	Coiled/ folded	Double head	Double tailed	% Sperm abnormalities
Normal Control	15	979.66 ± 6.21	4.83 ± 2.48	5.16 ± 0.75	3.33 ± 1.03	7 ± 4.24	0.00 ± 0.0	0.00 ± 0.0	2.03 ± 0.85
Gum acacia control	15	978.50 ± 6.15	5.66 ± 3.55	4.16 ± 0.75	3 ± 1.26	8.16 ± 3.06	0.00 ± 0.0	0.83 ± 0.5	2.15 ± 0.94
50mg/kg	15	980.83 ± 5.11	6.16 ± 2.71	5.16 ± 0.98	2.5 ± 1.04	5.16 ± 2.85	0.00 ± 0.0	0.16 ± 0.4	1.91 ± 0.79
100mg/kg	15	978.16 ± 6.04	5.66 ± 2.25	5.16 ± 0.98	3.66 ± 0.81	7.33 ± 3.55	0.00 ± 0.0	0.00 ± 0.0	2.18 ± 0.75

Data represented as mean ± SD from six animals. No significant differences were found between normal control Vs. treated groups.

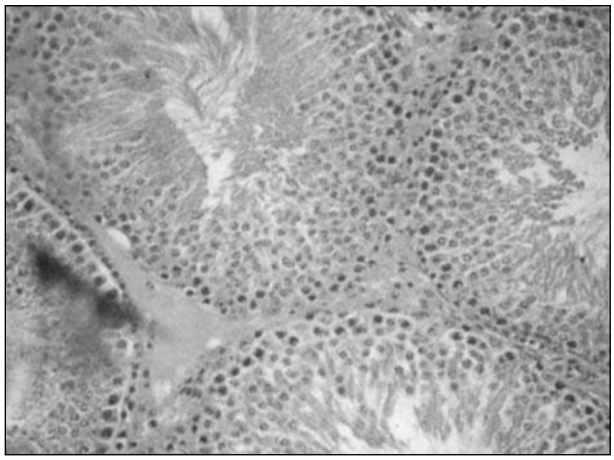

Fig. 1: Photomicrograph of testicular section of normal control rat (x 200)

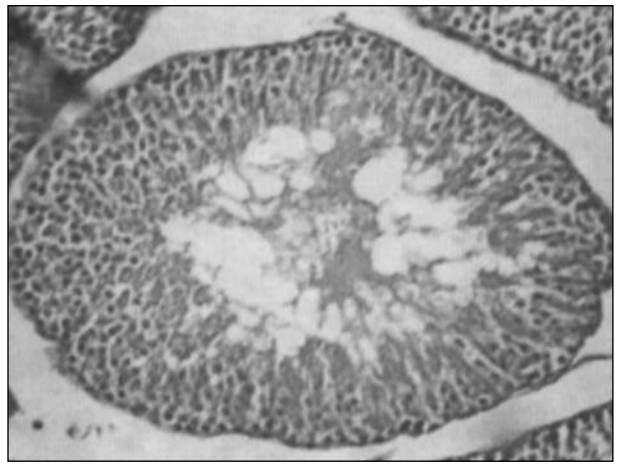

Fig. 2: Photomicrograph of testicular section of rats treated with 50 mg phenytoin sodium (x 200)

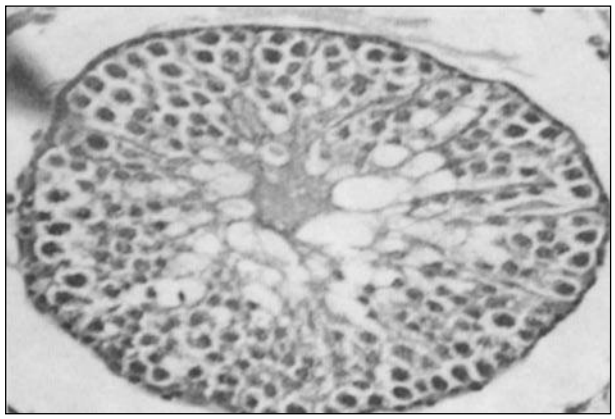

Fig. 3: Cross section of testes of rats treated with 100 mg phenytoin sodium showing the presence of vacuoles (x 200)

2nd week, the incidence of sloughing was elevated by both the doses and showed progressive increase till the 7th week. However, complete recovery was observed by the 15th week. The cytoarchitecture of the epididymis did not show any disturbance.

Effect on gross architecture of testes

Weight of the testes was not altered. At higher dose the seminiferous tubular diameter showed a linear decrease as the sampling weeks increased and highest drop in the diameter was seen during the 7th week. However at the lower dose the tubular diameter showed a significant increase in diameter during the 2nd week and showed gradual decrease in the diameter in the following sampling weeks. The least tubular diameter was seen during the 5th sampling week. Recovery period was same for both the doses and returned to normal control levels by the 15th week (Table 5).

At the 2nd week there was significant decrease in the epithelial height regardless of the dose. Similar trend was also seen during the other sampling weeks and recovery to normal height was seen only by the 10th week. Even though dose dependent decrease was seen in epithelial height during the sampling time, values were not significant. The peak decline of epithelial height was observed during the 5th week for both the doses. The time response graph shows that phenytoin sodium affects the epithelial height of the seminiferous tubules in a time dependent manner (Table 6)

DISCUSSION

Sperm count is one of the most sensitive tests for spermatogenesis, since, it gives the cumulative result of all stages in sperm production, and it is highly correlated with fertility[16]. Our results show that phenytoin sodium is cytotoxic to the sperm since it decreased the sperm count significantly

Table 5: Effect of phenytoin sodium on seminiferous tubular diameter (in μ).

Dose	Sampling Time					
	2 weeks	4 weeks	5 weeks	7 weeks	10 weeks	15 weeks
Normal Control	289.2 ± 6.26	284.3 ± 7.4	286.4 ± 5.6	288.4 ± 5.73	301.4 ± 7.35	315.7 ± 4.34
Gum acacia control	288.9 ± 5.72	286.7 ± 7.04	286.3 ± 5.07	285.1 ± 6.93	302.6 ± 6.27	313.7 ± 5.75
50 mg/kg	302.2 ± 6.26*	273 ± 4.18	266.4 ± 5.73***	275 ± 3.09**	315.5 ± 7.03*	320.2 ± 3.01
100 mg/kg	286.2 ± 1.22aa	266.3 ± 6.6**	245.2 ± 4.28***aaa	240.3 ± 3.02***aaa	300.6 ± 6.35a	316.7 ± 5.05

Each dose from a particular time represents mean ± SD from six animals. Significant values are, normal control Vs. treated *$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$; 50 mg/kg Vs. 100 mg/kg, a$p < 0.05$, aa$p < 0.01$

Table 6: Effect of phenytoin sodium on seminiferous epithelial height (in μ)

Dose	Sampling Time					
	2 weeks	4 weeks	5 weeks	7 weeks	10 weeks	15 weeks
Normal control	89.89 ± 3.87	90.31 ± 3.41	90.78 ± 3.10	89 ± 3.16	90.15 ± 3.36	90.89 ± 3.35
Gum acacia control	89.15 ± 3.27	91.05 ± 3.18	90.78 ± 3.33	88.10 ± 3.50	89.15 ± 3.03	91.1± 3.33
50 mg/kg	80.6 ± 3.23**	75.35 ± 3.25***	68.25 ± 3.41***	72.9 ± 3.53***	85.65 ± 3.40	89 ± 3.34
100 mg/kg	77.05 ± 4.14***	70.5 ± 3.68***	65.25 ± 3.617***	71.85 ± 3.48***	86 ± 3.22	89 ± 3.36

Each dose from a particular time represents mean ± SD from six animals. Significant values are, normal control Vs. treated, **$p < 0.01$, ***$p < 0.001$. No significant differences were found between 50 mg/kg Vs. 100 mg/kg groups.

in a linear manner from 2nd to 7th week sampling time, regardless of the dose. In adult mice, duration of spermatogenic cycle is 34 to 35 days[10,17] and these sample times correspond to spermatids and spermatocytes in origin respectively. However, the duration of spermatogenic cycle in rats is 52 to 60 days and our findings point out that the germ cells affected are approximately the spermatids, spermatocytes and spermatogonia. The sperm count returned close to normal values by the end of the 10th week. Phenytoin sodium appears to be more toxic to the spermatocytes as the sperm count was least by the end of the 5th week.

Phenytoin sodium decreased the percentage of sperm motility in a time dependent manner. Similar results were observed by earlier workers[17,31,32]. The decrease in motility was observed right from the 2nd week sample time and complete recovery was observed by the end of 10th week. The sperm motility largely depends on the microtubular apparatus of the sperm tail[33]. In the current study it was also observed that a considerable number of abnormal sperms were with a defect in their tail. It is possible to confirm that sperm motility might have been hindered mainly because of the presence of a large number of abnormal sperms between the 2nd and 7th week as well as the interference of these drugs on the sperm membrane.

Phenytoin sodium increased the number of abnormal sperms in a time dependent manner. Sperm abnormalities were observed in both doses. The number of dysmorphological sperm was significantly high during the 4th to 7th week sampling time. It is essential that, to label any drug as mutagen, it should induce double the sperm abnormality compared to the control level[11]. Phenytoin sodium treatment resulted in more than double the percentage of abnormal sperms and hence they could be considered as mutagens. Their mutagenic effect was more pronounced during the 4th to 7th week sampling time. As mentioned earlier, motility of sperm was also least during these sampling weeks, which indicates that sperm motility and morphology are related to each other. The higher dose of phenytoin sodium induced highest percentage of abnormal sperms at the end of 7th week. This indicates that spermatogonia are more vulnerable to phenytoin sodium. However, it is not known as to how this drug affect the fertility of rats and, moreover, it is not known how much percentage of abnormal sperms are required for infertility to occur. Earlier reports however suggest that the tail and head deformities are indicators of infertility[34,35]. Moreover, it is not possible to say whether these antiepileptics induce any chromosomal aberrations or mutations in germ cells as this assay identifies only point mutations. Future studies could therefore address these specific effects of phenytoin sodium.

A change in the weight of testes is an indicator of reproductive toxicity. In the current study, weight of the testes in the treated group did not differ significantly from that of the control group. It may be because of the lower dose in addition to the shorter duration of treatment. It must be considered that changes in the other important end points related to reproductive function may not be accompanied by a change in organ weight. A significant increase or decrease in testis weight can indicate an adverse effect, but it can be due to processes other than seminiferous tubular damage, such as edema, inflammation, cellular infiltration, Leydig cell hyperplasia or fluid accumulation due to blocked efferent ducts[36,37]. Therefore, it is insufficient to evaluate organ weight alone to assess reproductive toxicity of an agent, as other end-points may be more sensitive indicators.

The present study confirms that phenytoin sodium decreases the diameter of the seminiferous tubules. On histological evaluation it had induced the formation of vacuoles and sloughing during the 2nd to 7th week sampling time. In some of the tubules structural deformity of the Sertoli cells were also observed, more so with the higher dose. The occurrence of vacuoles was more frequent during the 5th and 7th week sampling time. In the case of phenytoin sodium the tubular diameter showed

a slight increase by the end of the 2nd week in rats treated with the lower dose whereas the tubular diameter did not show any significant change with the higher dose. The increase in tubular diameter with the lower dose of phenytoin may be due to the induction of secretion of seminiferous tubular fluid as seen after the ligation of efferent ductules in the rat[38].

Intratesticular testosterone is thought to play a very important role in spermatogenesis; however, it is very rarely measured. According to Bauer *et al*[39], and Kuhn-Velten *et al* [40], valproate and phenytoin act directly on the testis to inhibit testosterone synthesis by the Leydig cells. It is now established that lowering of intratesticular testosterone concentration results in the apoptotic death of some germ cells (*e.g.*, pachytene spermatocytes) in association with nuclear DNA fragmentation in the dying cells[4,41,42]. Previous studies of spermatogenesis in the rat have shown that the experimental reduction of intratesticular testosterone to low enough levels results in germ cell loss[4-6] and that the re-administration of testosterone restores spermatogenesis[7,8]. Androgen receptor expression in the seminiferous epithelium is restricted to the somatic Sertoli cells[43]. Therefore, in response to changes in intratesticular testosterone concentration, the Sertoli cell presumably communicates a signal to the attached and developing germ cells, which lack the androgen receptor, resulting either in the loss or restoration of germ cells[44].

Regulation of the reproductive axis begins at the level of the hypothalamus where neurosecretory cells synthesize and release gonadotropin-releasing hormone (GnRH) in a pulsatile fashion into the hypothalamic-hypophysial-portal circulation. In both men and women, gonadal failure results in increased LH, from loss of the negative feedback of estrogen at the hypothalamus and pituitary in women and from decreases in both androgen and estrogen feedback in men. In response to the decreased levels of the sex steroids and the loss of inhibin, FSH levels are also elevated following gonadal damage. Luteinising Hormone (LH), Follicle Stimulating Hormone (FSH), and testosterone are commonly analyzed. The sensitivity of this approach is limited, however, since serious disturbances in spermatogenesis are often observed with normal FSH[45]. The male reproductive system can be affected adversely by disruption of the normal endocrine balance. In adults, effects that interfere with normal concentrations or action of LH and / or FSH can decrease or abolish spermatogenesis, affect secondary sex organ (*e.g.*, epididymis) and accessory sex gland (*e.g.*, prostate, seminal vesicle) function and impair sexual behavior[46]. Significant alterations in circulating levels of testosterone, LH or FSH may indicate pituitary or gonadal injury and may be related to alterations in spermatogenesis, sperm maturation, mating ability or fertility. Furthermore, such hormonal effects can help understanding of the site or mechanism of toxicant action, especially for short-term exposures.

CONCLUSION

Findings from this study point out the gonadotoxic and cytotoxic potential of phenytoin sodium. Hence the work should pave way for the rational use of this drug unambiguously to control the adverse effects without compromising its efficacy.

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Case Report

Sweet's Syndrome

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Kuwait Medical Journal 2009, 41 (1) 52 - 53

ABSTRACT

Sweet's syndrome (acute febrile neutrophilic dermatosis) is characterized by classical skin lesions accompanied by fever and malaise. Systemic involvement may be present and lung involvement in Sweet's syndrome has been reported in the form of bilateral pulmonary infiltrates, bronchiolitis obliterans organizing pneumonia and pleural effusion. There are dense papillary neutrophilic infiltrates on histopathology. We present a case of Sweet's syndrome with right lower lobe consolidation and persistent fever which was non-responsive to antibiotics but showed clinical improvement with clearing of radiological opacities on oral steroid therapy.

KEY WORDS: acute febrile neutrophilic dermatosis, pulmonary involvement, steroid therapy,

INTRODUCTION

Sweet's syndrome was first described by Robert Douglas Sweet in 1964 as acute febrile neutrophilic dermatosis[1]. Since his description the disease has been referred to by his name. As described, the classic symptoms consist of an acute onset of erythematous plaques, nodules and occasionally pustules, asymmetrically distributed over the face, neck and extremities. This eruption is often accompanied with fever and a neutrophilic leukocytosis. The rash may last from one week to several years.

The importance of correctly identifying this disease lies in its association with other diseases. Involvement of eyes, joints and oral mucosa has been described. Para-inflammatory and para-neoplastic conditions have also been described in patients with Sweet's syndrome. Involvement of internal organs such as the lung, liver, kidneys and central nervous system was reported earlier. Some studies have suggested that the condition represents a variable manifestation of hypersensitivity to bacteria or chemical allergens[2].

CASE REPORT

A 45-year-old Indian lady presented with fever, dry cough, malaise and erythematous plaques over the face, chest, forearm and neck of two weeks duration. She had an upper respiratory tract infection three weeks prior to the onset of skin lesions. There were no previous similar episodes. There was no history of bleeding disorder, bowel or urinary symptoms. There was no history of drug intake prior the onset of the lesions. On physical examinations; she was febrile (38.2 ^{o}C) with a blood pressure of 120/80 mmHg. There was no pallor or lymphadenopathy. Examination of the cardiovascular, abdominal and neurological systems was normal. Respiratory system examination revealed crepitations in the right lower lobe. Laboratory data showed a total white blood cell count of 16,000 X 10^9/l with 80% neutrophils, 18% lymphocyte, 2%eosinophils and hemoglobin of 13 gm/dl. Serum chemistry was un-remarkable. Chest radiograph revealed right lower zone consolidation with right pleural effusion (Fig. 1). Sputum and blood cultures were negative for micro-organisms. She was diagnosed as a case of community acquired pneumonia and was started on intravenous cefotaxime and erythromycin. Five days later she continued to have fever, cough and malaise. Computerized tomography (CT) scan of the chest showed ill-defined opacities in the right lower zone with right pleural effusion. Skin biopsy was done which showed a dense dermal neutrophilic infiltrate involving the upper dermis. There was no blister formation (Fig. 2). On the sixth day, she was diagnosed as a case of Sweet's syndrome and started on oral corticosteroid in a dose of 1 mg/kg body weight for a period of two weeks, which was subsequently tapered off. A good response was anticipated with resolution of malaise and fever within two days and a complete normalization of chest radiograph within three weeks.

