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Congratulations and best wishes to all our contributors and collaborators.

Professor Adel Kahader Ayed
Editor
Deschooling Doctors and Patients

Belle M Hegde
The Journal of the Science of Healing Outcomes, Maryland, USA and Mangalore, India*
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Thanks to Ivan Illich for this beautiful word, deschooling which he used successfully in his book Deschooling Society in the 1930s[1]. “Science is making models, mostly mathematical constructs, which, with verbal explanations, are supposed to work,” wrote John von Neumann, an American scientist of Hungarian origin[2]. I couldn’t agree more. Medical science, basically a statistical science, follows the biological model of linear mathematical construct to understand a very complex, non-linear, chaotic model in biology, the human body. The latter is a dynamic model that runs continuously on food and oxygen and is powered by the electromagnetic energy from the sun[3] (Schumann rings of energy around the globe). Human physiology can never follow the linear laws of deterministic predictability of Isaac Newton[4]. Consequently, our present scientific base of medicine does not qualify to be classed as pure, hard science!

According to the new science of holism, otherwise called the science of chaos, even a very small change in the initial state of the organism could have catastrophic end results[4]. Peter Petros, an Australian gynaecologist, in his paper, non-linearity in clinical medicine, brings out clearly the fallacy in our present thinking which this author had been expounding in the last four decades in many of his publications[5]. It is time to take this message to the future doctors, the medical students, who can be converted as the present lot of teachers and practitioners are already converted to the linear model on which depends our bench mark scientific base of Randomized Controlled Trials (RCTs), meta-analysis, cross-sectional studies etc. All these have, of course, been shown to be not only useless but, could even be dangerous[6].

How else will one be able to reconcile to the fact that the medical profession, according to a few recent audits in the west, has not acquitted itself honorably in the field of healing outcomes in the sick population? If one gets into the largest medical business of routine screening of the apparently healthy population, our present model fails miserably[7]. Doctors have been predicting the unpredictable future of mankind all along[8]. Mary Tinnetti, from Yale, in her landmark paper on ‘The end of the disease era’ put it very succinctly thus: “The time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and non-biological factors, the ageing population, and the inter-individual variability in health priorities render medical care that is centered on the diagnosis and treatment of individual diseases at best out-of-date and at worst harmful. A primary focus on disease may inadvertently lead to under treatment, overtreatment, or mistreatment”[8]. Based on studies of medical literature as also the results of their own studies, Dunn et al showed the picture in greater detail in their paper on Death by doctors[9]. One example will suffice. Statins are now being marketed for anything under the sun although the main thrust is in vascular disease prevention. The truth about statins, when looked at more carefully, is anything but satisfactory.

Medicine had been practiced on the bed side, with emphasis on the art of medicine, from time immemorial up until the birth of the first clinic: then came the hospital. It is only in the last 50 odd years that medicine started riding piggyback on technology which has now resulted in ‘medicalizing’ the whole population. Doctors have succeeded in schooling the population to believe that health depends on medical intervention alone; while the truth is that the health of the society does not depend on doctors and hospitals. In fact, recent audits have shown, in a fourteen
industrialized countries study, that those countries with a higher doctor-patient ratio and bigger bed strength had worse health status of the population and shorter life expectancy! While trillions of dollars had been spent in the last quarter of a century in the west for medical intervention only 3% of the life expectancy increase has been attributed to medical interventions including vaccinations. Rest of the improvement came from nutrition, sanitation, education, better mode of living and affluence[10].

Time honored doctor-patient relationship, on which depended relief from illnesses in the past, has all but vanished what with doctors practicing medicine based on an array of scopes, shadows and laboratory reports rather than on the suffering human being’s bedside. This scenario has brought American medicine to its nadir. The recent movie SICKO by the celebrated US film maker, Michael Moore, and an editorial in a recent issue of the Texas Heart Institute Journal entitled Hyposkillia, document all that there is for the common man to know about the sad state of the medical world in that country[11].

A recent study combined data from RCT’s of statins to look at over 70,000 patients without coronary heart disease (CHD), but with risk factors. They report that statin use led to a 12% reduction in death, a 30% reduction in heart attacks, a 20% reduction in stroke, and no increased risk of cancer. The effects were regardless of age, sex or diabetes. Can we now say that all patients with risk factors for CHD should get statins? The answer is unfortunately no because we are not told properly about risks, safety and cost-effectiveness. Although the death rate dropped by 12% (relative risk reduction or RRR), it actually only fell from 5.7% to 5.1% with statin therapy (a 0.6% absolute risk reduction or ARR). Bottom line - you need to treat 170 people with statins for four years to prevent one death. For heart attacks, there is a 1.2% ARR, and this means that we would have to treat 80 people with statins for four years to prevent one heart attack. For strokes, there was a 0.4% ARR, and 240 people have to be treated to prevent one stroke. These numbers look less impressive than the relative risk reductions and tell us more about how costly it would be to treat everybody with risk factors (but no CHD) in the population,” wrote Dr. Biswas[12].

Time has come for doctors to analyse the entire medical “scientific” clap trap about drugs and interventional devices before using them on poor patients. The real audits do not show any of them in good light. Douglas C Wallace, writing in the journal Genetics, came to the conclusion that all modern western pharmacological drugs damage the hardware inside every human cell; the latter runs the human body holistically. He also showed, using a new research tool MITCHIP, that most Asian herbal drugs which had thousands of years of observational research base in assessing the true healing outcomes, are better suited as they only help the human cell to perform its function better[13]. Healing outcomes should be the future research modality and not the RCTs that have no hard scientific base. No two individuals are alike. Even minor changes in the initial state might end up in catastrophic long term outcomes in a dynamic system, as shown above.

Our present research base of RCTs use one broad brush to cover all human beings grouped together as a cohort. This could never be scientifically correct as no two individuals, even uni-ovular twins, are one hundred percent alike. Human consciousness being unique to each one of us with the mind playing a vital role in healing outcomes, one can never rely on our RCT base as scientific[14]. Randomization cannot and, does not correct this inequality.

We need a new base model of non-linear mathematics for future research. David Eddy, a former professor of cardiovascular surgery at Stanford, who has now become a great mathematician has succeeded in creating a new non-linear virtual human physiology model, using more than ten thousand differential equations, which could be utilized for medical research (http://www.archimedesmodel.com). However, this, in itself, is not the be all and end all of future research. We need to concentrate on long term observational studies that could not be done by a small group of researchers but by the whole profession. In this direction we have started a new journal, Journal of the Science of Healing Outcomes, (http://www.thejsho.com) which is in its second year, exclusively for publishing studies, small and big as also single case studies, where the end point should be successful healing outcome[15].

Over the years this will provide a good scientific base for drawing long term successful healing methods that could be applied safely for patient care. There is an equally good effort by Richard Smith, former editor and CEO of BMJ group, who has started a new journal, Cases Journal, which again publishes case reports of successful healing outcomes. Both the above journals do not bother as to what are the healing modalities as long as they stand the scrutiny of hard science. In our journal we have dispensed with the conventional peer review system as a peer might be unaware of a new methodology used in the study. We have identified world renowned leaders in each field of science, physics, chemistry, medicine etc, and the papers are reviewed by a specialist in the field. In the past, some studies did show that long term observational research was better than our conventional RCT based cohort studies. Using and abusing statistics to show good results is the bane of our present research as shown above in the statin studies.

Other vital area that needs to be tackled is the present stranglehold of the pharmaceutical lobby on medical education, both during the graduate days
in medical school as also the continuing medical education all through a doctor’s life. Earlier this ends the better. The pharmaceutical lobby’s influence on doctors is the main reason why the latter do not see through their game of distorting research data\textsuperscript{[16,17]}. After having said that, I should hasten to add that we should not throw out the baby with the bath tub just because the water in the tub is dirty. Modern medical hi-tech is useful in emergency care and corrective surgery although both those areas need refinement in view of the new physiology enumerated above.

REFERENCES

Review Article

Present and Future Biochemical Markers of Cardiac Diseases

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ABSTRACT

Biochemical markers play an important role in the diagnosis of myocardial injuries and adopting a therapy that would improve clinical outcome. The earliest biomarkers, such as alanine aminotransferase and lactate dehydrogenase, have become redundant with the development of more sensitive and specific assays for latest cardiac markers. This development of assays for new marker proteins has contributed to a greater understanding of the pathophysiology of the disease spectrum of many myocardial diseases.

KEY WORDS: cardiac markers, isoenzymes, lactate dehydrogenase, myeloperoxidase

INTRODUCTION

Biochemical markers play an important role in accurate diagnosis of myocardial injuries and also for assessing the risk factors and adopting a therapy that would improve clinical outcome. Over the past three decade, research and utilization of biomarkers has evolved substantially. The earliest biomarkers, such as alanine aminotransferase and lactate dehydrogenase, have fallen out of use with the development of more sensitive and specific assays for latest cardiac markers[1]. National Institutes of Health (NIH) in 2001 defined biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[2]. The development of assays for new marker proteins has contributed to a greater understanding of the pathophysiology of the disease spectrum of many myocardial diseases[3]. Such biomarkers should not be present in non-cardiac tissues under any physiological or pathological conditions. It should be myocardial tissue specific and its concentration in the myocardium should be high but should be absent in non-myocardial tissues[4]. The marker should be rapidly released into the blood after myocardial ischemia with a direct proportional relationship between the extent of myocardial ischemia and the measured level of the marker as shown in Fig. 1[5]. It should be detectable in blood soon after the myocardial injury (i.e., the sensitivity should be high). To allow suitable detection, biomarkers should persist in circulation for hours to days following the acute necrotic event as shown in Table 1. It must be assayed by a simple and quick method. The nature of the biomarker should allow quantitative measurement by reliable, rapid, precise, and cost-effective methodology that is readily available[1,4].

PRESENTLY USED MARKERS

Aspartate Aminotransferase (AST)

The normal value is 4 – 17 IU/ l[6]. The levels of serum AST activity begin to rise 3 - 8 hours after the onset of the myocardial injury with peak levels on an average at 24 hours and finally it returns to normal levels in 3 - 6 days. It is also increased in pericarditis, muscle and hepatic diseases, hence its use is limited[4].

Creatine Kinase (CK) and its Isoenzyme (CKMB)

The biomarker is found in high concentration in skeletal muscle, myocardium and brain, but not found in RBC. Serum CK activity increases following myocardial infarction (MI) beginning within six hours and peaking on an average at 24 hours and returns to normal within 2 - 3 days[4]. Cytoplasmic CK is a dimer, composed of M and / or B subunits, which associate forming CK-MM, CK-MB and CK-BB isoenzymes[7]. Creatine kinase acts as a regulator of high-energy phosphate production and utilization within contractile tissues. It also has a more general role in shuttling high-energy phosphate bonds via creatine phosphate from the site of ATP production in the mitochondria to the site of utilization within the cytoplasm[3]. The advantage of CK-MB (as shown by Janise et al) is that it is the most sensitive early marker for MI (6 hours after onset) followed by myoglobin[8]. The disadvantage is that trace amounts of CK-MB subforms are found in skeletal tissue and their assay are expected to be falsely positive in patients with muscular dystrophy and severe skeletal-muscle damage[9].

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Myoglobin

Myoglobin is a heme protein that is present in the cytoplasm of cardiac and skeletal muscle cells; its function is to transport intracellular oxygen. It is elevated 2 - 3 hours after myocardial injury. The advantage of this marker is the high negative predictive value of serum myoglobin for excluding early infarction. This has encouraged its use along with more specific markers such as CKMB and cardiac troponin to improve the diagnosis of MI. The disadvantage is that myoglobin is found both in skeletal and cardiac muscle, so its specificity is compromised in the presence of skeletal muscle damage. Development of rapid immunoassay techniques has enabled the use of myoglobin as an early marker of myocardial damage and is thus recommended by the National Academy for Clinical Biochemistry.

Lactate Dehydrogenase (LDH)

An increase in serum LDH activity is found following myocardial infarction beginning within 6 - 12 hours and reaching a maximum at about 48 hours. It remains elevated for 4 - 14 days before coming down to normal levels. The prolonged elevation makes it a good marker for those patients admitted to the hospital several days after MI. RBC’s are rich in LDH and hence, hemolysis may give falsely elevated results. However, its use is discouraged due to its non-specificity as increased levels are found in progressive muscular dystrophy, myoglobinuria, leukemia, pernicious anemia, megaloblastic and hemolytic disease.