DISCUSSION

Classic Sweet's syndrome occurs mostly in middle aged women after a non-specific infection of respiratory or gastrointestinal tract[3]. It is characterized by raised erythematous plaques with pseudoblistering and pustules occasionally on the

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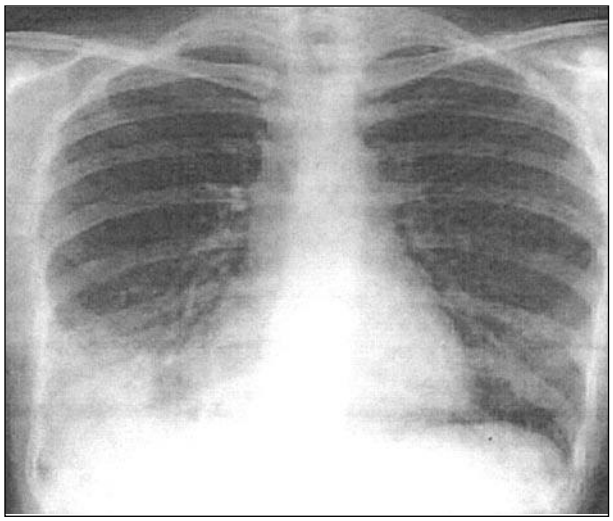

Fig. 1: Right lower lobe pneumonia

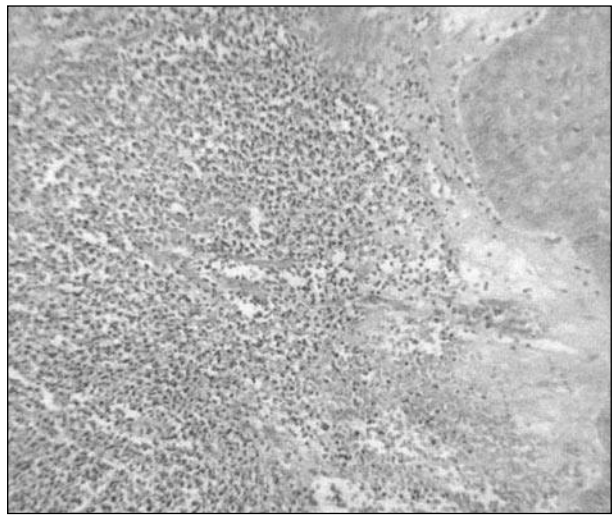

Fig. 2: Skin biopsy showing dermal neutrophilic infiltration

face, neck, chest and extremities accompanied by fever, general malaise and dense papillary neutrophilic infiltration on biopsy specimen[4]. Von Den Dreisch summarized seven series and categorized Sweet's syndrome cases into four groups: classic idiopathic (71%), para-inflammatory (16%), para-neoplastic (11%), and pregnancy related (2%)[5]. However, more recently in a large series of patients from Mayo Clinic, 54% had either a malignancy or some type of hematologic disease. A variety of infections have been associated with the syndrome and these include upper respiratory infections, urinary tract infections, viral pneumonia, Yersinia infection, typhus, salmonellosis, toxoplasmosis, tuberculosis and other mycobacterial infections, histoplasmosis, cytomegalovirus infections, tonsillitis, hepatitis and *Helicobacter pylori* infection. Pulmonary manifestations of acute febrile neutrophilic dermatosis consist of bilateral pulmonary infiltrates, bronchiolitis obliterans organizing pneumonia and pleural effusion. Pulmonary involvement has been described earlier and has been documented by lung biopsy in only seven previous cases in world literature. Studies have shown that acute febrile neutrophilic dermatosis may also involve the mucous membrane of the bronchial tree. Histologically, the bronchial inflammation resembles that seen in skin and mucosal lesions consisting predominantly of mature neutrophils infiltrating the interstitium in the absence of pathogenic organisms[6,7].

In 1986, Su *et al* proposed two major and four minor criteria for diagnosis of acute ferbile neutrophilic dermatosis of which two major and two minor criteria should be fulfilled[8]. The major criteria are: (i) abrupt onset of tender or painful erythematous or violaceous nodules and plaques and (ii) predominantly neutrophilic infiltrates in the dermis. The minor criteria are: (i) preceded by fever or infection (respiratory or gastrointestinal tract), (ii) accompanied by fever, arthralgias, conjunctivitis or underlying malignancy, (iii) leukocytosis and (iv) good response to systemic steroids and not antibiotics. Our patient fulfilled two major and three minor criteria required for the diagnosis of Sweet's syndrome. Infection was probably the etiology as other causes were ruled out by the absence of symptoms and normal laboratory investigations. Further, a therapeutic response to steroid therapy was seen in the form of resolution of fever and radiological lesions in our case.

CONCLUSION

This case is reported to increase awareness among physicians in the diagnosis of unresolving pneumonia.

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Case Report

Soft-Tissue Recurrence of Giant Cell Tumor of Bone: A Case Report

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ABSTRACT

We report a rare complication of giant cell tumor (GCT) of bone. A soft tissue recurrence without intra-osseous involvement developed in a 35-year-old lady treated for grade III GCT with intralesional excision, local adjuvant phenol and filling the cavity with bone cement. The different imaging modalities used for work-up and staging are discussed. This report emphasizes that a soft tissue recurrence may be not recognized if a thorough clinical examination is not performed and MRI is not done. Review of relevant literature addressed different factors that influence recurrence, as well as the role of osteoinductive growth factors in stimulating the osteoblastic differentiation and metaplastic bone formation in such lesions.

KEY WORDS: giant cell tumor of bone, soft tissue recurrence

INTRODUCTION

Giant cell tumor (GCT) of bone is a benign but locally aggressive tumor that usually involves the end of long bones[1]. The most frequent locations, in deceasing order, are the distal femur, the proximal tibia, and the distal radius[2]. It is characterized by a proliferation of mononuclear stromal cells and the presence of many multinucleated giant cells with homogenous distribution[1]. The stromal cells interact with hematopoietic cells in an autocrine manner to produce tumoral osteoclastogenesis and bone resorption[3]. Since GCT is a benign aggressive lesion, absence of local recurrence rather than survival of the patient is a major criterion used to assess the outcome of surgical treatment [4]. The rate of recurrence varies according to surgical techniques, site and grade of GCT, and ranges from 8.3[5] to 50% [6]. Soft tissue recurrence is a rare complication of GCT[7] which requires en-block resection[8,9].

CASE REPORT

A 35-year-old lady presented five months after intralesional excision of giant cell tumor (GCT) of bone affecting the proximal end of left tibia with painless soft tissue swelling in the antero-lateral aspect of proximal third of the affected leg. The initial assessment before the index surgery was carried out at the Orthopedic Oncology Unit, Al-Razi Orthopedic Hospital, Kuwait. She was referred with a two month history of increasing pain and swelling at the upper end of her left leg. Physical examination revealed tender fullness at the antero-lateral aspect of proximal part of left leg. Radiographic evaluation reported an epiphyseo-metaphyseal eccentric osteolytic lesion involving the lateral tibial condyle with well-defined intra-osseous borders, slight bone expansion, erosion of the lateral cortex and extra-osseous soft tissue extension (Fig. 1; a, b). CT examination confirmed radiographic findings (Fig. 2; a, b). Since the radiographic assessment was suggestive of GCT, we went through the staging strategy recommended by Turcotte[1]. Radiograph of the chest reported clear lung fields. The delayed whole body bone scan images using 99mTc-MDP showed increased uptake tracer in the proximal part of left tibia. Rest of the skeleton was unremarkable. Ultrasound guided fine needle aspiration cytology reported GCT. Based on the carried work-up the diagnosis was GCT grade III according to Campanacci was made[2].

The patient was managed with intralesional excision. The pseudocapsule over the extra-osseous soft tissue extension was dissected circumferentially and excised completely. The intra-osseous part of

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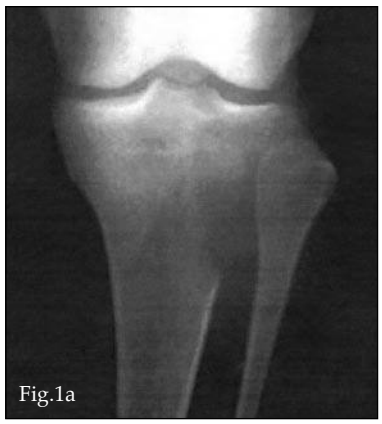


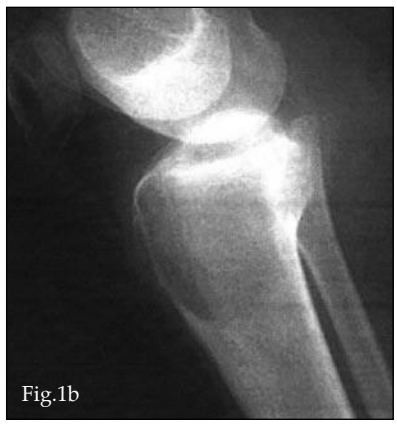


Fig. 1 a: AP view. **b:** LAT view, osteolytic lesion involving lateral tibial condyle

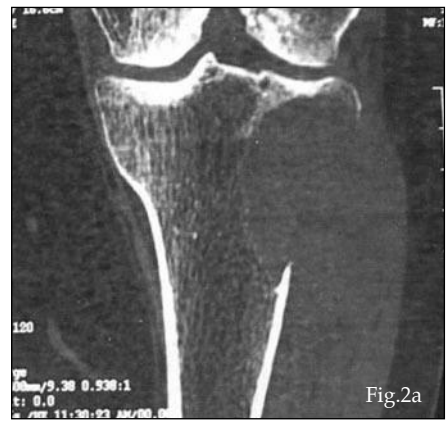


Fig. 2a: Pre-operative CT (a) axial cut

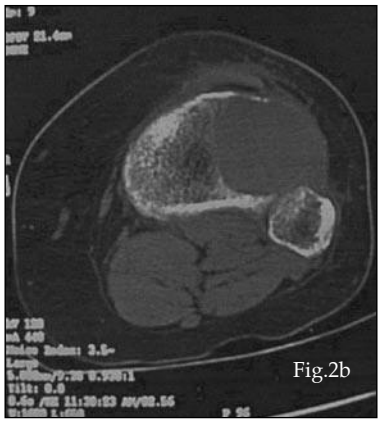
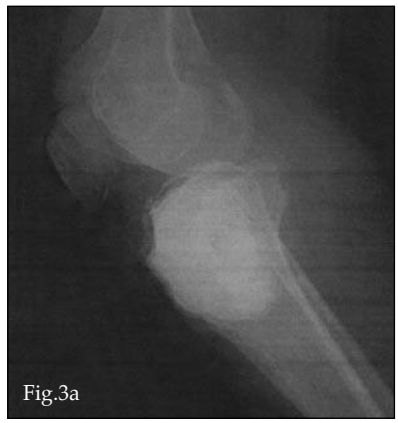


Fig. 2b: Coronal reconstruction



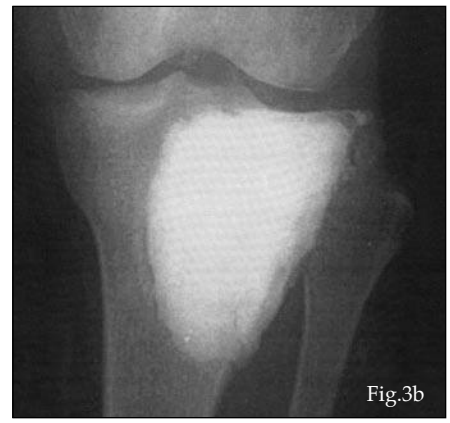


Fig. 3: Postoperative X-ray (a) AP (b) LAT view

the tumor was curetted using curettes of different sizes and high-speed power burr. The cavity was painted with adjuvant 5% phenol to improve the margin. Phenol was washed by absolute alcohol and pulsatile irrigation with normal saline. Finally the cavity was filled with cement (Fig 3; a, b). The histopathology study of the curetted materials described a tumor infiltrating the skeletal muscle and composed of many evenly distributed giant cells mixed with mononuclear stromal cells. Numerous nuclei were present in the giant cells (Fig. 4). There was frequent mitosis and focal osteoid formation. A diagnosis of an aggressive GCT of bone was made.

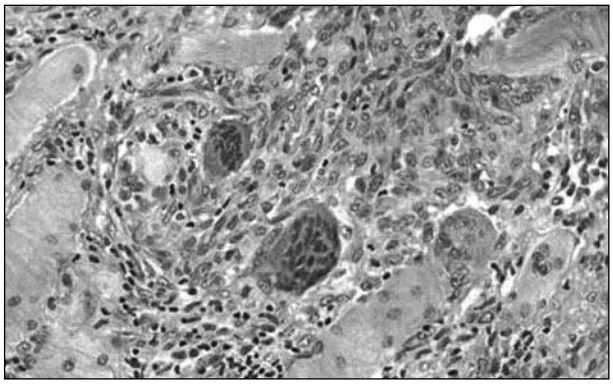


Fig. 4: Giant cell tumor of bone infiltrating skeletal muscle. Giant cells have numerous nuclei (H & E x 200).

A work-up was carried out to evaluate the recent presentation. CT scan showed a soft tissue shadow without any detected calcification. The bone-cement interface was delineated with a rim of sclerosis without any osteolytic areas (Fig. 5). MR scan showed masses measuring a maximum diameter of five cm involving the muscles of the anterior compartment of the leg. Soft tissue masses were

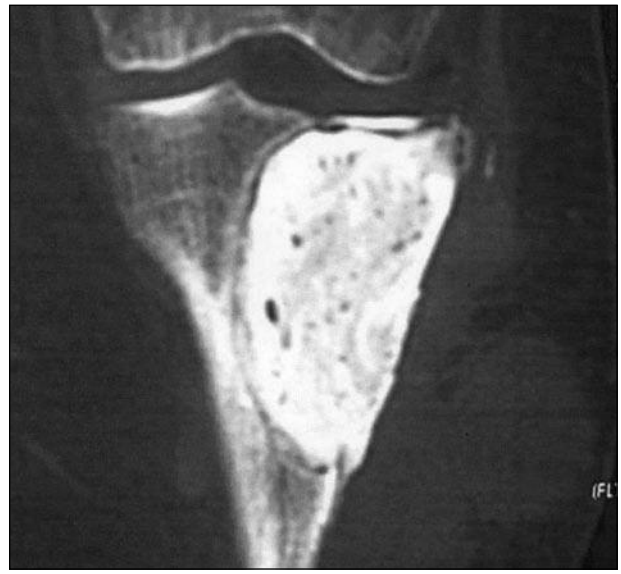
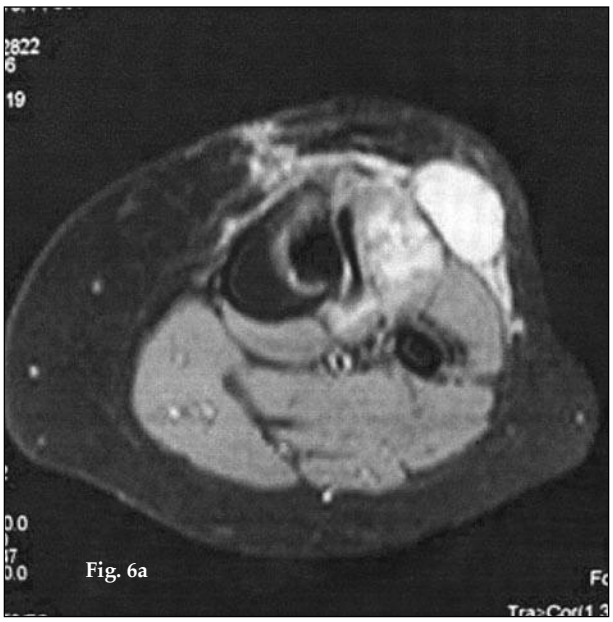
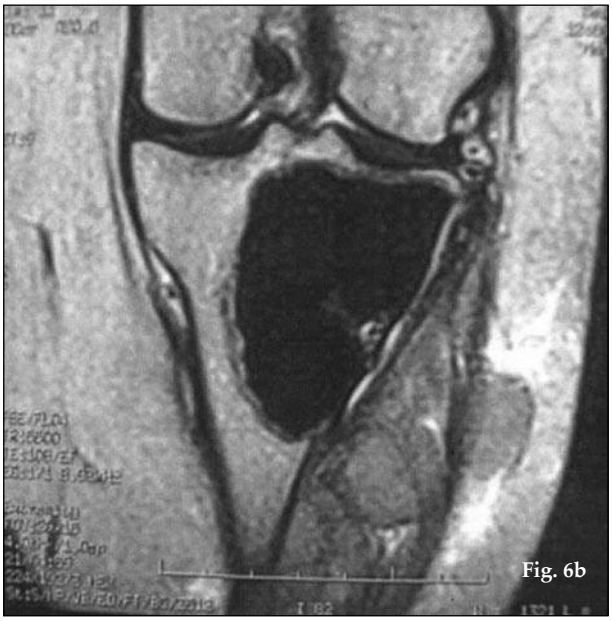
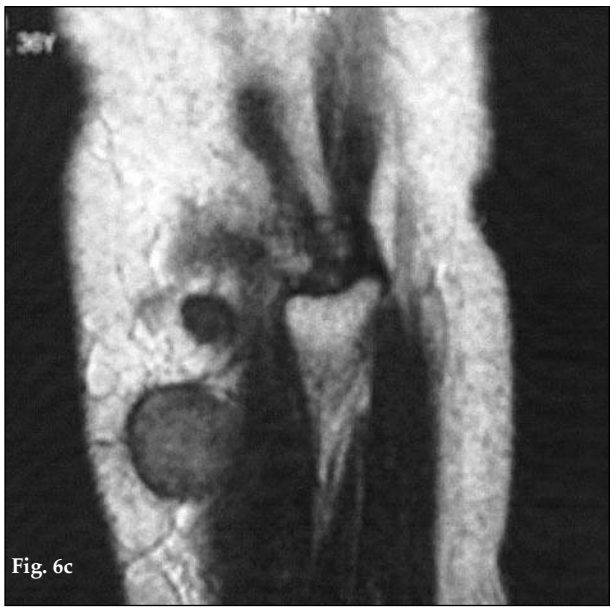


Fig. 5: CT, coronal reconstruction; soft tissue recurrence







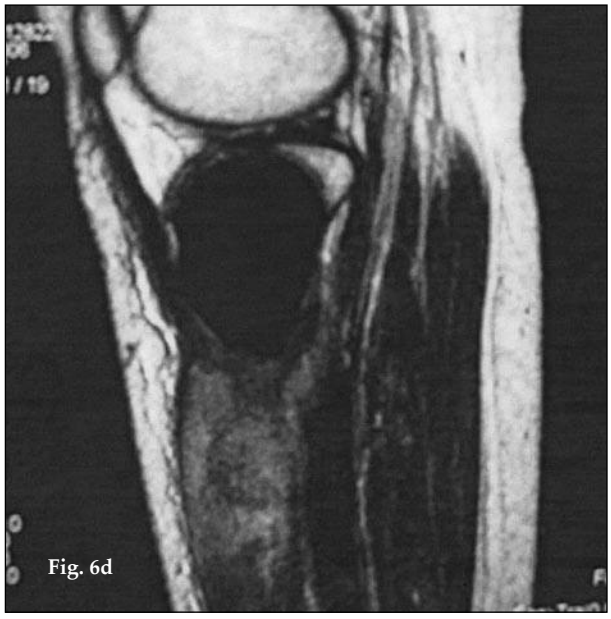


Fig. 6: MRI **(a)** axial cut **(b)** coronal cut **(c)** sagittal cut at the level of fibular head **(d)** sagittal cut at the level of lateral tibial condyle and interosseous space

also noted in the subcutaneous tissue anteriorly (Fig. 6; a,b,c,d). The impression was that of a soft tissue recurrence of GCT and this was confirmed by fine needle aspiration cytology.