Cardiac troponins (cTns)

The troponins are regulatory proteins found in skeletal and cardiac muscle. The three subunits that have been identified include cardiac troponin I (cTnI), cardiac troponin T (cTnT) and cardiac troponin C (cTnC). The complex regulates the calcium-modulated interaction between actin and myosin on the thin filament. Each troponin subunit is encoded by a separate gene, whereas TnI and TnT exist as specific skeletal and cardiac muscle isoforms. The function of cTnI is to inhibit actinomyosin ATPase activity. The cTnC interacts tightly with cTnl, reversing the inhibitory effect. Most intracellular cTnl and cTnT is bound to the myofilbrils in the cardiac myocyte. However, a small percentage exists in a cytosolic pool. These cardiac troponins (cTns) appear in the blood as early as 3 - 4 hours after the acute episode and remain elevated for 4 - 14 days. The advantage is that the cTnl from the plasma of patients with AMI showed dominant form of cTnl released which was in the form of cTnl/cTnC complex. The maximal amount of free cTnl was released shortly after the injury due to breakdown of the myofibrillar complex in damaged myocytes; cytosolic troponins reach the blood stream quickly resulting in a rapid peak of serum troponin which is observed during the first few hours. This is followed by the release of structurally bound troponin resulting in a second peak lasting for several days. An increase in the concentration of serum cardiac troponins reflects myocardial damage but does not indicate mechanism. The disadvantage of this marker is its elevation in patients with myocarditis and where cardiac damage might not be expected such as stroke, pulmonary embolism, pulmonary hypertension and severe renal dysfunction. Because of their sensitivity and specificity when compared with other markers, The National Academy of Clinical Biochemistry and the Joint ESC / ACC Committee for the redefinition of Myocardial Infarction have both recommended troponins as the markers of choice in the evaluation of acute coronary syndrome.

PROMISING NEW MARKERS: XANTHINE OXIDASE

Xanthine oxidoreductase, under normal conditions, exists in dehydrogenase form and uses NAD+ and there is no or very little production of super oxide anion. Depletion of ATP and subsequent loss of membrane Ca2+ gradient is seen under ischemic conditions. Increased Ca2+ levels activates Ca2+ dependent proteases which cause selective proteinolysis of the dehydrogenase to convert it into xanthine oxidase which acts both on hypoxanthine and xanthine at the expense of molecular oxygen to produce super oxide ion. Xanthine oxidase produces oxy-free radicals which oxidize cellular proteins and membranes.

Table 1: Various biomarkers in circulation

<table>
<thead>
<tr>
<th>Marker</th>
<th>Detection (hrs)</th>
<th>Peak (hrs)</th>
<th>Disappearance (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>1 - 4</td>
<td>6 - 7</td>
<td>0 - 1</td>
</tr>
<tr>
<td>Total CK</td>
<td>4 - 8</td>
<td>12 - 30</td>
<td>3 - 4</td>
</tr>
<tr>
<td>cTnT</td>
<td>4 - 12</td>
<td>12 - 48</td>
<td>5 - 15</td>
</tr>
<tr>
<td>cTnl</td>
<td>4 - 12</td>
<td>12 - 48</td>
<td>5 - 10</td>
</tr>
<tr>
<td>LDH</td>
<td>6 - 12</td>
<td>24 - 48</td>
<td>4 - 14</td>
</tr>
</tbody>
</table>

Fig 1: The levels and the duration of various cardiac markers

AMI = acute myocardial infarction
resulting in myocardial cellular injury\textsuperscript{[12]}. Thus, xanthine oxidase in ischemic conditions of the heart, as in myocardial infarction, may play an important role in contributing free radical mediated damage. The elevated levels of xanthine oxidase activity in the blood of patients with myocardial infarction and highly significant increase of malondialdehyde, serving as an index of lipid peroxidation and free radical mediated damage found in myocardial infarction patients is the main advantage of this marker\textsuperscript{[13]}. But the disadvantage of this marker is that it is also found elevated in non-cardiac conditions like liver disorders\textsuperscript{[14]}.

**Adiponectin**
Adipose tissue itself is capable of producing a variety of cytokines and hormones (called adipocytokines). Its association has been found relevant for coronary heart disease (CHD) development\textsuperscript{[20]}. Obesity is a major risk factor for CHD with 1.5 to 2.0 fold increased risk in obese persons\textsuperscript{[21]}. Adiponectin (also called ARCP30, AdipoQ, apM1, and GBP28) is a 247 amino-acid peptide hormone, circulates at relatively high concentrations in the blood stream, accounting for 0.05\% of total serum proteins and is inversely associated with obesity, insulin resistance, type 2 diabetes and cardio-vascular disease (CVD)\textsuperscript{[20]}. Adiponectin expression declines following stimulation with insulin, endothelin-1 and glucocorticoids. Adiponectin is no longer inversely related to systemic inflammation once CHD is established as shown by Maximilian \textit{et al}\textsuperscript{[22]}. Among CHD patients adiponectin is positively related with high density lipoprotein cholesterol (HDL-C) and negatively related to triglyceride (TG) without apparent signs of heart failure. Adiponectin is also positively related to plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker primarily for heart failure\textsuperscript{[20]}. Currently, plasma adiponectin levels have also been seen to correlate with surrogate markers of atherosclerosis\textsuperscript{[23]}.

**Myeloperoxidase (MPO)**
Myeloperoxidase catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite which is stored in azurophilic granules of polymorphonuclear neutrophils and macrophages. It is released into extra cellular fluid during inflammatory process\textsuperscript{[15,16]}. When released it is found that MPO consumes endothelial-derived nitric oxide (NO), thereby reducing NO bioavailability and impairing its vasodilating and anti-inflammatory properties. Thus, MPO is involved in oxidative stress and inflammation and hence it is a possible marker of myocardial infarction\textsuperscript{[17]}. Even though MPO participates in the inflammatory process of acute coronary syndromes, the disadvantage of this marker is that its elevated levels may not likely be specific to cardiac diseases, as activation of neutrophils and macrophages can occur in any infectious, inflammatory or infiltrative disease process\textsuperscript{[18]}. Zhang \textit{et al} showed that blood and leukocyte MPO activity were higher in patients with CAD than angiographically verified normal controls. In the same study they found that results were independent of the patient’s age, sex, hypertension, smoking, diabetes status, LDL concentration, leukocyte count, and Framingham global risk score\textsuperscript{[19]}.

**Glycogen phosphorylase**
Glycogen phosphorylase (-1, 4-D-glucan: orthophosphate D- glucosyltransferase; EC 2.4.1.1) is a glycolytic enzyme that plays an essential role in the regulation of carbohydrate metabolism\textsuperscript{[19]}. Glycogen phosphorylase is a dimeric enzyme having two identical subunits each of molecular mass 97kDa. Three isoenzymes: GPLL (liver), GPMM (muscle), and GPBB (brain) are found in human tissues. The BB and MM isoenzymes are found in the human heart, but the BB isoenzyme is the predominant isoenzyme in myocardium. It catalyzes the first step of glycogenolysis, in which glycogen is converted to glucose 1-phosphate. During hypoxia and hypoglycemia it leads to emergency supply of glucose. GPBB is in the form of sarcoplasmic reticulum glycogenolysis complex. It is released within 2 - 4 h after the onset of myocardial damage and returns to the reference range within 1 - 2 days after MI. The release of GPBB in parallel with myoglobin or heart-type fatty acid binding protein indicates irreversible myocardial damage\textsuperscript{[18,26]}. At the time of tissue hypoxia glycogen is broken down, GPBB is converted to a soluble form and becomes free to move in the cytoplasm. During ischemic condition, rapid increase in glycogenolysis and simultaneously increase in plasma membrane
permeability occurs which favors early release of GPBB[18]. Thus GPBB serves as an accurate marker for the detection of ischemic myocardial damage but is yet to be confirmed with high-quality GPBB assays.

**Heart-type fatty acid-binding protein (H-FABP) and unbound free fatty acids (FFA)**

Heart-type fatty acid-binding protein (H-FABP), a small (15kDa) cytoplasmic protein involved in lipid homeostasis, is abundant in heart muscle[27]. The rapid release of H-FABP into plasma during ischemia indicates the possibility of using this protein as a biochemical marker for ischemic myocardial injury[28]. After myocardial damage H-FABP is released into the intercellular space and appears in the bloodstream. The magnitude of the increase in plasma H-FABP has a good correlation with the size of the infarction[27]. H-FABP increases within three hours after acute myocardial infarction (AMI) and returns to reference values within 12 - 24 hours[29]. H-FABP as a sensitive early marker for myocardial injury has been investigated by several groups and was found to have advantage over or similar to CK-MB, Myoglobin and Troponin[29,30]. The disadvantage is that it lacks in complete cardiac specificity when compared with any other specific markers[27]. But in combination with cardiac troponins, H-FABP may be diagnostic for patients presenting with acute coronary syndrome (ACS) and AMI[30]. Most serum free fatty acids (FFA) are bound with albumin, and only a small fraction of the total FFA present are in the free soluble form[18]. In ischemic condition increased FFA release through adipose lipolysis is a result of catecholamines which are found to be elevated in blood. One of the disadvantages of this marker is that increases in serum FFA are likely attributable to FFA originating from other tissues, such as adipose, along with a reduction of FFA use after ischemia[18]. Furthermore, circulating non-esterified fatty acid concentrations have also been shown to be predictive for sudden death in non-ischemic patients[18]. Hence in patients presenting with ischemic symptoms, plasma FFA monitoring may provide an early indication of cardiac ischemia.

**Choline**

Phosphodiesteric cleavage of membrane phospholipids leads to the formation of choline and phosphatidic acid by phospholipase D. During the activation of cell surface receptors in tissue ischemia, a rapid increase in whole-blood choline (WBCHO) and plasma choline (PLCHO) is seen due to the stimulation of phospholipase D (PLD)[18]. Release of choline into plasma followed by a secondary uptake into blood cells by a choline transport system along with phospholipid breakdown by phospholipases was observed due to early ischemic membrane damage[31]. WBCHO was a high predictor of MI in the follow-up phase than PLCHO in patients with undetectable cTnI[32]. With high-resolution proton magnetic resonance spectroscopy technique increased WBCHO concentrations were first identified as a promising marker for ACS[32]. The determination of choline in whole blood (WBCHO) may be advantageous because it reflects intracellular concentration changes responsible for infiltration and activation of blood cells, where as many proposed cardiac markers of plaque inflammation and plaque instability are based on measurements in plasma or serum[30]. Development of rapid point-of-care tests and laboratory assays of WBCHO and PLCHO will be necessary to evaluate whether these markers will help to identify high-risk patients in clinical practice[18].

**Brain natriuretic peptide (BNP)**

Brain natriuretic peptide (BNP) is a 32-aminoacid counter-regulatory peptide released in response to cardiac stretch. It is synthesized as a pro-peptide and then cleaved to the active moiety by a protease called corin[30]. BNP is synthesized and stored in atrial and ventricular myocytes, although plasma BNP originates mainly from the left ventricle. The ventricular myocyte stretch results in release of BNP and the effect is to increase the glomerular filtration
rate and inhibit sodium reabsorption, increase central venous pressure and left ventricular dysfunction. The plasma concentration is related to the magnitude of the atrial or ventricular overload[37]. The increase in the circulating concentrations of BNP was found soon after AMI as shown by Morita et al[38], whereas Morrison et al[39] have shown that the increased value of BNP helps in differentiating cardiac and pulmonary causes of dyspnea. Disorders associated with right ventricular dysfunction, such as primary pulmonary hypertension, and pulmonary embolism[40] are also associated with increased plasma BNP concentration. Wolde et al[40] showed that plasma BNP is a predictor of fatal pulmonary embolism and their results indicated that high BNP levels were associated with mortality during three months of follow-up in patients with pulmonary embolism. Plasma BNP is also elevated in conditions associated with diastolic dysfunction, such as aortic stenosis, and restrictive cardiomyopathy[41].

CONCLUSION

Biochemical markers have become increasingly important in the investigation of myocardial diseases. The National Academy of Clinical Biochemistry and ESC / ACC have recommended Myoglobin, CK-MB and cTnT as they are more specific among present markers. New promising markers such as H-FABP, BNP, IMA and Adiponectin are in the phase of trial. As found in many studies combination of markers such H-FABP / cTnT and CKMB / cTnT are being used as diagnostic aids.