Through an extensile antero-lateral approach the common peroneal nerve and anterior tibial vessels were explored. En-block resection of two subcutaneous masses from the antero-lateral aspect of the upper leg was carried out. It was possible to excise a 3 x 5 cm mass with a cuff of normal tissue around most aspects of the anterior compartment of the leg. Microscopic examination of the excised specimen showed infiltration of the fibromuscular tissue by a tumor with similar features as described above (Fig. 7). A diagnosis of soft tissue recurrence of aggressive GCT of bone was made.

The planned follow-up is every three months for two years, then every six months for three years, and then annually thereafter. Follow-up assessment includes physical examination, and radiographs of the involved limb. If soft tissue masses are detected, MRI will be necessary.

DISCUSSION

Curettage has been the preferred treatment for most cases of GCT. Prosser *et al* treated 137 cases of GCT with curettage without any adjuvant therapy or filling agent. The local recurrence rate of Grade I and II was only 7% compared with 29% in grade III, with an overall incidence of 19%. He found that the efficacy of the initial curettage was the most important factor, regardless of the adjuvant

therapy used[10]. Blackley *et al* managed 59 cases of GCT with curettage using a high-speed burr and reconstruction with autogenous bone graft with or without allograft bone. He reported a 12% local recurrence rate and concluded that the adequacy of removal of the tumor rather than the use of adjuvant modalities was what determined the risk of recurrence[11]. Campanacci *et al* reported rate of local recurrence of 27% after intralesional excision, only 8% after marginal excision, and zero percent after wide or radical excision. He concluded that the surgical margin was the factor that influenced the outcome[2].

O'Donnell *et al* correlated rate of recurrence to tumor site. The highest rate was in the distal part of the radius (five out of 10 patients, 50%), followed by the proximal part of the tibia (seven out of 25 patients, 28%) and the distal part of the femur (three out of 23 patients, 25%)[6].

Various investigators recommended the use of adjuvant agents to destroy any tumor cells remaining after curettage. Phenol was employed by many authors[2,6,12-14]. It destroys cells non-specifically by coagulation necrosis[14]. Bone cement (polymethylmethacrylate) was applied as a local adjuvant and to fill the resultant cavity left after curettage[2,6,12,13]. Its usage provides immediate mechanical stability, allowing for early weight bearing[1]. Early detection of recurrence is easier as lysis always occurs on the extralesional side of cement-bone interface and the most specific radiological sign on plain radiograph is lysis of 5 mm or more at the cement-bone interface[15]. Based on the previous observation we excluded intra-osseous recurrence in our case (Fig. 5). Saiz *et al* reported a local recurrence rate of 12.5% among a series of 40 patients treated with intralesional excision of the tumor with adjunctive phenol and cement[13] .

Few reports described the use of radiation therapy as adjuvant to surgery for benign GCT[2,16]. Zhen *et al* observed local recurrence in 12 out of 92 patients with GCT (13%) treated with curettage, local application of 50% aqueous zinc chloride solution and bone grafting[4]. Recently, argon beam coagulation was used as adjuvant to curettage and cementation and was associated with a low rate of local recurrence (8.3%)[5]. Based on experimental work, Chang *et al* suggested that topical or systemic use of bisphosonates pamidronate or zoledronate could be a novel adjuvant therapy for GCT by targeting osteoclast like giant cells, mononuclear giant cell precursor cells, and the autocrine loop of tumor osteoclastogenesis[3].

A rare complication of GCT, observed in only 17 of 1,100 GCTs reported from the Mayo Clinic, is recurrence within the adjacent soft tissue[7]. Extra-

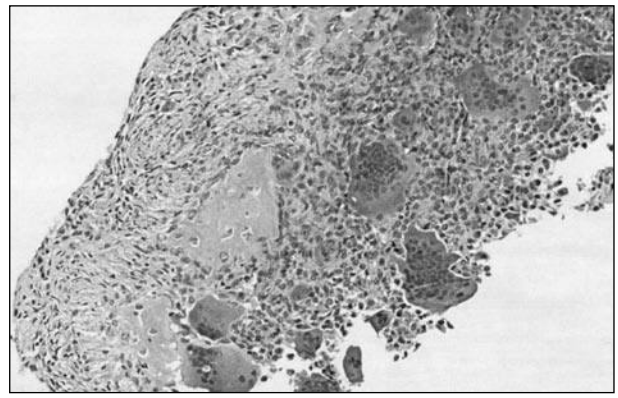


Fig. 7: Extra-osseous component of an aggressive giant cell tumor of bone. Osteoid is seen to the left of the giant cells in the lower half of the field (H & E X 100).

osseous implantation (seeding) may be the result of either accidentally breaking into the tumor through pathological fracture or transplanting of tumor tissue on surgical instruments after curettage[9,17,18]. In cases with extension of the tumor into the soft tissue, it is recommended to dissect the pseudocapsule circumferentially and excise it completely[4].

In a series of 218 cases of GCT, soft tissue recurrence was observed in seven patients treated by primary curettage, in one treated by curettage and bone graft, in two treated by resection, and in two treated by resection and bone graft[18]. Frangakis *et al* reported soft tissue recurrence in one patient with GCT involving distal radius treated by en-block resection[9].

Often, the soft tissue implants show a radiographically detectable rim of metaplastic bone formation[7,19]. Cases in which peripheral ossification was not detected on radiograph, histopathological examination revealed a few foci of ossification within the tumor as well as the periphery of the lesion[8]. Our case is an example of that phenomenon (Fig. 5 and 7). Teot *et al* described primary and recurrent extra-osseous GCT[19]. In our case, the previous surgery, made the diagnosis of recurrent GCT more likely.

In situ hybridization showed messenger RNA (mRNA) for transforming factor ß1 (TGF- ß1) and transforming growth factor ß2 (TGF- ß2) in neoplastic stromal cell and osteoclast-like giant cell within the recurrent and primary extraosseous tumor. Production of these osteoinductive growth factors by GCT may have a paracrine effect on mesenchymal progenitor cells, thereby stimulating the osteoblastic differentiation and metaplastic bone formation[19].

Holst reported the rare occurrence of a primary giant cell tumor of soft tissue (GCTST) occurring primarily in the dermis. Immunohistochemically and histologically, it is similar to its bony counterpart and differentiation is based on clinical and radiograph examination[20].

Follow-up evaluation after operative treatment of GCT should include clinical examination and plain radiograph of the involved bone. If a palpable soft-tissue mass is not apparent on plain radiograph, additional diagnostic studies, particularly MRI or FNAC under the guidance of CT is indicated to exclude extra osseous soft-tissue recurrence[8].

Soft tissue recurrence of GCT requires en-block wide resection[8,9]. Blackley *et al* considered soft tissue recurrence more difficult to control and described the use of radiotherapy in two cases of such recurrence[11].

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Case Report

Chediak-Higashi Syndrome: Report of a Case with an Accelerated Phase and Review of Literature

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ABSTRACT

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by partial albinism, recurrent pyogenic infection and large granules in all granule-containing cells.

We present a case of 1 $^1/_2$ year- old non Kuwaiti boy who presented in the accelerated phase of CHS with fever, pancytopenia, lymphadenopathy and hepatosplenomegaly.

High dose of methylprednisolone and sandglobulin were given for treatment of the accelerated phase with clinical response to the therapy. Unfortunately, allogenic bone marrow transplantation for HLA-matched father was postponed as the procedure is not available in Kuwait and could not be done abroad because of financial reasons.

KEY WORDS: accelerated phase, bone marrow transplantation (BMT), Chediak-Higashi syndrome (CHS)

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by severe immunodeficiency, occulocutaneous albinism, bleeding diathesis, recurrent infections, progressive neurological defects and lymphoproliferative syndrome.

Patients with CHS enter an accelerated phase that often results in death.The first accelerated phase of CHS may occur shortly after birth or several years later. Most patients undergo a variable period of recurrent infections before going into the accelerated phase[1].

Typical laboratory findings are the presence of giant cytoplasmic granules in all granule-containing cells in peripheral blood and in the bone marrow. The treatment of choice for CHS is bone marrow transplantation and should be proposed as early as possible before the accelerated phase of disease develops[2].

CASE REPORT

An 18-month-old non-Kuwaiti boy presented with a two week history of fever and cervical lymphadenopathy not responding to oral antibiotics given in a private clinic. His parents are consanguineous with no family history of blood diseases or similar conditions. He was admitted to several hospitals in Kuwait since the age of four months for mild recurrent infections.

On physical examination he looked well- grown with fair skin and grey hair. In addition, he had pallor, jaundice, bilateral cervical lymphadenopathy, hepatomegaly (7 cm below RCM) and splenomegaly (5 cm below LCM). No evidence of meningeal signs or neuropathy was noted.

Investigations showed pancytopenia. Results of investigation were as follows: Hb 8 gm/dl, WBCs 5.9x10^9/l, neutropenia (ANC 400), platelets 60 x 10^9/l. Peripheral smear revealed giant granulation of neutrophils, monocytes and lymphocytes (fig. 1). Transaminases; ALT 209 u/l, AST 190 u/l, total bilirubin 180 umol/l with direct 154 umol/l, coagulation profile; PT 19.1 sec, PPT 50.3 sec, ratio 1.63, LDH 250 u/l, triglycerides 3.5 mmol/l, and ferritin 2500 ng/ml. No growth of micro-organisms was observed in either urine or blood cultures, and the IgM antibodies against Ebstein Barr virus (EBV) and cytomegalovirus(CMV) were positive. Bone marrow smear showed giant granules in the cytoplasm of granulocytic series (fig. 2) with accentuation of peroxidase-positive granules. There were no abnormal blast cells (fig. 3). Based on the clinical presentation and hematological findings a diagnosis of accelerated phase of CHS was made.

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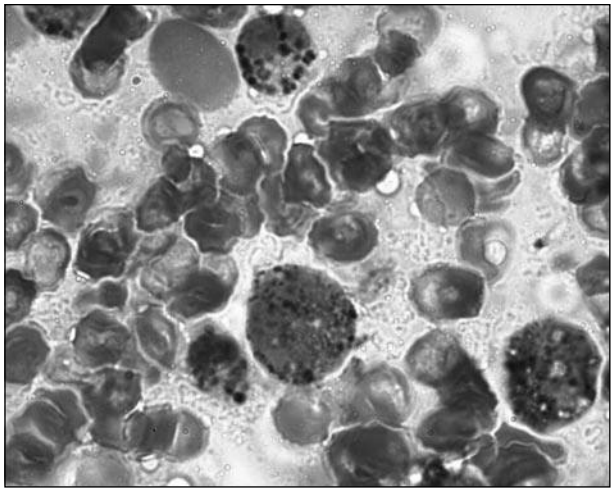

Fig. 1: Pelger - Huet anomaly (abnormal neutrophil) with abnormal granules in peripheral smear of CHS

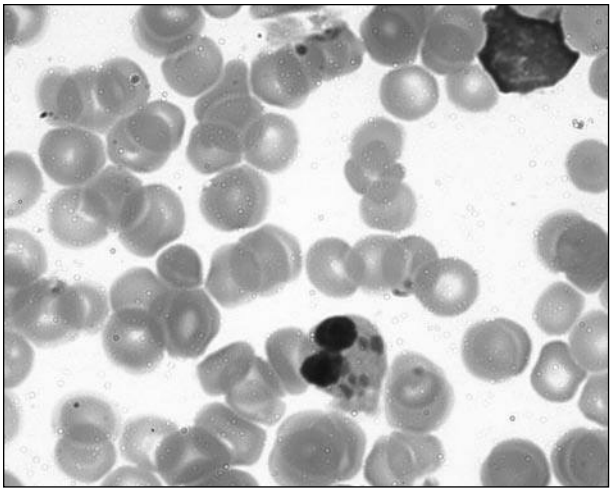

Fig. 2: Bone marrow smear showing abnormal granules in the precursor cells of leukocytes

The patient was treated with empirical antibiotics, gancyclovir, high doses of methyl prednisolone, prednisolone and intravenous immunoglobulin. Improvement of clinical well being, pancytopenia and reduction in hepatosplenomegaly were noticed as a clinical response to the therapy. Since the father is HLA-identical to the patient, bone marrow transplantation (BMT) was highly recommended. Unfortunately the procedure is not available in Kuwait and could not be done abroad because of financial reasons.

DISCUSSION

The Chediak-Higashi syndrome (CHS) is a rare but global disease. It is inherited as an autosomal recessive disease with equal sex distribution affecting predominantly phagocytes and melanocytes. Apart from human beings, this disease has been recognized in aleutin mink, beige mice, cats, cattle and killer whales[3].

A high proportion of CHS cases reported have been offspring of consanguineous marriage as in our case, although other cases have also been reported in children of unrelated parents. CHS is a disease of infancy and early childhood. Children with CHS usually manifest by partial occulo-cutaneous albinism and later with recurrent pyogenic infections including those of the respiratory tract, mouth and skin[4]. Increased bleeding tendency is also a frequent feature in these children. However, in more than 85% of cases the disease remains mostly quiescent in early childhood with minor infections until it changes to the accelerated phase characterized by non-responding fever, pancytopenia, coagulopathy, peripheral neuropathy and widespread lymphohistiocytic organ infiltrates leading to infection and death[5]. The first accelerated phase may occur shortly after birth or several years later, and the average life span of affected children without BMT is six years. Neurological manifestations such as peripheral neuropathy, long tract signs, seizures and mental impairment occur in approximately half of the patients[6]. Our case did not have such a manifestation, probably due to the early detection. Subtle pigmentary abnormalities with normal eyes and absence of family history of the disease in our case made the clinical diagnosis difficult.

The first clue to the diagnosis was the laboratory reports of giant granules in the leucocytes of the peripheral blood smear which were confirmed by bone marrow examination with accentuation of peroxidase stain[7]. Characteristic giant granules in all leucocytes result from abnormal fusion of both lysosomal azeurophil (primary) and specific (secondary) granules which contain CD65 and myeloperoxidase, an enzyme characteristic of primary and secondary granules. These abnormal inclusions in CHS neutrophils are unable to adequately metabolize and digest microbes leading

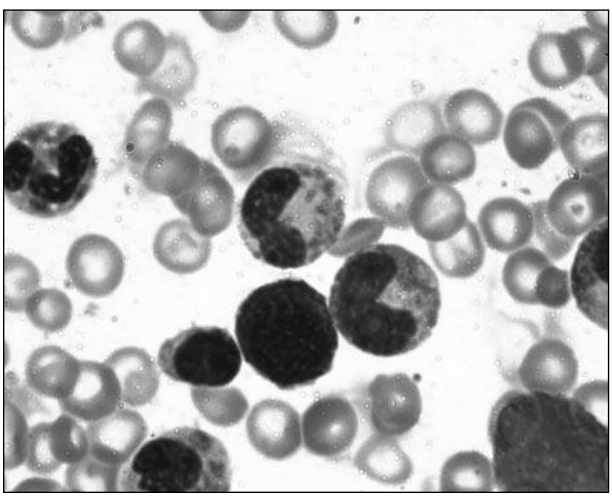

Fig. 3: Bone marrow smear showing peroxidase-positive granules in the precusor cells of leukocytes

to recurrent infections in early childhood[8]. In melanocytes, the defective granules produce a dilute pigment which is responsible for partial albinism.

Though the common organism associated with infection in chronic stable phase of the disease are *S. aureus and Streptococcus supp.* Ebstein barr virus (EBV) is implicated in the accelerated phase[9]. It is believed that the inability to clear the EBV infection leads to a state of constant lymphoproliferation, as seen in the phase of disease acceleration. The same virus may be responsible for the hemophagocytic syndrome[10].

The CHS gene was identified in 1996 and has been mapped onto chromosome 1q42-44, a region code for a protein[7]. However, its function remains unknown. Referring to a recent study, the results suggested that the CHS / beige protein interacts with at least two different partners and affects cellular events such as PtdIns (4,5) P2 localization, in addition to regulating lysosome size[11]. Moreover, a study showed the apparent allelic genotype-phenotype relationship among the various clinical forms of CHS. Homozygous protein-null alleles were associated with severe childhood CHS, and at least some homozygous disease mutant alleles were associated with clinically milder forms of the disorder[12].

Other immune-deficiencies can present clinical manifestations similar to those of CHS. Griscelli syndrome, described in 1978, was characterized by partial oculocutaneous albinism, cellular and humoral immuno-deficiencies, neurological deterioration and an accelerated phase similar to that described in CHS. However, the granular phenotype in the bone marrow is a clear indication of CHS[13].

The treatment of CHS is still controversial. Parenteral vitamin C administration in the stable phase may normalize neutrophil bactericidal activity, but it has little benefit in the accelerated phase[14]. In some patients, high dose methyl prednisolone with or without immunoglobulin may be effective. Chemotherapy with etoposide in association with steroid and intrathecal methotrexate can induce transient remission of the accelerated phase but relapses become less responsive to the treatment[15]. Receiving G-CSF maintenance treatment in case of CHS prevents further infectious episodes within a six months period according to a report[16].