REFERENCES


Original Article

Recurrence of Primary Spontaneous Pneumothorax: Rate and Risk Factors

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²Department of Surgery, Faculty of Medicine, Kuwait University and Chest Diseases Hospital, Kuwait

ABSTRACT

Objectives: To study the recurrence rate of primary spontaneous pneumothorax (PSP) in our practice and to identify the factors that influence it
Design: Retrospective data analysis
Setting: Chest Diseases Hospital, Kuwait
Subjects: Two hundred and eight patients with PSP
Intervention: Observation or tube thoracostomy
Main Outcome Measures: Recurrence of PSP with reference to the following factors: age, sex, height, BMI, smoking status, and type of primary treatment
Results: Recurrence of PSP occurred in 72 patients with a recurrence rate of 34.6 percent. The majority of recurrences occurred in the first year - 45 out of 72 (62.5%). PSP was eleven times more common in men than in women. Female sex was associated with higher recurrence rate. Ten out of 17 (58.8%) females had recurrence whereas 62 out of 191 (32.5%) males had recurrence (p = 0.02). The recurrence rate in patients who continued to smoke and those who stopped smoking was 53/144 (36.8%) and 2/18 (11%) respectively (p = 0.03). However, no association could be demonstrated between recurrence rate and age, height, BMI and type of treatment.
Conclusion: Female sex and smoking behavior are significant prognostic factors for future recurrences of PSP.

INTRODUCTION

Pneumothorax is defined as the presence of gas in the pleural space. A spontaneous pneumothorax is one that occurs without antecedent trauma to the thorax. Spontaneous pneumothorax can be divided into primary spontaneous pneumothorax (PSP) occurring in patients without clinically apparent underlying lung disease and secondary spontaneous pneumothorax (SSP) which is related to the presence of clinically apparent underlying lung disease such as asthma, COPD, diffuse parenchymal lung disease, AIDS, lung cancer, etc.

PSP occurs usually due to rupture of apical pleural blebs[1]. It is a common clinical problem with a reported incidence of 7.4 - 28/100,000 per year for men and 1.2/100,000 per year for women[2]. The recurrence rate after the first spontaneous pneumothorax is reported between 23 and 54.2 percent[3-8] with a mean recurrence rate of 30 percent[9]. Radiographic evidence of fibrosis, asthenic habitus, female sex, a history of smoking, and younger age have been reported to be independent risk factors for recurrence[9-10].

The aim of this study was to evaluate the recurrence rate of PSP in our experience and to determine the various risk factors predisposing to the recurrence of PSP with particular reference to age, sex, height and BMI, smoking status and the type of primary treatment employed.

PATIENTS AND METHODS

The study was conducted at the Chest Diseases Hospital in Kuwait. A total of 254 patients with a diagnosis of PSP were identified from a data-base for the period from January 1999 to December 2002. Forty six patients with a diagnosis of secondary pneumothorax were excluded from the analysis. The following data were collected: (1) age and sex, (2) height and weight, (3) smoking status, (4) side of pneumothorax, and (5) type of primary treatment. The patients were followed up for a period of 30 to 54 months with a mean follow up period of 42 months. During the follow up period, details of recurrence and changes in smoking status were noted.

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Mob: (965) 9905-6523, Fax: (965) 2244-7584, E-mail: aliamed@yahoo.com
The following definitions were employed: PSP was defined as pneumothorax occurring in an individual without underlying lung disease. Secondary pneumothorax was defined as pneumothorax occurring in patients with underlying lung disease. Recurrence was defined as occurrence of pneumothorax more than 30 days after the completion of treatment in patients who had achieved full lung expansion following the initial pneumothorax.

This study was approved by the local ethical committee.

Statistical analysis

Data were expressed as mean ± SD; data analyses were made using SPSS software windows version 8 packages (SPSS, Chicago, IL). The cut-off level for statistical significance was a p-value of less than 0.05. The unpaired Student’s t test was used to assess the significance between the means of variables in the two groups. The Pearson χ² test was used to ascertain the significance of association between two categorical variables. The χ² test was replaced by Fisher’s exact test if the cell frequencies of any of the 2 x 2 contingency table went below five. The combined effect of variables on the probability of recurrence was modeled using logistic regression.

RESULTS

Two hundred and eight patients with PSP were included in the study. This included 191 male and 17 female patients with a male : female ratio of 11:1. Ages ranged from 16 to 46 years with a mean (SD) of 24.5 (5.8) years and the age distribution was similar in both sexes. The height of the patients ranged from 105 to 195 cm with a mean of 170.7 cm. Pneumothorax occurred on the right side in 118 patients (56.7%) and on the left side in 90 patients (43.3%). One hundred and sixty-two patients (78%) were smokers. Eighteen patients (11%) stopped smoking after their first pneumothorax. This group had a significantly lower recurrence rate (11% versus 36.8% for patients who continued to smoke, p = 0.03, Table 1). An analysis of tabulation of recurrence by time showed that smokers tend to develop recurrences earlier than non-smokers and majority of recurrences occurred within the first year. Recurrences in smokers were 39 in year one, 10 in year two and six thereafter. In non-smokers, six recurrences occurred in year one, six recurrences occurred in year two and five recurrences occurred thereafter (p = 0.02).

A logistic regression model was fitted for probability of recurrence with sex and smoking cessation. The results are in keeping with the finding that female sex and smoking cessation are two predictors of recurrence (Table 2). When account was taken of the number of recurrences and the same variables were tested, smoking status and age were found to significantly affect recurrence (Table 3).

DISCUSSION

This study confirms that the recurrence rate of PSP in our population (34.6%) is similar to that of

Table 1: Primary risk factors in the recurrence of spontaneous pneumothorax

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Recurrence n (%)</th>
<th>Odds Ratio</th>
<th>95% CI*</th>
<th>p-value χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (32.5)</td>
<td>0.3</td>
<td>0.1 - 0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>10 (58.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55 (33.9)</td>
<td>0.8</td>
<td>0.4 - 1.7</td>
<td>0.7</td>
</tr>
<tr>
<td>No</td>
<td>17 (36.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (11)</td>
<td>0.2</td>
<td>0.04 - 0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>No</td>
<td>53 (36.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>5 (35.7)</td>
<td>1</td>
<td>0.3 - 3.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Chest tube</td>
<td>67 (34.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>34 (37.8)</td>
<td>1.2</td>
<td>0.7 - 2.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Right</td>
<td>38 (32.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency admission</td>
<td></td>
<td>1</td>
<td>0.5 - 2</td>
<td>0.9</td>
</tr>
<tr>
<td>Yes</td>
<td>56 (34.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Confidence Interval, ** t-test

Not shown to have a significant effect on recurrence (Table 1). One hundred and sixty-two patients (78%) were smokers on entry into the trial. Data on changes in smoking habit were available for all 162 smokers. Eighteen patients (11%) stopped smoking after their first pneumothorax. This group had a significantly lower recurrence rate (11% versus 36.8% for patients who continued to smoke, p = 0.03, Table1). An analysis of tabulation of recurrence by time showed that smokers tend to develop recurrences earlier than non-smokers and majority of recurrences occurred within the first year. Recurrences in smokers were 39 in year one, 10 in year two and six thereafter. In non-smokers, six recurrences occurred in year one, six recurrences occurred in year two and five recurrences occurred thereafter (p = 0.02).

A logistic regression model was fitted for probability of recurrence with sex and smoking cessation. The results are in keeping with the finding that female sex and smoking cessation are two predictors of recurrence (Table 2). When account was taken of the number of recurrences and the same variables were tested, smoking status and age were found to significantly affect recurrence (Table 3).
Female ratio in our study was 11:1. This was confirmed typically between the ages of 10 to 30 years the fact that PSP occurs most often in young adults were excluded from our study. This also confirms patients with secondary spontaneous pneumothorax less than 46 years). This is probably due to the fact that after one recurrence serious consideration should be given to achieving permanent pleurodhesis. The rate of recurrence after the first recurrence has been reported to be substantially higher with rates ranging from 45 to 62 percent[6,8]. This would indicate that after one recurrence serious consideration should be given to achieving permanent pleurodhesis. The rate of recurrence after a second pneumothorax in our study (14.7%) is lower than that previously reported. The majority of recurrences occur within six months to two years[11] regardless of what treatment is used. Majority of recurrences in our study occurred in the first year.

All patients in the present study were young (age less than 46 years). This is probably due to the fact that patients with secondary spontaneous pneumothorax were excluded from our study. This also confirms the fact that PSP occurs most often in young adults typically between the ages of 10 to 30 years[6].

PSP occurs predominantly in men. The male:female ratio in our study was 11:1. This was confirmed previously in several studies with male:female ratio ranging between 6:1 to 8:1[2,11].

Several studies have been performed concerning the possible relationship between patient’s characteristics and the development of recurrence of PSP. Smoking was found to increase the relative risk of contracting a first spontaneous pneumothorax approximately nine fold among women and 22 fold among men[12]. Our study supports the fact that smoking increases the risk of contracting a first pneumothorax with 78 percent of our patients being smokers on entry. Furthermore, smokers tend to develop ipsilateral recurrence earlier than non-smokers[7]. In another study, smoking cessation did not decrease the incidence of PSP except when patients had stopped smoking for at least one year before their first pneumothorax[9]. Smoking increases the risk of spontaneous pneumothorax and smoking cessation has been shown to reduce the recurrence rate[7,9] suggesting that the effect of smoking on the pathogenesis of pneumothorax is reversible. The effect of smoking cessation on the recurrence of PSP was confirmed in our study. A plausible explanation to the increased risk of pneumothorax in smokers is that smoke related influx of neutrophils and macrophages leads to degradation of elastic fibers in the lung leading to formation of bullae. After bullae have formed, inflammation-induced obstruction of small airways increases alveolar pressure resulting in an air leak into the lung interstitium. The air then moves to the hilum causing pneumomediastinum[13].

Other independent risk factors for recurrence of PSP were reported to be: patient’s physical characteristics; age, female sex and pulmonary fibrosis detected on chest radiographs[17,9]. However, presence of blebs or bulla in patients with PSP has no predictive value for recurrence[14]. As for risk factors predisposing to recurrence, we found that females are at a higher risk compared to men. This finding was previously reported in two studies[7,9]. Sadikot et al[7] proposed that this higher rate of recurrence in women is probably progesterone related with low levels of progesterone induced by the cyclical hormonal variation predisposing women to recurrence of PSP.

PSP tend to occur in tall thin persons with previous studies showing the height/weight ratio[9] and the height of male patients[7] to be predictors of recurrence. We found that neither the patient’s height nor BMI were related to the recurrence.

Although age was found to be a risk factor for recurrence[9], other authors have been unable to show a relationship between pneumothorax recurrence and age[6,7]. Our study did not show age to be a risk factor for recurrence.

Management of spontaneous pneumothorax with tube drainage has not been shown to alter the recurrence rate in this study and in the literature[8,15].
In fact, neither needle aspiration nor tube drainage will have an influence on the natural course of PSP because conditions in the pleural cavity will only be slightly altered by the procedures\textsuperscript{[1]}. Attitudes toward the management of spontaneous pneumothoraces have varied. This have led to the development of management guidelines by the American College of Chest Physicians in 2001\textsuperscript{[16]} and by the British Thoracic Society in 2003\textsuperscript{[17]}. The guidelines agreed that a small and asymptomatic first episode of PSP should be observed for several hours, followed by discharge from hospital when the patient is stable. A large or symptomatic first episode of PSP should be treated by an air evacuation technique. Since the minority of patients with PSP has small pneumothoraces, most patients are treated with invasive procedures\textsuperscript{[1]}. This is evident in our study as 93.3\% of the patients were treated with chest tube insertion.

CONCLUSION
Recurrence of PSP is not related to the age, height, BMI and type of treatment initially used. It is influenced by female sex and cessation of smoking. The majority of recurrences occur in the first year. A better understanding of the risk factors for the recurrence of PSP will assist physicians in the selection of patients for preventive treatment. To advocate prevention of further attacks after the first attack of PSP in females is a subject for a future large and randomized study.

ACKNOWLEDGMENT
This study was supported by a grant from the Environment Public Authority.

REFERENCES
DIAGNOSTIC SIGNIFICANCE OF TISSUE DOPPLER IMAGING IN PATIENTS WITH ACUTE INFERIOR MYOCARDIAL INFARCTION AND PRECORDIAL ST SEGMENT DEPRESSION

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ABSTRACT

OBJECTIVES: To evaluate patients presenting with acute inferior myocardial infarction (IMI) and ST segment depression in the chest leads and to identify patients with anterior ischemia from those with reciprocal ECG changes using Tissue Doppler Imaging (TDI) derived variables

DESIGN: Cohort observational study

SETTING: Department of Medicine, Sabah and Farwania Hospitals, Kuwait

SUBJECTS: One hundred and fifty patients with acute ST segment elevation IMI, stratified into: Group I: 105 patients with acute IMI and precordial ST segment depression and Group II: 45 patients with acute IMI without precordial ST segment depression.