Allogenic bone marrow transplantation has been proposed as the only possible curative treatment when performed early before the onset of the accelerated phase. It corrects the immunologic status but does not affect pigment dilution[17]. Allogenic bone marrow transplantation from HLA-matched sibling is the treatment of choice. If no matched family donor is available, an unrelated donor or plancental blood graft is a good alternative. Without BMT, children with CHS usually die before the age of 10 years[18,19].

CONCLUSION

We suggest that peripheral blood film examination for abnormal giant granules in granulocytes is an essential investigation in all young children with frequent infection or who are suspected to have virus associated hemophagocytic syndrome or familial hemophagocytic lymphohistiocytosis. The early detection CHS cases can lead to BMT which is the only curative treatment of this disorder.

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Case Report

Blunt Injury to the Renal Artery

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ABSTRACT

Renal artery injury is an uncommon complication of blunt abdominal trauma. We report a case of blunt injury to the renal artery in a 13 year-old girl who presented with low grade fever and microscopic hematuria, following a fall from the horse-back. Although Computed tomography (CT) done initially reported normal, a subsequent imaging revealed a diffuse subcapsular hematoma in the left kidney compressing the non-functioning renal tissue as well as left renal artery and a diffuse renal cortical infarct. This result was similar to what was found in the subsequent isotope scan, which revealed poor left renal function of 3%. Increasing the use of CT scan to evaluate blunt abdominal trauma helps to identify more cases of renal artery injury, which might otherwise be missed.

KEY WORDS: blunt renal artery injury, CT scan in blunt renal injury, reno- vascular hypertension

INTRODUCTION

Injury to the renal vasculature is an uncommon occurrence in the setting of blunt abdominal trauma. Renal artery thrombosis after blunt trauma has usually been diagnosed too late to salvage the kidney. Ideally rapid diagnosis by intravenous urography (IVU) and early surgical intervention should allow early renal salvage before permanent parenchymal damage has occurred[1]. Microscopic hematuria alone, however, is a poor predictor of significant genitourinary tract damage. Our review suggests that asymptomatic victims of blunt trauma who have only small amounts of blood in the urine may safely be observed with routine emergency IVU. Computed tomography (CT) is a very useful diagnostic tool in childhood trauma[2]. Successful management of patients with renal trauma requires definition of the extent of the injury and a knowledge of the indications for exploration[3]. In cases of bilateral renal artery injury, immediate bilateral exploration is indicated; whereas in cases of unilateral injury, repair is indicated only if it is diagnosed early and promptly in a young, stable patient[4].

CASE REPORT

A 13-year-old girl was admitted to a private hospital complaining of transient loss of consciousness and vomiting accompanied by left loin pain after falling down from horse-back. Her medical history entailed multiple recurrent attacks of left pyelonephritis secondary to left vesico- ureteric reflux and she was under medical follow up for her condition. Her clinical data were all normal. CT scan of the head and ultrasound (US) of the abdomen and pelvis were done and the results were within normal limits. Twenty-four hours after admission she was transferred to our ward suspecting renal injury because of persistent left loin pain accompanied by constant backache. A second CT scan (abdomen and pelvis) was done which revealed enlarged irregular outline of the left kidney with diffuse low attenuation, no parenchymal enhancement and minimal bilateral pleural collection, more on the left side (Fig. 1).

The patient started to have low grade fever three days after admission (37.8 ^{0}C) associated with microscopic hematuria. A CT angiography was scheduled 24 hours later, which showed diffuse left renal subcapsular hematoma compressing irregular non-functiong renal tissue and renal artery insuffiency with diffuse cortical infarct, with vascular compromise to left renal architecture. This result was similar to an isotope scan showing poor left kidney function (3%) suggestive of severe parenchymal contusion but good functioning right kidney (Fig. 2a , 2b). She was treated conservatively, her condition improved and she was discharged for follow up in the Urology OPD. She was scheduled for isotope scanning after one month.

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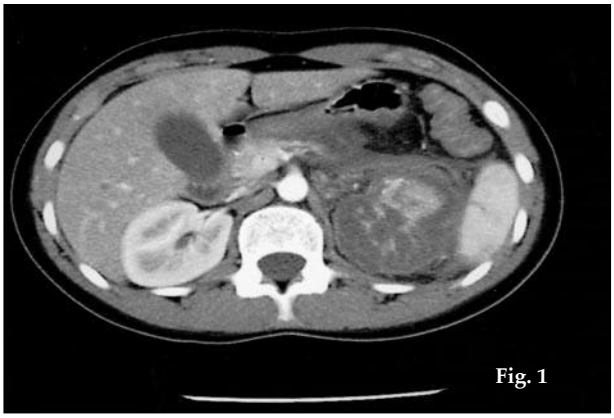
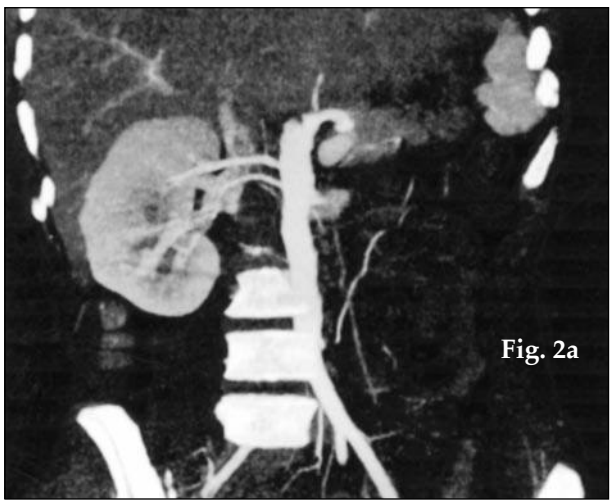


Fig. 1: CT abdomen done four days after trauma showing large left kidney with diffuse low attenuation and normal right kidney.

artery injuries that may have otherwise been missed. In addition to renal dysfunction, post-traumatic reno-vascular hypertension may result, although the true incidence of this complication is unknown. In patients with blunt abdominal trauma, the absence of a nephrogram on contrast enhanced CT scans is a useful sign of main or segmental renal artery occlusion . Termination of enhancement within the affected artery (renal artery cut off sign) was observed in some cases and a thin peripheral rim of cortical enhancement in an otherwise unenhanced renal segment (rim sign) was observed in certain cases[8]. Assessment of the traumatically injured pediatric patient with CT has become a standard medical practice. We report the unique finding of retrograde flow of intravenous



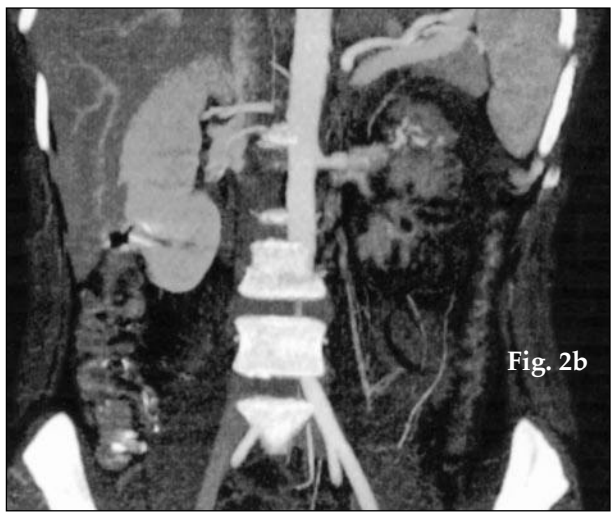


Fig. 2: CT angiogram done on the sixth day showing diffuse left renal subcapsular hematoma with non-visualization of distal renal vasculature and non-functioning left kidney (2a) and normal right kidney (2b).

DISCUSSION

Injury to the kidney from blunt trauma occurs rather frequently in the active, pediatric patients. Early evaluation and treatment of these injuries is essential in order to preserve maximum renal function[5]. Deceleration trauma which lead to cephalic, caudal and ventral movements of the kidney are regarded as predominant causes of renal vascular blunt injuries. In accidents involving a deceleration force, the possibility of renal vascular lesions should be considered[6].

Hematuria is common following blunt abdominal trauma. Most trauma centers routinely perform limited intravenous urography (IVU), usually with cystography, in individuals presenting with any degree of hematuria in order to identify urinary tract injury[7].

Majority of the patients respond well to careful conservative, non-operative treatment, followed by surgical intervention conducted as an elective procedure within the first week after injury. Increasing the use of CT scans to evaluate blunt abdominal trauma helps to identify more blunt renal contrast material into the renal vein as a diagnostic indicator of traumatic renal artery injury. With the increasing use of high-speed CT as the initial study to evaluate and stage blunt abdominal trauma, this finding may assist the physicians in the early diagnosis of severe renovascular injury[9]. Renal lacerations and avulsion usually require surgical exploration but the treatment of renal artery thrombosis is controversial. More distal injury affecting branches of renal artery is treated conservatively, whereas injury to the main renal artery is treated by surgical exploration[10].

CONCLUSION

Renal arterial damage may occur after blunt trauma, and early imaging and intervention are essential to salvage renal function. Contrast-enhanced CT scan remains the most widely available investigation for accurate staging of blunt renal trauma. Non-operative management should be considered as an acceptable therapeutic option in selected cases. Hemodynamic instability and injury to main renal vessels remain indications for surgical exploration.

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Case Report

Endoscopic Removal of Accidentally Swallowed Toothbrush

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ABSTRACT

Foreign body ingestion is a very well recognized problem that confronts surgeons. Toothbrush ingestion is rare, with only a few cases reported. We report a case of accidental swallowing of a long toothbrush and review the available literature on the complication and management of toothbrush swallowing. A 15-year-old female presented to the emergency room in Al-Sabah hospital, Kuwait, complaining of having swallowed her toothbrush. In addition to routine biochemical investigations, abdominal and chest X-ray were done. Abdominal X-ray revealed a foreign body (toothbrush) in the stomach. Endoscopy was used successfully to remove the toothbrush with no complication. The case is reported because of its rare nature.

KEY WORDS: endoscopic removal, foreign body, toothbrush

INTRODUCTION

Accidental swallowing of a toothbrush is rare but requires immediate medical intervention in one way or the other. It is known that 80% of swallowed foreign bodies pass spontaneously through the gastrointestinal tract[1], but there is only one report regarding swallowed toothbrush passing through the pylorus[2,3], which makes the condition a potential risk for complications such as pressure necrosis causing gastritis, ulceration and perforation[4].

The only documented case in which a toothbrush passed the pylorus was in 2006. In that case, the most serious complication of large bowel perforation and liver injury occured. Laparotomy was required for repairing the colo-hepatic penetration[3].

Our case is one of the rare cases that has been managed quickly and successfully using endoscope to remove the toothbrush.

CASE REPORT

A 15-year-old female presented to surgical emergency room complaining of having swallowed her toothbrush accidentally during tooth brushing. Six hours later she started developing mild epigastric discomfort without vomiting or any other symptoms.

She had no psychiatric illness or history of bulimia, and no previous hospitalization.

The patient was immediately assessed. She was clinically stable. Inspection of the oropharyngeal cavity was unremarkable with no signs of injury such as laceration, abrasion, contusion or bleeding. Also, there were no signs of neck emphysema. Chest was clear with good bilateral air entry. Abdomen was soft and lax with no area of tenderness, and no guarding.

Chest X-Ray AP and lateral and neck X-Ray were obtained. No abnormality was noted. Abdomen AP X-Ray showed a foreign body shadow opposite the level of lumbar 2-3 vertebrae, no air-fluid level and no free air under diaphragm (Fig. 1). Patient was admitted to the surgical ward for further management. The decision was made for urgent endoscopic examination and trial of foreign body removal. Flexible upper gastrointestinal endoscopy was done under general anesthesia for better patient control and patient was intubated for airway protection. The oral, esophageal and gastric mucosa was normal, A 19 cm toothbrush was found in the stomach fundus and a polypectomy snare was used to remove it successfully without intraoperative complications (Fig. 2).

The patient did well post- endoscopy. Repeat chest and abdomen X-rays were normal. Oral fluid was started followed by normal diet, which was well tolerated. The patient was discharged home with no complaint 48 hours after the procedure. The patient's family refused psychiatric consultation.

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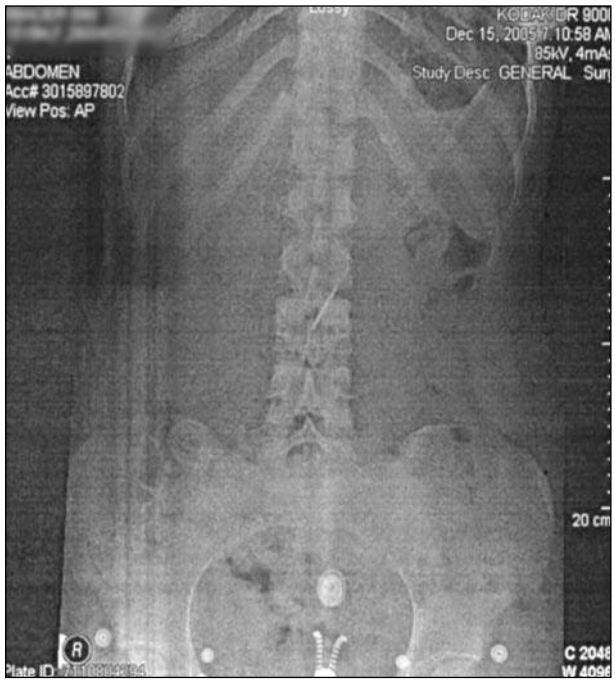

Fig.1: AP X-Ray showing a foreign body shadow opposite the lumbar 2-3 vertebrae

DISCUSSION

Ingestion of a foreign body is commonly encountered in the medical field among children, adults with intellectual impairment, psychiatric illness or alcoholism, and dental prosthetic-wearing elderly subjects[1,5]. In fact, swallowing of foreign bodies has been reported as early as 1200 BC[6].

A wide variety of objects may be swallowed, but coins, pins, bones, and razor blades predominate[1,7]. Most of these objects (80%) can be managed by observation with serial examinations and abdominal radiographs. They usually pass spontaneously through the gastrointestinal tract[1]. However, more invasive ways of retrieval are required in case of complications.

Toothbrush swallowing is rare with few reported cases, the first one being in 1882[8]. No cases of spontaneous passage of the swallowed toothbrush were reported[2]. This fact makes the possibility of complications such as gastritis, ulceration and perforation higher[4]. That is why some of the reported cases required surgical intervention in the form of a laparotomy[9,10].

In one reported case the 20 cm long swallowed toothbrush passed through the pylorus, duodenal loop, ileo-cecal valve and perforated the proximal transverse colon and then penetrated the liver[3]. Laparotomy was performed with repair of the perforated organs. The first reported death from a toothbrush occurred in 1889 as a result of gastric perforation three days after ingestion[8].

Swallowed foreign bodies particularly, stick-like objects such as toothbrushes may cause injury to any part of the gastrointestinal tract or the adjacent vital organs. However, such injury could escape diagnosis at the emergency department. In one reported case, the toothbrush penetrated the oropharyngeal region of a 10-year-old boy, a broken part wedged close to the carotid artery. The initial examination did not reveal the fatal injury[11].

Intervention must be quick and effective according to the availability of equipment to avoid complications. Treatment options for swallowed foreign bodies continue to evolve. In the past, patients were subjected to emergency laparotomy to remove the objects and prevent perforation[8]. An initial extraction strategy to start with is endoscopy. The first successful performance of this procedure was reported by Ertan *et al* in 1983[12]. Endoscopic removal of swallowed toothbrush should be done under general anesthesia with the patient intubated to avoid complications. There is a potential risk for aspiration, perforation, or surgical intervention[3,11]. In one report, the success rate for endoscopic removal of ingested foreign bodies was 48%[13]. In another report, surgery was rarely required[14].

Laparoscopic intervention is considered in cases of failed endoscopic removal. In fact, the laparoscopic approach may be an alternative to laparotomy[10]. Wishner *et al* reported the first successful laparoscopic removal of a swallowed toothbrush in 1997 [10].

A Medline search yielded some reported cases in which, endoscopy was used successfully to remove

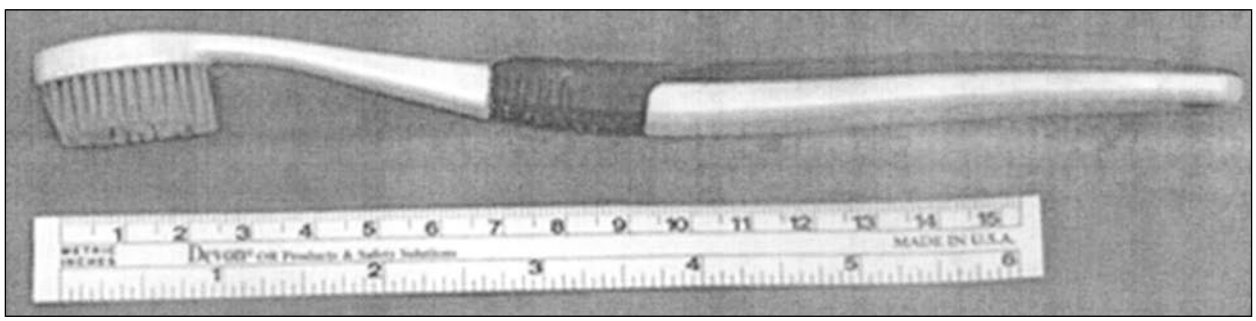

Fig. 2: The 19 cm toothbrush endoscopically removed from the stomach

the swallowed toothbrush. Some of these cases failed to be managed by endoscopy and laparoscopy had to be used.

CONCLUSION

We suggest that endoscopic removal of ingested toothbrush should be attempted under general endotracheal anesthesia with available surgical backup.

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Case Report

Association of Spinal Cord Dysfunction with Hereditary Spherocytosis

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ABSTRACT

Hereditary spherocytosis is a familial hemolytic disorder of red cell membrane cytoskeleton characterized by anemia, jaundice and splenomegaly. There are very few cases on record, of spinal cord dysfunction associated with this disorder, which are considered to be due to an abnormality in the cytoskeletal protein present in red cells, neuronal and dendritic cell membranes. We describe a rare case of hereditary spherocytosis which presented with spinal cord dysfunction.