INTERVENTIONS: Transthoracic echocardiography with TDI and coronary angiography

RESULTS: Predictive indices revealed that impaired Systolic velocity (Sm) is a predictor for coronary artery stenosis in the non-infarcted region. Sensitivity was 86%, specificity 80%, accuracy 84%, positive predictive value 88% and negative predictive value 77%. Multivariate logistic analysis revealed that the site and persistence of ST-segment depression, ST-depression > 2 mm, coronary collaterals, left circumflex coronary artery dominance and 0.2SWM score index increment are significantly associated with impaired Sm velocity of TDI corresponding to anterior non-infarct region, (p < 0.05). Receiver operating characteristic (ROC) curve data revealed that the best cut-off value of Sm was 7.1 cm/sec with sensitivity 86%, false positive 17%, positive likelihood ratio 4.78 and negative likelihood ratio 0.160 for prediction of likelihood of multivessel coronary artery disease.

CONCLUSION: TDI can be used to identify patients with likelihood of significant coronary artery disease in the non-infarcted region after acute IMI.

KEY WORDS: acute inferior myocardial infarction, tissue Doppler imaging

INTRODUCTION

Echocardiography has evolved as a well-established tool for the non-invasive evaluation of regional and global myocardial function[1]. Tissue Doppler Imaging (TDI) is a new ultrasound technique that uses shifts in Doppler frequencies for quantifying myocardial motion[2]. As it does not depend on the amplitude of the reflected wave, it is possible to get information regarding myocardial wall motion from an area that may not have satisfactory gray scale information on 2D echocardiography[3]. During its initial application, TDI was limited to real time visualization of only a single myocardial segment. Currently, TDI has evolved into a useful technique for quantifying the nature and the extent of myocardial dysfunction in several diseased states[4].

The overall function of the left ventricle depends on a normal contraction of the longitudinal and circumferentially oriented myocardial fibers. Quantification of the left ventricular function in the longitudinal axis may be clinically relevant since the contraction in this direction is mainly due to subendocardial fibers. In particular, in case of ischemia which specifically alters subendocardial layers, first abnormalities of wall motion will appear in the longitudinal axis. As the apex of the heart remains remarkably stationary, long axis changes are reflected in movements of the base of the heart[5,6].

In 1980, Shah et al[7] first reported that precordial ST segment depression was a marker for increased risk in patients with an inferior myocardial infarction (IMI). Three potential etiologies for precordial ST segment depression have been proposed: 1) that it represent purely reciprocal changes resulting from inferior ST segment elevation; 2) that it results from inferior myocardial ischemia during an inferior infarction,
and thus is a marker for multi-vessel coronary artery disease; and 3) that it results from a more extensive inferior infarction involving the posterolateral wall or the right ventricle, or both.[8]

The aim of the study was to investigate the value of pulsed-TDI to predict significant coronary artery stenosis supplying the non-infarcted region and the likelihood of multi-vessel disease in the patients with acute ST segment elevation IMI.

**SUBJECTS AND METHODS**

**Study patients:**

One hundred and fifty patients with ST segment elevation acute anterior myocardial infarction were included. All patients were admitted by their physicians to the coronary care unit (CCU) from January 2000 to August 2004. All patients were evaluated clinically by looking at history, physical examination, 12-lead ECG, plain chest X-ray and routine laboratory investigations.

Exclusion criteria included patients with rheumatic heart disease, mitral valve prolapse, previous myocardial infarction, intraventricular conduction disturbances, atrial fibrillation, atrial flutter, acute pulmonary edema, mitral regurgitation and patients with contraindications to thrombolytic therapy. None of the patients had a revascularization procedure before the qualifying myocardial infarction.

Exclusion was based on: medical history, physical examination and a 12-lead ECG.

**Thrombolytic therapy**

Forty-eight patients received streptokinase intravenous infusion (1.5 million U over 60 minutes) followed by heparin IV infusion. Patients with history of previous use of streptokinase were excluded. One hundred and two patients were treated with 100 mg of rt-PA administered intravenously over 90 minutes. Immediately before the initiation of rt-PA therapy, an intravenous bolus of 5000 IU of heparin was administered and followed by continuous infusion of 1000 IU / h for at least five days. Aspirin was given on admission to CCU at a daily dose of 100 mg.

**Cardiac enzymes**

Blood samples were obtained every eight hours during the 1st 24 h and once daily from the second day for determination of total serum creatine kinase (CK), MB isoenzyme (CK-MB) fraction and troponin I.

**Electrocardiogram**

Standard 12-lead ECG was recorded on admission to CCU and every three hours thereafter during the 1st 24 h after admission. Beyond the 1st 24h, a 12-lead ECG was recorded daily throughout the hospital stay. All ECGs were recorded with identical (marked) positions of the chest leads. Voltage criteria for diagnosis of acute IMI was the presence of new > 0.2 mV (> 2 mm) ST segment elevation in leads II, III and aVF.

**Transthoracic echocardiography**

Transthoracic echocardiography was performed with the use of GE vivid 7 and a 3.5 MHZ phased array transducer. The leading edge to leading edge convention was used. Left ventricular dimensions were measured at or immediately below the tips of mitral leaflets and averaged over five heart cycles. Left ventricular end-diastolic volume, end-systolic volume and ejection fraction were determined from apical two and four chamber views using the Simpson’s formula. Tracing of endocardial borders in end-diastole and end-systole was performed in the technically best cardiac cycle. Left ventricular segmental wall motion score index was calculated. Wall motion for each segment was graded as normokinesia 1, hypokinesia 2, akinesia 3 and dyskinesia 4. Wall motion score index was calculated by summing the scores for each segment and dividing by the number of analysed segments[9].

Pulsed mitral inflow Doppler and color-coded Doppler was obtained from the standard apical four chamber view. The transducer was then manipulated to obtain the maximal flow velocity as assessed by the auditory and spectral outputs. The Doppler measurements were made during at least three cardiac cycles using the darkest part of the spectral recording and were then averaged.

**Pulsed-Tissue Doppler imaging pattern during sinus rhythm**

A normal TDI pattern consists of three major signals: a single systolic signal (Sm) and two distinct signals in early (Em) and late (Am) diastole, timed by the onset of early inflow and atrial contraction, respectively. During isovolumetric contraction time (IVCTm) and isovolumetric relaxation time (IVRTm), the displayed , smaller biphasic signals are presumed to be the result of brief geometrical changes that occur in the LV (induced by different timing of long-axis and circumferential axis dynamics and by ventricular interdependence[10,11].