KEY WORDS: familial hemolytic disorder, spectrin, splenomegaly

INTRODUCTION

Hereditary spherocytosis (HS) is an autosomal dominantly transmitted familial red cell membrane disorder which commonly presents in early childhood as chronic hemolytic anemia, jaundice and splenomegaly. Milder cases remain asymptomatic into adult life. Its morphological hallmark on blood smear is the microspherocyte[1]. The red cell membrane defect due to cytoskeleton abnormality leads to loss of the normal biconcave red cell shape. The common membrane cytoskeleton protein implicated is spectrin. A quantitative or qualitative abnormality of spectrin can lead to HS. Studies in mice show that β - subunit of spectrin is also present in the dendritic and neuronal cell membranes[2,3]. There are a few cases described in the literature of spinal cord dysfunction associated with HS[1]. It is postulated that this is because of the common cytoskeleton protein abnormality found in red cell, neuronal and dendritic membranes.

CASE REPORT

A 28-year-old male patient, working as a driver presented with complaints of progressive weakness and difficulty in walking over a period of one month. The weakness had increased gradually to involve both his lower limbs. He also complained of unsteady gait and feeling stiff while walking. His friends had also noticed that his sclera looked yellow. He had no complaints of numbness or paraesthesia. There was no history of trauma, previous neurological problems, back pain, urinary or bladder dysfunction, fever, preceeding URTI or any past family history of any medical illness. Smoking and alcohol history was negative. He also had a normal dietary history and was not taking any medications. On examination, he was jaundiced but not pale and the tip of the spleen was palpable. Neurological examination showed intact higher mental functions and cranial nerves were normal. The lower limbs showed mild weakness with power 4/5 bilaterally, distally and proximally. Tone was increased and the deep tendon reflexes showed bilateral hyperreflexia for both knee and ankle with patellar and ankle clonus. Plantars were extensors bilaterally. Sensations were normal for all modalities. He had a spastic, scissor gait.

His investigations showed the following results: Hb: 13.4 g/dl, MCHC: 37, Retics: 7.2%, Reticulocyte Production Index > 2.5, T. bilirubin: 79.2, D. bilirubin: 3.6, LDH: 405 (N < 200), S. Haptoglobin: 0.055 (N 0.360 – 1.95 g/l), Coomb's test negative, G-6PD: Normal. The blood film showed many microspherocytes and the osmotic fragility test was positive on 24 hrs incubation. Vit. B12 and Red cell folate levels were normal. His virology (HIV, HTLV) and autoimmune screen were normal, VDRL and BAT were negative. Magnetic resonance images (MRI) of the brain (Fig. 1) and spinal cord (Figs. 2 , 3) were normal. Taking the clinical picture and laboratory results into account a diagnosis of hemolytic episode of HS with spastic paraparesis due to spinal cord dysfunction was made. He was given folic acid 1 mg/day and physiotherapy was started for his spasticity. His hematological condition improved during his stay in the hospital and for his neurological condition he was referred to the neurology hospital for follow up.

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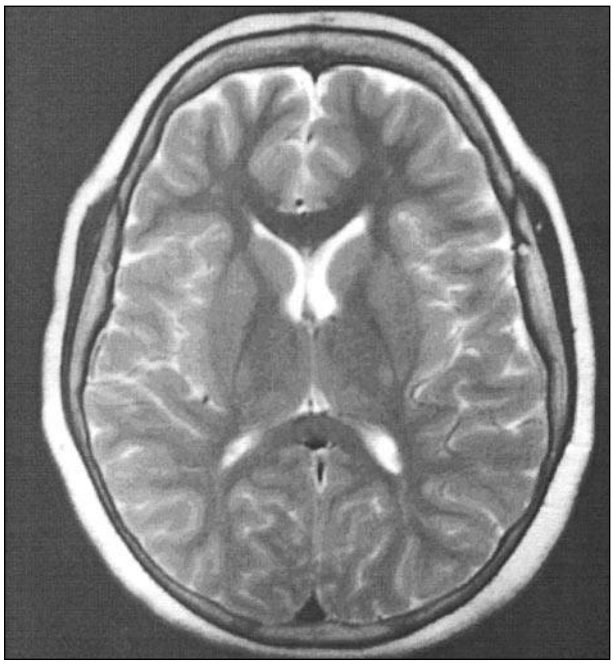

Fig.1: MRI brain T2 axial image showing normal signal intensity

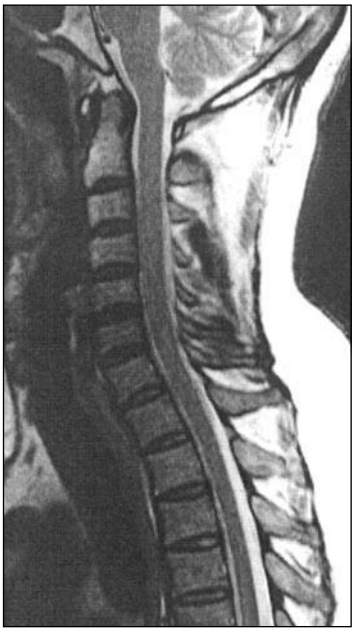

Fig.2: MRI cervical spine T2 sagittal image showing normal spinal cord

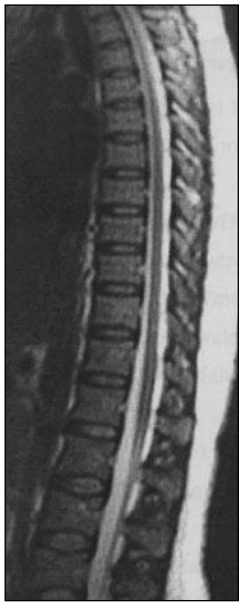

Fig.3: MRI dorsal spine T2 sagittal image showing normal spinal cord

DISCUSSION

Spinal cord dysfunction associated with HS is a very rare phenomenon. Very few case reports are found in the literature. In 1976, Mcann *et al* reported two unrelated patients with HS who developed spinal cord dysfunction[1]. The clinical presentation of these two cases described by them was similar to that of our patient. They have also referred to a few sporadic cases in the old European literature. The described lesion of the spinal cord in HS patients was a degenerative disorder. The demyelinating process in such patients is slowly progressive. They put forward a hypothesis that both the lesions of spinal cord and HS were due to an abnormality in the membrane cytoskeleton proteins. Studies in mice have shown that the β - subunit of membrane protein spectrin is present both in red cell, dendritic cells and neuronal cell membranes[2,3]. It is suggested that a mutation involving spectrin may be responsible for both red cell and nerve cell defects. A similar hypothesis has tried to explain the association of red cell membrane abnormalities with some muscular dystrophies[4]. Other associations described include myoclonic epilepsy with amyostatic syndromes, cerebellar disturbances, muscle atrophy and tabes like picture. The age of presentation is usually in the fifth decade but can be found in younger patient. Our case presented with mild spastic paraparesis due to spinal cord lesion with an episode of hemolysis. This episode was the first in his life. Though the patient had spastic paraparesis and scissor gait he was ambulatory. He was given folic acid supplement of 1 mg/day for his HS. Splenectomy was not contemplated as this was the first hemolytic episode in his life and his HS had a silent course over the years. His paraparesis was treated with physiotherapy and he was followed up after this episode in a specialty neurological hospital.

CONCLUSION

This rare case is presented to highlight the association of neurological dysfunction with HS. Though the exact pathophysiology is still unknown, it is postulated that the membrane cytoskeleton protein abnormalities may be the common factor between the red cell and neuronal cell pathology.

ACKNOWLEDGEMENT

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Case Report

Neurocysticercosis in Two Kuwaiti Children

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ABSTRACT

Neurocysticercosis (NCC) is the most common parasitic disease of the central nervous system (CNS). We report two cases of NCC presented with focal convulsion, where neuroimaging studies showed ring enhancing lesions with significant serological test results. Management was conservative in both cases with improvement of both symptoms and radiological lesions. Awareness of the disease is important especially in Islamic countries like Kuwait where pork or its products are prohibited.

KEY WORDS: management, neurocysticercosis, ring enhancing lesions

INTRODUCTION

Neurocysticercosis (NCC) is an infection of the nervous system caused by the metacestode of the pork tapeworm *Taenia solium*. It is transmitted by fecal-oral contact by ingesting eggs of the porcine tapeworm, heteroinfection from a contact harboring the adult tapeworm or by autoinfection. It is now considered the most common parasitic disease of the central nervous system (CNS). Millions are affected by *T. solium* in Latin America, Asia and Africa[1]. In these countries, NCC is a public health problem and a leading cause of acquired epilepsy in adults[2]. NCC is uncommon in childhood and patients younger than 17 years of age constitute 0.8 - 27.8% of the diagnosed cases of NCC[3]. The disease is expected to be a rare condition in Islamic states like Kuwait, where pork or its products are prohibited. However, employment of people from endemic areas can be a source of infection. In this report, we present two Kuwaiti children with NCC diagnosed within two months of each other in the Pediatric Department of Al-Amiri hospital, Kuwait.

CASE REPORT

Patient 1

A five year-old Kuwaiti boy was admitted with two attacks of afebrile focal convulsion involving the left upper limb associated with loss of consciousness lasting for two and five minutes respectively. There was no preceding history of fever, flu-like symptoms, vomiting, and ingestion of drugs or head trauma. There was no family history of epilepsy. On admission, he looked generally well, with stable vital signs. Examination of CNS and fundus were normal. Other systemic examination revealed no abnormalities. Computerized tomography (CT) scan showed a wedge shape area in the right parietal lobe with no midline shift or mass effect. Magnetic resonance imaging (MRI) showed a ring-enhancing lesion in the cortico-medullary junctions in the right parietal lobe and surrounded with edema (Fig. 1). Differential diagnosis of tuberculoma, brain tumor, metastasis and abscess were entertained. CT scan and ultrasound of the abdomen ruled out primary abdominal malignancy. Bone scan was normal. Tuberculosis was ruled out by normal chest X-ray and negative PPD test. The possibility of NCC was raised and enzyme linked immunosorbent assay (ELISA) for cysticercosis was significant with a titer of 1.8 (normal value < 0.5). The patient was started on carbamazepine as anticonvulsant, and no anticysticercal (ACC) medication was given since the lesion was degenerated as shown by the MRI. The patient had no further convulsion and repeated MRI after six months showed resolution of the edema and significant reduction in the size of the lesion. As the patient was symptom free, anticonvulsant medication was stopped after one year.

Patient 2

An 18-month-old Kuwaiti girl was admitted with five days of recurrent focal convulsions in the form of twitching of the face, eyes and left side of the mouth. On two occasions, it was associated with tonic clonic movement of the left upper limb.

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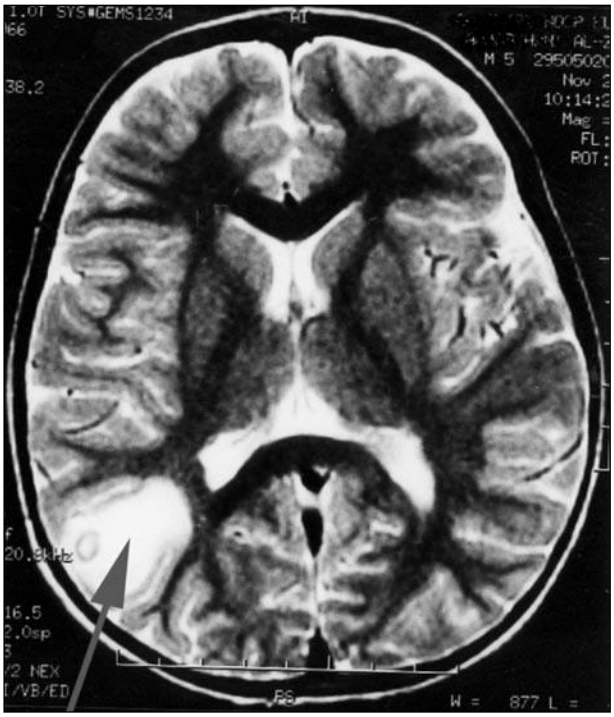

Fig. 1: Focal lesion seen in the cortico-medullary region in the right posterior parietal lobe with abundant amount of surrounding edema

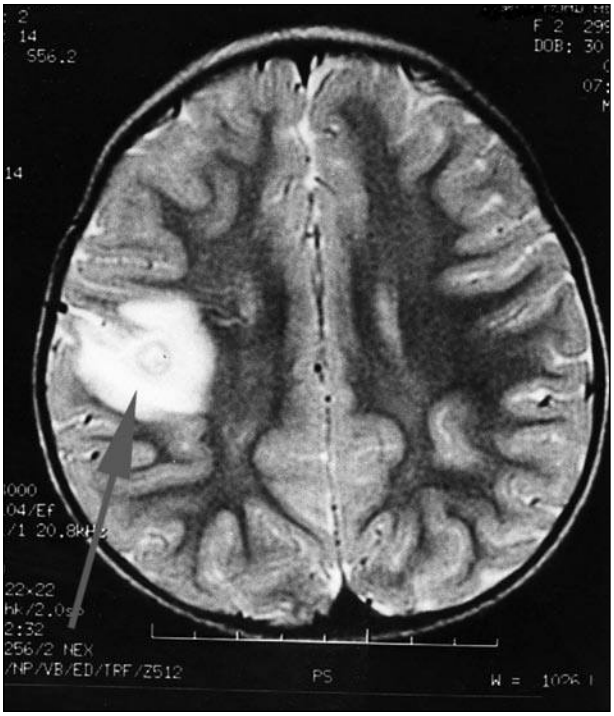

Fig. 2: Focal lesion seen in the cortico-medullary region in the right parietal lobe measuring 1.5 cm in diameter surrounded by massive edema

The attacks lasted for a few minutes and stopped spontaneously. There was no history of fever, upper respiratory tract infection, vomiting, drug ingestion or head trauma. There was no family history of epilepsy. On examination, vital signs were stable. Examination of all systems including neurological examination were normal. CT scan of head showed a well-defined focal lesion at the right frontotemporal region 1.25 cm in diameter with marked enhacement pattern and moderate surrounding edema. MRI was advised which showed ring enhancing lesion in the right parietal lobe measuring 1.5 cm in diameter surrounded by massive edema (Fig. 2). Tuberculosis was ruled out by normal chest X-ray and negative PPD test. ELISA for cysticercosis revealed a significant high titer (3.68). The patient was started on carbamazepine as an anticonvulsant only and no ACC drugs were given. MRI repeated after two years from presentation showed significant reduction of the lesion with prominent calcification (Fig. 3). The anticonvulsant was stopped after two years from presentation as the patient was symptom free.

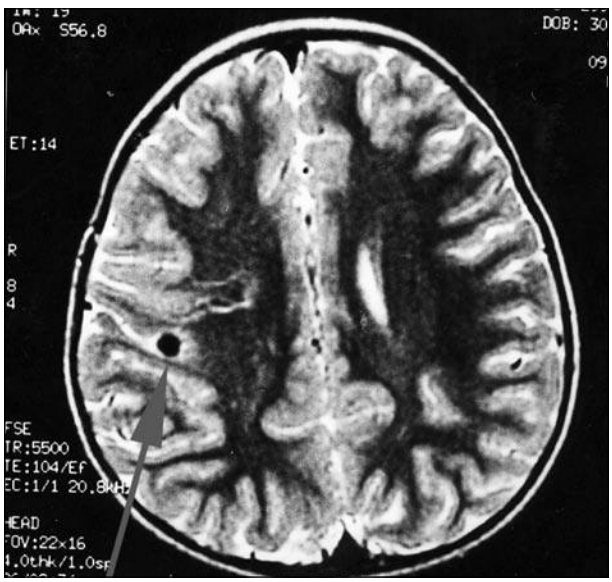

Fig. 3: Reduction of the lesion in the right parietal lobe with prominent calcification

DISCUSSION

NCC can be a serious public health problem in countries where poor sanitation and socio-economic conditions combine to perpetuate its dissemination[4]. As NCC is not a reportable disease, the exact incidence in Kuwait is not known but assumed to be very rare because of religious dietary laws which prohibit pork or its products. Khan and his colleagues reported two adult cases of NCC in Kuwait and both of them were from India[5]. Hira *et al* studied 16 patients with NCC. Nine of them were Kuwaitis (six children and three adults)[6]. Another study by Husain *et al* showed that seven patients had NCC and 56% of them were Kuwaiti children. She emphasized that NCC should be an important differential diagnosis of any enhancing lesions in the brain among Kuwaiti patients[7].

There was no history of travel to an endemic area where these Kuwaiti patients may have acquired the disease.The authors in these studies had attributed this to the employment of domestic servants from developing countries which are endemic for cysticercosis and were infected with it. The Kuwaiti patients were infected either by ingesting ova in contaminated food or after direct contact and transfer of ova from hand to mouth[6,7]. Both of our patients had Indian cooks who might have been the probable source of infection.

Seizures are the most common presentation in adult and children but it is more frequent in the latter. Singhi and his colleagues studied 500 children with NCC. Seizures were present in 94.8% of cases and 83.7% of them were focal[8]. Other presentations include headache, intracranial hypertension, encephalitis and psychiatric disorders.

The diagnosis of NCC may be made by neural biopsy. However, alternative means are used for diagnosis[9]. An accurate diagnosis of NCC requires interpretation of clinical and epidemiological data plus neuroimaging studies and result of specific serological tests. A recent consensus statement proposed diagnostic criteria for NCC based on objective, clinical imaging, immunologic and epidemiologic data[10]. Proper use of these criteria will allow physicians to avoid most diagnostic pitfalls.

The diagnosis of NCC in case 1 was delayed as several differential diagnosis were proposed initially including tuberculoma, brain tumors and abscess which led to a battery of investigations to reach the final diagnosis. But for case 2, the diagnosis of NCC was suggested from the beginning due to similarities with case 1 in presentation and MRI finding.

The correct diagnosis of NCC is based on imaging finding and laboratory tests. Neuroimaging studies are the main methods for diagnosing NCC. Computerized tomography is the best method for detecting calcification associated with prior infection. However, MRI is more sensitive than CT for depicting cysts in the brain parenchyma, for identifying inflammation associated with the cysts and for identifying cysts in the ventricles and basilar cisterns[11]. Both of our patients presented with focal convulsions and MRI showed ring enhancing lesions.

A wide range of serological tests have been used in diagnostic and epidemiological studies of NCC. Unfortunately, most of the tests use unfractionated antigen which is associated with high rate of false-positive and false-negative results[12]. The enzyme linked immunoelectrotransfer blot (EITB) assay is the serological test of choice with 100% specificity and 90% sensitivity for patients with at least two lesions[13]. Limitations of this diagnostic method include markedly decreased sensitivity in patients with single parenchymal lesions or calcifications.

The treatment of NCC is individualized, based on the viability, size, location of the cysts, the severity of the host immune response, and the presence or absence of complication such as hydrocephalus[4,9,14]. The therapeutic approach to most patients with NCC include symptomatic drugs and specific antiparasitic agents. Surgical procedures are indicated in those with hydrocephalus from subarachnoid or ventricular cysts that require venticulo-peritoneal shunting. Since seizures occur in 50-87% of patients with NCC, anticonvulsants are almost always used. For most patients seizures can be controlled with a single anticonvulsant as in our cases[9,14]. Many patients can eventually discontinue anticonvulsant therapy without recurrence of convulsion[15]. Cysticidal drugs have been used to treat NCC for more than 20 years, and several studies have shown that both albendazole and praziquantel destroy from 60% to 85% of viable intracranial cysticerci[4,16,17]. Viable cysts are defined by absence of ring enhancement or calcification on CT or MRI. Several studies had shown strong correlation between the use of ACC drugs and the rate of seizure control[15,18]. Recent randomized, blinded, controlled trial using albendazole showed the clinical benefit of decreased seizures and enhanced resolution of cysts after treatment[19]. Most children with NCC have only a single parenchymal lesions with ring enhancement and these cases like our patients do not require any ACC medications as most disappear spontaneously[3,8,14,20].

CONCLUSION

While Kuwait is non-endemic for NCC, the employment of individuals from endemic areas can be a source of infection. Awareness of this disease is very important to prompt early diagnosis and treatment. It should be considered in any child who presents with afebrile convulsion and ring enhancing lesion in neuroimaging studies with significant serological tests.

ACKNOWLEDGEMENT

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2009, 41 (1) 75 - 79

Nonlinear Pattern of Pulmonary Tuberculosis among Migrants at Entry in Kuwait: 1997-2006

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BMC Public Health 2008; 8:264

Background: There is a paucity of published data on the pattern of pulmonary tuberculosis among migrant workers entering Middle Eastern countries particularly Kuwait. The objectives of this study were to use routine health surveillance data i) to estimate the prevalence of pulmonary tuberculosis among migrant workers at entry in Kuwait and ii) to determine the occurrence of any time trends in the proportions of pulmonary tuberculosis positive workers over the study period.
Methods: The monthly aggregates of daily number of migrants tested and the number of pulmonary tuberculosis cases detected during routine health examinations of migrant workers from tuberculosis high-prevalence countries were used to generate the monthly series of proportions (per 100,000) of pulmonary tuberculosis cases over 120 months between January 1, 1997 and December 31, 2006 and analysed using time series methods.
Results: The overall prevalence (per 100,000) of documented pulmonary tuberculosis cases among screened migrants was 198 (4608/2328582). Year-specific prevalence (per 100,000) of tuberculosis cases consistently declined from 456 (95% CI: 424-490) in 1997 to 124 (95% CI: 110-140) in 2002 before showing a steady increase up to 183 (95% CI: 169-197) in 2006. The second-order polynomial regression model revealed significant ($P < 0.001$) initial decline, followed by a significant ($P < 0.001$) increasing trend thereafter in monthly proportions of tuberculosis cases among migrant workers.
Conclusion: The proportions of documented tuberculosis cases among migrant workers showed a significant nonlinear pattern, with an initial decline followed by a significant increasing trend towards the end of the study period. These findings underscore the need to maintain the current policy of migrants' screening for tuberculosis at entry. The public health authorities in Kuwait and perhaps other countries in the region may consider complementing the current screening protocol with interferon-gamma assays to detect migrants with latent Mycobacterium tuberculosis infection. An appropriate curative or preventive chemotherapy of detected tuberculosis cases may help in further minimizing the risk of local transmission of M. tuberculosis, while contributing in global efforts to control this public health menace.

Serum Leptin and Its Relationship with Metabolic Variables in Arabs with Type 2 Diabetes Mellitus

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Ann Saudi Med 2008; 28:367-70

Background and objectives: Most studies on serum leptin in type 2 diabetes mellitus have focused on white populations. We studied serum leptin concentrations and parameters related to glycemic control and the association between leptin levels and anthropometric and metabolic factors in Arab patients with type 2 diabetes and in Arab control subjects.

Subjects and methods: Ninety-two patients (65 females and 27 males) with type 2 diabetes and 69 matched normal control subjects (48 females and 21 males) were included. Anthropometric measures (including body mass index [BMI] and waist:hip ratio) were assessed in all subjects. After an overnight fast, blood was collected for serum leptin assay. Other metabolic parameters including glucose, insulin, C-peptide, intact proinsulin, insulin resistance index (HOMA-IR), insulin-like growth factor 1 (IGF-1), lipids and hemoglobin A1c (HbA1c) were determined.
Results: Fasting serum leptin levels, IGF-1 and high-density lipoprotein (HDL) cholesterol were similar in patients with type 2 diabetes and control subjects. When obese subjects (BMI > or =30 kg/m^2) were analyzed separately, serum levels of leptin were significantly lower in patients compared to controls. In contrast, patients had higher fasting glucose, insulin, C-peptide, intact proinsulin, insulin resistance, total cholesterol, triglycerides, HbA1c, and a larger waist circumference and waist-to-hip ratio than controls. Serum leptin correlated positively with BMI, negatively with waist-to-hip ratio, and demonstrated no relationship to other parameters.
Conclusion: Patients with type 2 diabetes in an Arab ethnic population showed evidence of an unfavorable metabolic profile despite having leptin levels similar to controls. Obesity influences serum leptin levels more significantly in type 2 diabetes, in which leptin levels tends to be low.

Postrenal Transplantation Urologic Complications

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Transplant Proc 2008; 40:2345-2346

Objectives: We sought to explore the incidence, risk factors, clinical presentation, management options, and outcomes of post renal transplant urologic complications.
Patients and methods: Between November 1993 and December 2005, we performed 646 renal transplantation procedures in 373 males and 273 females, of whom 81 were children. Kidney grafts were obtained from 461 living and 185 cadaveric donors. The medical records were retrospectively reviewed for urologic complications. Affected patients presented clinically with impaired kidney function: the diagnosis was confirmed by ultrasound scanning, isotope renal scanning, magnetic resonance urography, and/or antegrade urography. Ureteric stricture was managed by percutaneous antegrade ureteric dilatation and stenting, or by surgical reconstruction. Urine leak was treated by prolonged bladder drainage or surgical reconstruction. Renal stones were treated with extracorporeal shockwave lithotripsy.
Results: Urologic complications were detected in 31 recipients (4.8%), including 21 males and 10 females, among whom 4 were children. They had received kidney grafts from 19 living and 12 cadaveric donors. Urologic complications were ureteric strictures in 15 (2.58%), urine leaks in 15 (2.58%), and ureteric stone in 1 (0.17%) recipients. There was no graft loss to urologic complications.
Conclusions: The incidence of post-kidney transplant urologic complications was 4.8%. They were more common among male recipients and after cadaveric kidney transplantation. Although ureteric stricture presented late posttransplantation and was more common among children (4.23%), urine leak presented early and was more common in the elderly (4.69%). All urologic complications were successfully managed, with no graft loss.

A Study of the Bacterial Flora before and after Antiseptic Skin Preparation of the Perineum in Male Urology Patients

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Urol Int 2008; 81:403-408

Objective: To establish the bacterial flora of the perineum before and after antiseptic preparation in male urology patients.
Patients/methods: Adult male patients undergoing cystoscopic procedures were studied. Three sets of swab specimens, labelled A, B and C, were taken from the perineum in the theatre. Specimen A was taken before cleaning and disinfection of the skin with Savlon (Chlorhexidine- cetrimide mixture), specimen B after disinfection and draping, and C after completion of the operative procedure. Specimens were processed on standard laboratory media for aerobic and anaerobic bacteria and yeasts.
Results: Of the 114 patients studied, 43 (37.7%) had a positive culture for significant microorganisms in specimen A, 7 (6.1%) in specimen B and 13 (11.4%) in specimen C (A vs. B $p < 0.001$, A vs. C $p < 0.001$, B vs. C $p < 0.01$). The commonest isolates in specimen A were Gram-positive organisms (84.1%). The positive-culture rate for patients with end-stage renal failure was 71.4%, for those with a urethral catheter it was 53.8%, for those without systemic diseases it was 36.6% and for patients with diabetic mellitus it was 28.1%.
Conclusion: About 38% of patients undergoing cystoscopic procedures had a significant positive perineal culture, with Staphylococcus species being the predominant skin flora. The bacteria culture rate was affected by the presence of systemic diseases. The use of Savlon to disinfect the perineum resulted in a significant reduction in the bacterial count of the perineum.

Pulmonary Hypertension Responding to Hyperthyroidism Treatment

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Respirology 2008; 13:923-925

Pulmonary hypertension in adults with hyperthyroidism is increasingly being reported. Although the mechanism is uncertain, the reversal of pulmonary hypertension following restoration to an euthyroid state supports a causal relationship. This case report is of a 43-year-old woman who presented with Graves disease and right ventricular failure. Echocardiography showed severe pulmonary hypertension, moderate to severe tricuspid regurgitation, normal left heart function and a negative bubble contrast study. Carbimazole therapy was instituted along with diuretics and captopril. The patient was followed for a period of 14 months. Clinical and biochemical euthyroidism was attained after 4 months of treatment. Resolution of right ventricular failure and normalization of pulmonary artery pressure occurred 11 and 14 months after initiation of therapy, respectively. Investigating thyroid status in patients with pulmonary hypertension is recommended. In patients with hyperthyroidism and (otherwise unexplained) pulmonary hypertension, restoration of euthyroidism may cure right ventricular failure and restore normal pulmonary artery pressure.

Papillary Thyroid Carcinoma: Evidence for Intracytoplasmic Formation of Precursor Substance for Calcification and Its Release from Well-preserved Neoplastic Cells

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Diagn Cytopathol 2008; 36:809-812

Psammoma bodies (PBs) are believed to represent a process of dystrophic calcification over nonviable and dying tissues. Light microscopic and ultrastructural observations suggest that PB formation follows the intracellular assembly of precursor substances and their calcification leading to death of tumor cells and their release. It may also be the result of local secretion of precursor substances like collagen by tumor cells into extracellular space and their calcification. In an earlier reported study, we demonstrated the extracellular localization of various precursor forms of PBs and of irregular calcification in fine-needle aspiration (FNA) smears of papillary thyroid carcinoma (PTC). In this report, we describe a PTC case with intracellular formation precursor substances for calcification and their release from the well-preserved neoplastic cells before undergoing calcification. Ultrasound-guided FNA smears from a small nodule in the left lobe of thyroid in a 40-year-old woman revealed a PTC with numerous intracytoplasmic targetoid bodies, which were magenta colored in MGG stain. On their release from the neoplastic cells, these targetoid precursor bodies were found to be forming pools of matrix material, some of which showed evidence of calcification. The cytologic findings were confirmed by histopathology of the tumor in the thyroidectomy specimen. For the first time, we demonstrate through cytomorpholgy the intracytoplasmic formation of targetoid bodies as precursor substances for calcification and their release from well-preserved cells in PTC. We suggest that the calcification in PTC may not necessarily be taking place over nonviable and dying cells.

Manipulation of Cytokine Production Profiles as a Therapeutic Approach for Immunologic Ppregnancy Loss

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Indian J Biochem Biophys 2008; 45:229-236

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Pregnancy is not as successful as one might think; it can be compromised by several complications such as recurrent spontaneous miscarriage, pre-term delivery, pre-eclampsia etc. Much attention has been paid to the possibility of the maternal immune system mediating deleterious effects on pregnancy. Research conducted during the last two decades has shed much light on cell-mediated immunologic effectors that might underlie these pregnancy complications. Of particular interest are the effects that pro-inflammatory and anti-inflammatory cytokines have on the foetus and placenta, and thus on the success and failure of pregnancy. This review presents evidences that certain cytokine profiles are associated with recurrent miscarriage and pre-term delivery and discusses possible pathways of effector function of cytokines in pregnancy loss and the redirection of cytokine profiles from one that is antagonistic to pregnancy towards one that is conducive to the success of pregnancy. Among the promising agents for the modulation of the Th1/Th2 balance are progestogens like progesterone and dydrogesterone; this review also discusses recent evidence that progestogens are capable of modulating cytokine production patterns in pregnancy loss.

Correlation of Proinflammatory and Anti-inflammatory Cytokine Levels with Histopathological Changes in an Adult Mouse lLung Model of Campylobacter Jejuni Infection

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Clin Vaccine Immunol 2008; 15:1780-1787

Campylobacter jejuni is a major cause of diarrhea in humans. A mouse lung model of infection was previously established for C. jejuni. We used this model to study cytokine production in the lungs and correlated it with pathological changes. C. jejuni strain 81-176 or sterile phosphate-buffered saline was intranasally inoculated into adult BALB/c mice. The levels of proinflammatory cytokines (gamma interferon, tumor necrosis factor alpha, interleukin-1beta [IL-1beta], IL-2) and anti-inflammatory cytokines (IL-4, IL-10), in addition to those of IL-6, were assessed on days 1, 3, and 5 postinfection by enzyme-linked immunosorbent assay, and the ratios of proinflammatory cytokines to anti-inflammatory cytokines were calculated. Since IL-6 is unique in that it is both a proinflammatory cytokine and a TH2 cytokine, it was considered to be both in the determination of these ratios. The significance of the cytokine levels and ratios were determined by the Mann-Whitney U test (P<or=0.05). The induction of proinflammatory cytokines in the lungs of infected mice, as indicated by the cytokine levels and ratios, coincided with the accumulation of neutrophils and activated macrophages, in addition to the clearance of the bacterial load and bacteriumlike structures that we have previously shown in the same groups of mice. This was followed by increased levels of anti-inflammatory cytokines and the resolution of inflammation and pathology in the lungs. This study demonstrates the dynamics of cytokine production and their correlation with tissue inflammation and the resolution of infection. This model is useful for further studies of the pathogenesis of C. jejuni infection and vaccine.

Quality Assurance of Item Writing: During the Introduction of Multiple Choice Questions in Medicine for High Stakes Examinations

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Med Teach 2008; 29:1-6

Background: One Norwegian medical school introduced A-type MCQs (best one of five) to replace more traditional assessment formats (e.g. essays) in an undergraduate medical curriculum. Quality assurance criteria were introduced to measure the success of the intervention.
Method: Data collection from the first four year-end examinations included item analysis, frequency of item writing flaws (IWF) and proportion of items testing at a higher cognitive level (K2). All examinations were reviewed before after delivery and no items were removed. Results: Overall pass rates were similar to previous cohorts examined with traditional assessment formats. Across 389 items, the proportion of items with >/=5% of candidates marking two or more functioning distracters was >/=47.5%. Removal of items with high p-values (>/=85%), this item distracter proportion became >75%. With each successive year in the curriculum the proportion of K2 items used rose steadily to almost 50%. 31/389 (7%) items had IWFs. 65% items had a discriminatory power, >/=0.15.
Conclusions: Five item quality criteria are recommended: (1) adherence to an in-house style, (2) item proportion testing at K2 level, (3) functioning distracter proportion, (4) overall discrimination ratio and (5) IWF frequency.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2009, 41 (1): 80 - 85

Family Medicine: Focus on **Dermatology**
Apr 10 - 20, 2009
Barcelona, *Spain*
Contact: Continuing Education, Inc.
Phone: 1-800-422-0711; Fax: 727-522-8304
E-Mail: sandra@continuingeducation.net

9th Annual **Neonatology** Meeting
Apr 14 - 16, 2009
Riyadh, *Saudi Arabia*
Contact: Abdellatif Rejjal
Phone: 00-966-1-442-7762; Fax: 00-966-1-442-7784
E-Mail: ebaylon@kfshrc.edu.sa

2009 Asian and Oceanian Congress of **Clinical Neurophysiology**
Apr 15- 18, 2009
Seoul, *Republic of Korea*
Contact: Meeting Organiser
Phone: 82-2-566-6067; Fax: 82-2-566-6087
E-Mail: seoul@aoccn2009.com

Update in **General Surgery**
Apr 16 - 18, 2009
Toronto, ON,*Canada*
Contact: Meeting Organiser
Phone: 416-978-2719; Fax: 416-946-7028
E-Mail: info-SUR0904@cmetoronto.ca

XII International Congress of IFPE **(International Federation of Psychiatric Epidemiology)**
Apr 16 - 19, 2009
Vienna, *Austria*
Contact: Austropa Interconvention
Phone: 43-158-800-510; Fax: 43-158-800-520
E-Mail: ifpe2009@interconvention.at
Joint Meeting, 3rd Congress Association of Southeast Asian **Pain Society** (ASEAPS) **and Neuropathic Pain Special Interest Group** (NeuPSIG)
Apr 17 - 20, 2009
Sanur Bali, *Indonesia*
Contact: Husni Tanra
Phone: 62-411-582-583; Fax: 62-411-590-290
E-Mail: joint_meeting@yahoo.co.id

39th Annual **Aesthetic Plastic Surgery** Symposium
Apr 17 - 18, 2009
Toronto, ON, *Canada*
Contact: University of Toronto CME Office
Phone: 416-978-2719 / 1-888-512-8173
E-Mail: ce.med@utoronto.ca

Cardiology Update
Apr 18- 25, 2009
Fort Lauderdale, FL, *United States*
Contact: Continuing Education, Inc.
Phone: 1-800-422-0711; Fax: 727-522-8304
E- Mail: sandra@continuingeducation.ne

17th Annual Meeting of the Internal Society for **Magnetic Resonance in Medicine**
Apr 18 - 24, 2009
Honolulu, HI, *United States*
Contact: ISMRM, 2030 Addison Street, 7th Floor, Berkeley, CA 94704 USA
Phone: 1 510-841-1899; Fax: 1 510-841-2340
E-Mail: info@ismrm.org

Short Course on **Abdominal Ultrasound** in Tropical Medicine and Infectious Diseases Apr 20 - 24, 2009
Pavia, *Italy*
Contact: Enrico Brunetti
Phone: 39-0-382-502-799
E- Mail: selim@unipv.it
Challenges in the Outcome of **Psychiatric Disorders**
Apr 21 - 23, 2009
Jeddah, *Saudi Arabia*
Contact: Dr Mohamed Khaled
Phone: 00-966-507-377-541; Fax: 00-96-626-835-874
E-Mail: moh.khaled.hamed@gmail.com

2nd World Congress of Total **Intravenous Anaesthesia** - TCI
Apr 21 - 25, 2009
Berlin, *Germany*
Contact: Liraz Bregman
Phone: 41-229-080-488; Fax: 41-227-322-850
E-Mail: tivatci@kenes.com

6th Vienna Interdisciplinary Symposium on **Aortic Repair**
Apr 22 - 24, 2009
Vienna, *Austria*
Contact: Kay Daniela Schulz
Phone: 43-18-674-944; Fax:43-18-674-944-9
E-Mail: office@ee-pco.com

Internal Medicine 2009
Apr 23 - 25, 2009
Philadelphia, PA, *United States*
Contact: Stephen Sye
Phone: 215-351-2563; Fax: 215-351-2537
E-Mail: ssye@acponline.org

6th Spring Symposium of the European Academy of **Dermatology and Venereology** Apr 23 - 26, 2009
Bucharest, *Romania*
Contact: EADV Office
Phone: 322-650-0090; Fax: 322-650-0098
E-Mail: office@eadv.org

Cardio Pulmonary for Primary Care Physicians
Apr 24 - 26, 2009
Key West, FL, *United States*
Contact: Linda Main
Phone: 303-798-9682
E-Mail: linda@mer.org

The Difficult Airway Course: **Anesthesia**
Apr 24 - 26, 2009
Las Vegas, NV, *United States*
Contact: Registration Center
Phone: 503-635-4761; Fax: 404-795-0711
E-Mail: registrations@theairwaysite.com

2009 Annual Meeting of the **American Urology Association**
Apr 25 - 30, 2009
Chicago, IL, *United States*
Contact: American Urology Association
Phone: 410-689-3700; Fax: 410-689-3800
E-Mail: registration@AUAnet.org

International College of **Neuropsychopharmacology 2009** Congress: Major Psychoses and Substance Abuse
Apr 25 - 27, 2009
Edinburgh, Scotland, *United Kingdom*
Contact: Meeting Organiser
Phone: 0-1-355-244-966; Fax: 0-1-355-249-959
E-Mail: cinp2009@glasconf.demon.co.uk

11th European Congress of **Endocrinology**
Apr 25 - 29, 2009
Istanbul, *Turkey*
Contact: European Federation of Endocrine Societies, Euro House, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, *UK*
Phone: 44-1-454-642-247; Fax: 44-1-454-642-222

XI International **Facial Nerve Symposium**
Apr 25 - 28, 2009
Rome, *Italy*
Contact: Bollani Gaia
Phone: 00-39-0-234-934-404
Fax: 00-39-0-234-934-397
E-Mail: bollani@mcaevents.org

Dubai DERMA 2009
Apr 26 - 28, 2009
Dubai, *United Arab Emirates*
Contact: Suhas Ganatra
Phone: 97-143-624-717; Fax: 97-143-624-718
E-Mail: suhas.ganatra@index.ae

BSR (**British Society of Rheumatology**) BHPR Annual Conference
Apr 28 - May 01, 2009
Glasgow, Scotland, *United Kingdom*
Contact: The British Society for Rheumatology, Bride House, 18-20 Bride Lane, London EC4Y 8EE
Phone: 44-0-2-078-420-900; Fax: 44-0-2-078-420-914
E-Mail: hgardner@rheumatology.org.uk

25th Iranian Congress of **Radiology**
Apr28 - May 01, 2009
Tehran, *Islamic Republic of Iran*
Contact: Iranian Society of Radiology
Phone: 982-144-462-078; Fax: 982-144-411-224
E-Mail: info@icr2009.ir

8th Congress of Turkish German **Gynecology** Association
Apr 29 - May 03, 2009
Antalya, *Turkey*
Contact: Tuba Celiker
Phone: 902-122-823-373
E-Mail: tuba.celiker@serenas.com.tr

11th Annual **Echocardiography Conference**: State-of-Art 2009
Apr 29 - May 01, 2009
New York, NY, *United States*
Contact: Rochelle Thomas
Phone: 212-305-3334; Fax: 212-781-6047
E-Mail: cme@columbia.edu

The 7th National and 2nd International congress of the Jordan Society of **Anaesthesia, Intensive care and Pain Management**
Apr 29 - May 01, 2009
Amman, *Jordan*
Contact: Susan Abu Zead
Phone: 00-962-795-316-964; Fax: 00-96-265-510-090
E-Mail: araborganizersjo@gmail.com

2009 Annual Meeting of the American Society for **Aesthetic Plastic Surgery** (ASAPS)
May 02 - 09, 2009
Las Vegas, NV, *United States*
Contact: American Society for Aesthetic Plastic Surgery (ASAPS)
Phone: 800-364-2147; Fax: 562-799-1098
E-Mail: asaps@surgery.org

III. International Congress of **Molecular Medicine**
May 05 - 08, 2009
Istanbul, *Turkey*
Contact: Prof. Dr. Turgay İsbir
Phone: 902-126-351-959; Fax: 902-126-351-959
E-Mail: tisbir@superonline.com

2009 Annual Meeting of the **American Society of Hypertension**
May 05 - 08, 2009
San Francisco, CA, *United States*
Contact: American Society of Hypertension, 148 Madison Avenue, Fifth Floor, New York, NY 10016
Phone: 212-696-9099; Fax: 212-696-0711
E-Mail: ash@ash-us.org

14th International Conference of the APPAC **"Neuropsychiatric, Psychological and Social Developments** in a Globalised World"
May 05 - 08, 2009
Athens, *Greece*
Contact: Mrs Demy Kotta
Phone: 302-106-842-663; Fax: 302-106-842-079
E-Mail: appachellas@yahoo.gr

The 17th Conference of the Union of Arab **Pediatricians**
May 05 - 08, 2009
Amman, *Jordan*
Contact: Miss Susan Abu Zead
Phone: 00-96-265-539-771 / 00 962-795-316-964
Fax: 00-96-265-510-090
E-Mail: araborganizers.com.jo

16th International **Surgical Pathology** Symposium
May 05 - 09, 2009
Berlin, *Germany*
Contact: Julie McAdams
Phone: 507-284-8599; Fax: 507-284-8016
E-Mail: mcadams.julie@mayo.edu

70th Annual Meeting of the Society for **Investigative Dermatology**
May 06 - 09, 2009
Montreal, QC, *Canada*
Contact: Viveca Kimble, Director of Meetings and Educational Programs, SID
Phone: 216-579-9344; Fax: 216-579-9333
E-Mail: kimble@sidnet.org

American **Society of Hypertension** 24th Annual Scientific Meeting and Exposition
May 06 - 09, 2009
San Francisco, CA,*United States*
Contact: American Society of Hypertension, 148 Madison Avenue, Fifth Floor, New York, NY 10016
Phone: 212-696-9099; Fax: 212-696-0711
E-Mail: ash@ash-us.org

International Mastercourse on **Endoscopic Sinus Surgery**
May 06 - 09, 2009
Brussels, *Belgium*
Contact: Mrs. K. Nuyts
Phone: 32-2-477-68-89; Fax: 32-2-477-68-80
E-Mail: karine.nuyts@uzbrussel.be

Urgent Care, **Sports Medicine** and Primary Care: An Evidence-Based Trifecta
May 11 - 15, 2009
Sarasota, FL, *United States*
Contact: Christy or Cristina
Phone: 1-866-267-4263 or 1-941-388-1766
Fax: 1-941-365-7073
E-Mail: mail@ams4cme.com

Cardiology & Vascular Medicine, Update and Perspective
May 11 - 13, 2009
Rotterdam, *Netherlands*
Contact: Meeting Organiser
E-Mail: m.bot@erasmusmc.nl

Infectious Disease Update
May 12 - 24, 2009
Southampton, England, *United Kingdom*
Contact: Eileen Tener, ACC
Phone: 813-333-6878
E-Mail: ETener@CruisersParadise.com

7th Croatian Congress on **Atherosclerosis** with International Participation
May 13 - 16, 2009
Island-Mali Losinj, *Croatia*,
Contact: Mr. Branimir Pavlin
Phone: 38-514-847-604; Fax: 38-514-847-606
E- Mail: top-tours@zg.t-com.hr

1st International Meeting on **Aesthetic and Reconstructive Facial Surgery**
May 13 - 17, 2009
Mykonos, *Greece*
Contact: Congress Organizers and Secretariat, Aktina, City Congress SA, 26 Filellinon Street, GR-10558, Athens, *Greece*
Phone: 302-103-232-433; Fax: 302-103-232-338
E-Mail: info@imafr2009.org

The Sixth pan Arab Congress of **Otorhinolaryngology Head & Neck Surgery** (ArabFOS)
May 13 - 15, 2009
Amman, *Jordan*
Contact: Miss Susan Abu Zead
Phone: 00-96-265-539-771 / 00-962-795-316-964
Fax: 00-96-265-510-090
E-Mail: araborganizers@index.com.jo

The 2nd Biannual International **Heart Failure Summit**
May 13 - 15, 2009
Tehran, *Islamic Republic of Iran*
Contact: Behnood Bikdeli, MD
Phone: 98-2-120-105-050 ext 511; Fax: 98-2-122-083-106
E-Mail: info@ihfsummit.com

Cosmetic Clinical Trials
May 14 - 17, 2009
Boca Raton, FL, *United States*
Contact: Meeting Organiser
Phone: 781-793-0088
E-Mail: info@cosmeticbootcamp.com

California Society of Anesthesiologists Annual Meeting and **Clinical Anesthesia** Update
May 15 - 17, 2009
Monterey, CA, *United States*
Contact: Terrie Rowe Phone: 650-345-3020
Fax:650-345-3269
E-Mail: trowe@csahq.org

10th Biennial Congress, Asian and Oceania Society of Regional **Anesthesia and Pain Medicine** - AOSRA-PM
May 15 - Oct 18, 2009
Jinan, *China*
Contact: Danny Yan
Phone: 86-10-62-174-061; Fax: 86-10-62-180-142
E-Mail: info@aosra2009.com

International Conference on **Alzheimer's Disease and Related Disorders in the Middle East**
May 15 - 17, 2009
Limassol, *Cyprus*
Contact: World Events Forum
Phone: 1-773-784-8134 / 1-773-782-6747
Fax: 1-208-575-5453
E-Mail:meetings@worldeventsforum.com

ISPOR 14th Annual International Meeting
May 16 - 20, 2009
Orlando, FL, *United States*
Contact: Sue Capon, Director of Meetings
Phone: 609-219-0773; Fax: 609-219-0774
E-Mail: info@ispor.org

12th Multidisciplinary International Conference of **Neuroscience and Biological Psychiatry "Stress and Behavior"** - 2nd International Stress and Behavior Society (ISBS) Congress
May 16 - 20, 2009
St. Petersburg, *Russian Federation*
Contact: Conference secretariat
Phone: 1-240-899-9571
E-Mail: isbs-2008@inbox.ru

162nd American **Psychiatric** Association Annual Meeting
May 16 - 21, 2009
San Francisco, CA, *United States*
Contact: American Psychiatric Association
Phone: 703-907-7300
E-Mail: apa@psych.org

10th Iranian Congress of T**oxicology and Poisoning**
May 18 - 20, 2009
Tehran, *Islamic Republic of Iran*
Contact: Shahin Shadnia
Phone: 989-121-947-601; Fax: 982-155-424-041
E-Mail: shadniatrc@sbmu.ac.ir

Trauma & Acute Care Management
May 18 - 21, 2009
Riyadh, *Saudi Arabia*
Contact: Dr Heythem Al-Zamel, MD (Trauma Surgery / Surgical Critical Care) & (Director of General Surgery Residency Training Program)
Phone: 00-96-61-252-0088 / ext 14-124 / 14-149;
Fax: 00-96-612-520-051
E-Mail: halzamel83@hotmail.com

SICOBAIR (Students' International Conference on **Biomedical and Interdisciplinary Research)** 2009
May 19 - 22, 2009
Tehran, *Tehran, Islamic Republic of Iran*
Contact: S.Mohamad Freshtenejad
Phone: 982-182-943-069; Fax: 982-182-943-069
E-Mail: Info@sicobair.com

International Congress on **Diabetes and its Complications**
May 19 - 21, 2009
Yazd, *Islamic Republic of Iran*
Contact: Congress Secretariat
Phone: 983-515-234-888 Fax: 983-515-258-354
E-Mail: icdc@ssu.ac.ir

2nd International Congress on **Leukemia-Lymphoma-Myeloma**
May 20 - 24, 2009
Istanbul, *Turkey*
Contact: Ipek Durusu
Phone: 903-124-909-897; Fax: 903-124-909-868
E-Mail: thdofis@thd.org.tr

6th **Metabolic Syndrome**, Type II Diabetes and Atherosclerosis (MSDA)
May 20- 24, 2009
Berlin, *Germany*
Contact: Lily-Claude LEVASSEUR
Phone: 33-139-042-424; Fax: 33-139-042-477
E-Mail: msda2009@agence-plb.com

Obstetric Anaesthesia 2009
May 20 - 22, 2009
Jersey, England, *United Kingdom*
Contact: Meeting Secretariat
Phone: 44-2-087-411-311; Fax: 44-2-087-410-611
E- Mail: www.oaameetings.info+

1st International Congress of **Airway Management/ and Anesthesia** in Head & Neck Surgery
May 20 - 22, 2009
Tehran, *Islamic Republic Iran*
Contact: Lili Poorazari
Phone: 982-166-581-537; Fax: 982-166-581-576
E-Mail: khanzh51@yahoo.com

Dermatologic Surgery: Focus on **Skin Cancer**
May 21 - 25, 2009
Austin, TX, *United States*
Contact: Meeting Organiser
Phone: 800-616-2767; Fax: 714-379-6272
E-Mail: execdir@mohssurgery.org

4th Romanian International Congress on **Anti-Aging Medicine**, 2nd International Congress on Lasers in Medicine and Surgery
May 22 - 24, 2009
Bucharest, *Romania*
Contact: Dr. Catalin Enachescu
Phone: 40-723-034-834; Fax: 00-40-214-130-212
E-Mail: office@amaa.ro

11th Conference of the **International Society of Travel Medicine** (CISTM11)
May 24 - 28, 2009
Budapest, *Hungary*
Contact: Heike Esmann
Phone: 00-49-893-071-011; Fax: 00-49-893-071-021
E-Mail: heike.esmann@cocs.de

Hepatocellular Carcinoma: Updates in Diagnosis and Therapy
May 25 - 27, 2009
Salerno, *Italy*
Contact: Mrs.SUITA CARRANO
Phone: 39-0-89-857-922; Fax: 39-0-89-858-570
E-Mail: info@weddingravello.it

XVIII European **Stroke Conference**
May 26 - 29, 2009
Stockholm, *Sweden*
Contact: ESC 2009, /o AKM Congress Service, Freie Strasse 90 PO Box 4002 Basel, Switzerland
Phone: -616-867-711; Fax: 41-616-867-788
E-Mail: esc@akm.ch

8th Congress of European Federation of **Internal Medicine**
May 27 - 30, 2009
Istanbul, *Turkey*
Contact: Hakan Biyikli
Tel: 903-124-405-011; Fax: 903-124-414-563
E-Mail: hakan.biyikli@serenas.com.tr

HIV Update: Contemporary Issues in Management
May 28 - 30, 2009
Boston, MA, *United States*
Contact: HMS-DCE
Phone: 617-384-8600; Fax: 617-384-8686
E-Mail: hms-cme@hms.harvard.edu

12th Annual Current Issues in **Anatomic Pathology**
May 28 - 30, 2009
San Francisco, CA, *United States*
Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 9411
Phone: 415-476-4251 / 415-476-5808
Fax: 415-476-0318 / 415-502-
E-Mail: info@ocme.ucsf.edu

4th European **Cardiology Conference for General Practitioners**
May 29 - 31, 2009
Istanbul, *Turkey*
Contact: Yesim Tanriverdi
Phone: 00-902-123-476-500; Fax: 00-902-123-476-505
E-Mail: sls@eccgp.org

Cardiology Update
May 31 - Jun 12, 2009
Rotterdam, *Netherlands*
Contact: Continuing Education, Inc.
Phone: -800-422-0711; Fax: -522-8304
E-Mail: sandra@continuingeducation.net

5th World Congress of **Neuroendoscopy**
May 31 - Jun 06, 2009
Athens, *Greece*
Contact: Mrs. Penelope Mitroyianni
Phone: 302-107-257-693; Fax: 302-107-257-532
E-Mail: info@erasmus.gr

FESSH 2009 (XIVth) (International Congress of Federation of the European Societies for **Surgery of the Hand**)
Jun 03 - 06, 2009
Poznan, *Poland*
Contact: Pawel Surdziel
Phone: 48-618-310-346; Fax: 48-618-310-163
E-Mail: pawelsurdziel@tlen.pl

5th International Congress **on Cardiovascular Diseases**
Jun 04 - 07, 2009
Kosice, *Slovakia*
Contact: Meeting Organiser
Phone: 421-55-640-3862; Fax: 421-55-640-3862
E-Mail: admin@icckosice2009.com

Annual Scientific Meeting of Australian **Gynecological Endoscopy** Society
Jun 04 - 06, 2009
Melbourne, VIC, *Australia*
Contact: AGES Conferences and Secretariat, Ms Michele Bender, Conference Connection, 282 Edinburgh Road, CASTLECRAG NSW 2068
Phone: 61-0-299-672-928; Fax: 61-0-299-672-627
E-Mail: secretariat@ages.com.au

The Difficult Airway Course: **Anesthesia**
Jun 05 - 07, 2009
Boston, MA, *United States*
Contact: Registration Center Phone: 503-635-4761
Fax: 404-795-0711
E-Mail: registrations@theairwaysite.co

Endocrinology Update Cruise
Jun 06 - 14, 2009
Rome, *Italy*
Contact: Dr. Martin Gerretsen
Phone: 1-888-647-7327 Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

XXVIII Congress of the European Academy of **Allergology** and **Clinical Immunology**
Jun 06 - 10, 2009
Warsaw, *Poland*
Contact: Congress Secretariat / Exhibition Organiser, Congrex Sweden AB, Att: EAACI 2009, P.O. Box 5619, SE-114 86 Stockholm, Sweden
Phone: 46-84-596-600; Fax: 46-86-619-125
E-Mail: eaaci2009@congrex.com

27th Annual Meeting of the European Society for **Pediatric Infectious Diseases** ESPID 2009
Jun 09 - 13, 2009
Brussels, *Belgium*
Contact: Liraz Bregman
Phone: 41-229-080-488; Fax: 41-227-322-850
E-Mail: espid@kenes.com

Focal Therapy and Imaging in **Prostate and Kidney Cancer**
Jun 10 - 13, 2009
Amsterdam, *Netherland*s
Contact: Mr Nikolas Dargonakis
Phone: 302-107-257-693; Fax: 302-107-257-532
E- Mail: info@erasmus.gr

The 12th World Congress of **Refractive Surgery**
Jun11- 13, 2009
Nice, *France*
Contact: Geraldine Schmück
Phone: 04-92-073-576; Fax: 04-92-073-586
E-Mail: geraldine@impact-events.net

Surgical **Pathology Update**
Jun 11- 14, 2009
Leipzig, *Germany*
Contact: Mareike Schandor
Phone: 0-364-135-332-701; Fax: 0-36-413-533-221
E-Mail: mareike.schandor@conventus.de

5th World Congress of the International Society of **Physical and Rehabilitation Medicine**
Jun 13 - 17, 2009
Istanbul, *Turkey*
Contact: Ms Sezen Elagoz
Phone: 902-123-438-003; Fax: 902-123-438-023
E-Mail: selagoz@teamcon.com.tr

Society of **Nuclear Medicine** 56th Annual Meeting
Jun 13 - 17, 2009
Toronto, ON, *Canada*
Contact: Kristie Morris, 1850 Samuel Morse Drive, Reston, VA 20190
Phone: 703-708-9000 ext 1229; Fax: 703-709-9274
E-Mail: kmorris@snm.org

20th Congress of the European Society of **Paediatric and Neonatal Intensive Care** ESPNIC
Jun 17 - 20, 2009
Verona, *Italy*
Contact: Liraz Bregman
Phone: 41-229-080-488; Fax: 41-227-322-850
E-Mail: espnic@kenes.com

WHO-Facts Sheet

1. Global Measles Deaths Drop By 74%
2. Preventable Injuries Kill 2000 Children Every Day
3. Checklist Helps Reduce Surgical Complications, Deaths
4. Tolerable Levels for Melamine Established at a WHO Meeting
5. Essential Medicines Out of Reach for Most People

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2009, 41 (1) 86 - 90

1. GLOBAL MEASLES DEATHS DROP BY 74%

The Eastern Mediterranean region achieves measles goal three years early

Measles deaths worldwide fell by 74% between 2000 and 2007, from an estimated 750,000 to 197,000. In addition, the Eastern Mediterranean region which includes countries such as Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates and Yemen has cut measles deaths by a remarkable 90% — from an estimated 96,000 to 10,000 — during the same period, thus achieving the United Nations goal to reduce measles deaths by 90% by 2010, three years early.

The progress was announced by the founding partners of the Measles Initiative: the American Red Cross, the United States Centers for Disease Control and Prevention (CDC), the United Nations Foundation (UN Foundation), UNICEF and the World Health Organization (WHO). "This achievement is a tribute to the hard work and commitment of countries in the Eastern Mediterranean region to combat measles," said Dr Margaret Chan, WHO Director-General. "With only two years until the 2010 target date, I urge all countries affected by measles to intensify their efforts to immunize all children against the disease."

The significant decline in measles deaths in the Eastern Mediterranean region was the result of intensified vaccination campaigns including several countries with hard-to-reach areas. In 2007, more than twice the number of children were immunized in the region through such campaigns as compared to 2006.

Thousands of health workers and volunteers from the Red Cross and Red Crescent family gave their time to literally go door-to-door informing, educating and motivating mothers and caregivers about the critical need to vaccinate their children

The African region was the largest contributor to the global decline in measles deaths, accounting for about 63% of the reduction in deaths worldwide over the eight-year period. In 2007, measles outbreaks occurred in a number of African countries due to gaps in immunization coverage, reinforcing the need to continue immunization support.

The progress in South-East Asia has been limited — with just a 42% decline in measles deaths. This is due to the delayed implementation of large-scale vaccination campaigns in India, which currently accounts for two thirds of global measles deaths. Political commitment in India is essential if the 2010 global goal is to be achieved.

"The progress that has been made shows what can be achieved through measles vaccination campaigns, but much more needs to be done," said Ann M. Veneman, Executive Director of UNICEF. "It is a tragedy that measles still kills more than 500 children a day when there is a safe, effective and inexpensive vaccine to prevent the disease."

The world's success in reaching the 2010 measles goal depends on ensuring that all children receive two doses of measles vaccine including one dose by their first birthday, strengthening disease surveillance systems, and providing effective treatment for measles.

For more information contact: Hayatee Hasan, WHO, Geneva, +41 79 351 6330. E-mail: hasanh@who.int Or, Christian Moen, UNICEF, New York, +1 212 326 7516. E-mail: cmoen@unicef.org

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Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/

2. PREVENTABLE INJURIES KILL 2000 CHILDREN EVERY DAY

More than 2000 children die every day as a result of unintentional or accidental injuries. Every year tens of millions more worldwide are taken to hospitals with injuries that often leave them with lifelong disabilities, according to a new report by WHO and UNICEF.

The World report on child injury prevention provides the first comprehensive global assessment of unintentional childhood injuries and prescribes measures to prevent them. It concludes that if proven prevention measures were adopted everywhere at least 1000 children's lives could be saved every day.

"Child injuries are an important public health and development issue. In addition to the 830,000 deaths every year, millions of children suffer non-fatal injuries that often require long-term hospitalization and rehabilitation," said WHO Director-General Dr Margaret Chan. "The costs of such treatment can throw an entire family into poverty. Children in poorer families and communities are at increased risk of injury because they are less likely to benefit from prevention programmes and high quality health services."

This report, result of a collaboration of more than 180 experts from all regions of the world, shows that unintentional injuries are the leading cause of childhood death after the age of nine years and that 95% of these child injuries occur in developing countries.

The report finds that the highest rate overall for unintentional injury deaths is 10 times higher in Africa than in high-income countries of Europe and the Western Pacific such as Australia, the Netherlands, New Zealand, Sweden and the United Kingdom.

However, the report finds that although many high-income countries have been able to reduce their child injury deaths by up to 50% over the past 30 years, the issue remains a problem for them, with unintentional injuries accounting for 40% of all child deaths in such countries.

The top five causes of injury deaths are:

- **Road crashes:** They kill 260,000 children a year and injure about 10 million. They are the leading cause of death among 10-19 year olds and a leading cause of child disability.
- **Drowning:** It kills more than 175,000 children a year. Every year, up to 3 million children survive a drowning incident. Due to brain damage in some survivors, non-fatal drowning has the highest average lifetime health and economic impact of any injury type.
- Burns: Fire-related burns kill nearly 96,000 children a year and the death rate is 11 times higher in low- and middle-income countries than in high-income countries.
- Falls: Nearly 47,000 children fall to their deaths every year, but hundreds of thousands more sustain less serious injuries from a fall.
- Poisoning: More than 45,000 children die each year from unintended poisoning.

Dr Etienne Krug, Director of WHO's Department of Violence and Injury Prevention and Disability said, "When a child is left disfigured by a burn, paralysed by a fall, brain damaged by a near drowning or emotionally traumatized by any such serious incident, the effects can reverberate through the child's life. Each such tragedy is unnecessary. We have enough evidence about what works. A known set of prevention programs should be implemented in all countries."

The report outlines the impact that proven prevention measures can have. These measures include:

- laws on child-appropriate seatbelts and helmets
- hot tap water temperature regulations
- child-resistant closures on medicine bottles, lighters and household product containers; separate traffic lanes for motorcycles or bicycles
- draining unnecessary water from baths and buckets
- redesigning nursery furniture, toys and playground equipment
- strengthening emergency medical care and rehabilitation services.

It also identifies approaches that either should be avoided or are not backed by sufficient evidence to recommend them. For example, it concludes

- that blister packaging for tablets may not be child resistant
- that airbags in the front seat of a car could be harmful to children under 13 years
- that butter, sugar, oil and other traditional remedies should not be used on burn
- that public education campaigns on their own don't reduce rates of drowning.

For more information contact: Laura Sminkey WHO, Geneva Telephone: +41 22 791 4547 Mobile: +41 79 249 3520 E-mail: sminkeyl@who.int

3. CHECKLIST HELPS REDUCE SURGICAL COMPLICATIONS, DEATHS

Surgical adverse events reduced by one third in trials in eight countries

Hospitals in eight cities around the globe have successfully demonstrated that the use of a simple surgical checklist, developed by WHO, during major operations can lower the incidence of surgery-related deaths and complications by one third.

The studies were undertaken in hospitals in each of the six WHO regions. Analysis shows that the rate of major complications following surgery fell from 11% in the baseline period to 7% after introduction of the checklist, a reduction of one third. Inpatient deaths following major operations fell by more than 40% (from 1.5% to 0.8%).

"The concept of using a brief but comprehensive checklist is surprisingly new to us in surgery. Not everyone on the operating teams were happy to try it. But the results were unprecedented. And the teams became strong supporters," said Dr Atul Gawande, main author of the study and team leader for the development of the WHO surgical safety checklist.

Data was collected from 7688 patients – 3733 before and 3955 after the checklist was introduced. The study was carried out in hospitals in both high and lower income settings—in Ifakara (Tanzania), Manila (Philippines), New Delhi (India), Amman (Jordan), Seattle (United States of America), Toronto (Canada), London (United Kingdom) and Auckland (New Zealand). The reductions in complications proved to be of equal magnitude in high and lower income sites in the study.

Implications for other medical fields

The safe surgery checklist, which was launched by WHO as a recommended guideline for safe practice last year, has since gained global recognition by operating theatre staff, including surgeons and anaesthetists.

It requires only a few minutes to complete at three critical points during operative care – before anaesthesia is administered, before skin incision and before the patient leaves the operating room. It is intended to ensure the safe delivery of anaesthesia, appropriate prophylaxis against infection, effective teamwork by the operating room staff and other essential practices in perioperative care.

"The immediate response to the checklist has been remarkable, and the studies undertaken in the pilot hospitals are significant. They will make a major contribution towards our goal of having 2500 hospitals around the world using the safe surgery checklist by the end of this year," said Sir Liam Donaldson, Chair of the WHO World Alliance for Patient Safety and Chief Medical Officer for England.

The results of the study are published on the web site of the New England Journal of Medicine. The material will appear in the the journal's printed issue on 29 January 2009.

Ten facts on safe surgery

Surgical care and its safe delivery affect the lives of millions of people. About 234 million major operations are performed worldwide every year.

The change in disease patterns worldwide is increasing the need for surgical services considerably. Epidemics and infections are giving way as leading causes of death to ischemic heart diseases, cancers, and trauma - which need surgical interventions.

Ensuring better access to surgical care and its safe delivery is crucial for its effectiveness. The available evidence suggests that as many as half of the complications and deaths arising from surgery could be avoided, if the following basic standards of care were followed.

1. Globally, about 234 million major surgical operations are conducted a year. This equates to about one operation for every 25 persons. Every year 63 million people undergo surgery to treat traumatic injuries, another 10 million for pregnancy-related complications, and 31 million more for treating cancers.

2. Studies suggest that complications following surgery result in disability or prolonged stay in 3-25% of hospitalized patients, depending upon complexity of surgery and hospital setting. These rates would mean that at least 7 million patients annually may have post-operative complications.

3. Rates of death following major surgery are reported to be between 0.4% and 10%, depending on the setting. Estimating the impact of these rates, at least 1 million patients would die every year during or after an operation.

4. Information regarding surgical care has been standardized or systematically collected only in a few research studies globally. As a result, most surgical interventions worldwide are not recorded. It is essential to measure surgical care on a global basis for promoting surgical safety, preventing disease and improving care.

5. In the developed world, nearly half of all harmful events (such as miscommunication, wrong medication, and technical errors) affecting patients in hospitals are related to surgical care and services. The evidence suggests that at least half of these events are preventable if standards of care are adhered to and safety tools, such as checklists, are used.

6. Surgical care has been shown to be cost effective in developing settings. Ensuring safe delivery of care will only improve its efficacy.

7. Dramatic improvements have been made in the administration of anaesthesia over the past 30 years, but not in all parts of the world. In some regions, anaesthesia-related mortality is as high as 1 in 150 patients receiving general anaesthesia.

8. Safety measures are inconsistently applied in surgery, even in sophisticated settings. Simple steps can reduce complication rates. For example, improving the timing and selection of antibiotics prior to skin incision can reduce the rate of surgical site infections by up to 50%.

9. WHO has developed guidelines for safe surgery and a checklist of surgical safety standards applicable in all countries and health settings. Preliminary results of an evaluation in eight pilot sites worldwide show that the checklist has nearly doubled the likelihood that patients will receive treatment as per standards of surgical care – such as an antibiotic before incision and confirmation that the surgery team has the correct patient for the correct operation.

10. The Safe Surgery Saves Lives initiative is collaborating with more than 200 ministries of health, national and international medical societies and professional organizations to reduce deaths and complications in surgical care.

For more information contact: Dan Epstein, WHO News Team Leader, email: epsteinda@who.int, Tel: +41 22 791 1492 or mobile: +41 79 475 5534. Vivienne Allan, Patient Safety Programme, WHO, Geneva. Mobile: +41 79 615 5065. E-mail: allanvi@who.int

4. TOLERABLE LEVELS FOR MELAMINE ESTABLISHED AT A WHO MEETING

International experts have established a tolerable daily intake (TDI) for melamine, the implicated chemical found recently in contaminated milk products. The TDI is the outcome of a meeting organized by the World Health Organization (WHO) held this week in Ottawa, Canada to address the issue. The TDI is lower than previous TDIs suggested for melamine by some national food safety authorities.

The international experts gathered by WHO have not set a "safe" level of melamine but they have established a "tolerable" level. Melamine is a contaminant that should not be in food, however, sometimes it is unavoidable. TDI represents the tolerable amount of unavoidable contaminant in food that a person can ingest on a daily basis without appreciable health risk. The TDI is meant to help national authorities set safe limits in food for withdrawal purposes should melamine be detected as a result of intentional adulteration.

The TDI for melamine has been established at 0.2 mg/kg body weight. Based on this, it leads a 50 kg person to a tolerable amount of 10 mg melamine per day.

The TDI applies to melamine alone. The TDI for cyanuric acid alone remains at 1.5 mg/kg body weight. Co-occurrence of melamine with cyanuric acid seems to be more toxic, however data are not adequate to allow the calculation of a health-based guidance value for this co-exposure.

For more information contact: Sari Setiogi, Media Relations Officer, World Health Organization (WHO) Headquarters Geneva, Tel: +41 22 791 3576; Mobile: + 41 79 701 94 67;e--mail SetiogiS@who.int

5. ESSENTIAL MEDICINES OUT OF REACH FOR MOST PEOPLE

Lack of medicines in public sector forcing patients to pay high prices, finds new study

An alarming lack of availability of essential medicines in the public sector drives patients to pay higher prices in the private sector or go without, according to a WHO study. The results confirm that governments must do more to improve access to essential medicines as part of their efforts to make national health systems more efficient and equitable.

The study analysed data from surveys in 36 countries from all WHO geographical regions and World Bank income groups. Results show an average public-sector availability of only 38% across surveys. This forces patients to buy medicines from the private sector where treatments are more expensive and frequently unaffordable. In Africa, for example, the lowest-paid government worker needs to spend two days' salary each month to purchase diabetes treatment using the lowest-priced generic medicine. When the originator brand is used, costs escalate to over eight days' wages.

"You should not have to choose between buying medication for an ailing parent or buying food for your children," said Carissa Etienne, WHO Assistant Director-General of Health Systems and Services. "It is not fair or necessary. That is why we are calling again for comprehensive primary health care, so that health systems in every country put the real health needs of people and communities first, and families are not impoverished or bankrupted because of health care payments."

On the pricing side, the study revealed that "cuts" taken by wholesalers, distributors and retailers plus government taxes and duties are driving prices beyond affordability in many countries. In some countries, add-on costs can double the public-sector price of medicine, while in the private sector, wholesale mark-ups ranged from 2% to 380%, and retail mark-ups ranged from 10% to 552%.

The study further asserts that these actions should all be part of national medicine policies that are measured and evaluated against predetermined benchmarks at least every two years, with routine monitoring and reporting more frequently.

The results cover 15 medicines included in at least 80% of surveys, as well as four specific medicines used to treat asthma, diabetes, hypertension and acute infections. The figures are adjusted to account for differences in buying power of local currencies and then compared to international reference prices, allowing for cross-country comparison.

The work is part of an ongoing joint effort between WHO and Health Action International (HAI) to highlight and improve availability and affordability of essential medicines, especially in low- and middle-income countries.

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