The peak TDI-derived velocities (Sm, Em & Am) were measured at six mitral annular sites corresponding to different regions of left ventricle. The following measurements were taken: two-chamber view to detect velocities at two sites corresponding to the anterolateral and inferior regions, 3-chamber view to detect velocities at two sites corresponding to the anterior septum and posterior regions and 4-chamber view to detect velocities at two sites corresponding to posterior septum and posterolateral regions. Infarcted regions including myocardial posterior septum, and inferior regions were considered to belong to the perfusion territory of the dominant right coronary
artery or dominant circumflex coronary artery. Non-infarcted regions (study region) included the anterior septum, and anterolateral regions of the heart myocardium. Posterolateral and posterior regions were considered to belong to the perfusion territory of the circumflex coronary artery. Anterior septum and anterolateral region were regarded as perfused by the left anterior descending coronary artery\textsuperscript{[12]}. For each region, we selected the lowest TDI-derived variables to have a single variable. The cut-off values of TDI-derived variables were calculated as median of reference group ± 2SD. Impaired TDI-derived variables are Sm, Em velocities and Em / Am ratio less than median of the reference group + 2SD, and Am velocity more than the median of reference group -2SD.

**Study Design**

There were two main groups in the study

Control group (Reference group): included 47 subjects with normal stress perfusion scintigraphy and normal coronary angiogram to get normal standard values of TDI variables. The cut-off value was calculated as median of the reference group ± 2SD. The cut-off value of Sm was < median - 2SD, Em was < median - 2SD, Am was > median + 2SD and Em / Am ratio was < median - 2SD.

**Patient sample**

One hundred and fifty patients with acute IMI were included. The agreement between the measurements was determined according to the method of Bland and Altman\textsuperscript{[13]} and expressed as the mean of the differences between two observations ± 2SD of the differences (coefficient of repeatability or variation). With low variability, the mean of the differences should approach zero and the coefficient of variation should be small.

**Coronary angiography**

Coronary stenoses were quantified visually to detect the extent and severity of the coronary lesions. The luminal narrowing of > 50% was considered a hemodynamically significant coronary artery lesion.

**Statistical analysis**

Continuous variables are summarized as mean ± standard deviation (SD). Comparison between two groups was performed using t-test for continuous variables and chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with impaired TDI of mitral valve annulus corresponding to the non-infarcted region. The strength of the association with impaired TDI of mitral valve annulus corresponding to the non-infarcted area is presented as 95% confidence intervals. Potential confounding of clinical variables was entered as independent variables.

The validity of systolic velocity (Sm) of TDI at mitral valve annulus after acute myocardial infarction to detect severity of coronary artery stenosis in the non-infarcted region was assessed by estimating the predictive indices and Kappa coefficient to determine the overall agreement with the data obtained from coronary angiography.

Kappa coefficient value (k) = (Observed frequency of agreement – Expected frequency of agreement) / (Total observed – Expected frequency of agreement).

**Predictive indices**

True positive (TP), true negative (TN), false positive (FP), false negative (FN), sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated.

Receiver operating characteristic (ROC) curve (grade of sensitivity versus false positive) was used to identify the sensitivity and false positive of certain values of the variable with area under curve and probability of error with sensitivity 100% to detect usefulness of TDI-derived variables at mitral valve annulus after acute myocardial infarction for prediction of severity of coronary artery stenosis at the non-infarcted region. ROC was calculated using likelihood ratio method. Likelihood ratio +ve = sensitivity/1-specificity and likelihood ratio -ve = 1-sensitivity/specificity. The best cut-off point should be close to the top left hand corner of the graph: high detection rate with low false positive rate.

The agreement between the measurements was determined according to the method of Bland and Altman\textsuperscript{[13]} and expressed as the mean of the differences between two observations ± 2SD of the differences (coefficient of repeatability or variation). With low variability, the mean of the differences should approach zero and the coefficient of variation should be small.

**RESULTS**

**Clinical characteristics**

With regards to the age of the patients, there was no significant difference between both groups of the study (53.38 ± 4.21 versus 48.9 ± 4.33 years, respectively, p < 0.13). There was no significant difference between both groups as regards the gender (94 (89.6%) versus 40 (89%) males, p < 0.10 and 11 (10.4%) versus 5 (11%) females, p < 0.09 respectively). There was no significant difference between both groups regarding a percentage of patients with history of smoking, hypertension, diabetes mellitus and hypercholesterolemia (43 (40%) versus 16 (35.5%) patients, p < 0.12, 30 (28%) versus 11 (24%) patients p < 0.10, 20 (19%) versus 9 (20%)
patients, p < 0.08 and 19 (18%) versus 6 (13%) patients, p < 0.19 respectively. There was no significant difference in the heart rate on admission and the systolic and diastolic blood pressure between the patients of both groups (98.15 ± 6.63 versus 89.5 ± 7.92 beat / minute, p < 0.10, 136.6 ± 11.63 versus 128.29 ± 8.31 mmHg, p < 0.14 and 90.7 ± 4.30 versus 89.41 ± 7.14 mmHg, respectively, p < 0.28).

**Presenting ECG**

The ECG of all patients from both groups showed sinus rhythm without ectopics and intraventricular conduction defects. There was no significant difference between both groups of the study as regards the electrical axis deviation, PR interval and heart rate corrected QT interval (+36° ± 8.2° versus +46° ± 9.4°, p < 0.08, 144.1 ± 13.9 versus 139.4 ± 8.5 msec, p < 0.16, and 345.3 ± 13.8 versus 367.6 ± 11.4 msec, p < 0.19, respectively). All patients presented with ST segment elevation > 2 mm in the leads II, III and avF.

Forty one patients in group I had ST segment depression in V1 to V4 leads and 34 patients had ST segment depression in V5 and V6. Thirty patients had ST segment depression in lead V3 to V5.

There was a non-significant difference between both groups as regards ST segment elevation in the inferior leads on admission (3.14 ± 1.23 versus 2.72 ± 1.41 mm, p < 0.12).

**ECG after thrombolysis**

There was a non-significant difference between both groups as regards ST segment elevation after thrombolysis (1.3 ± 0.5 versus 1.6 ± 0.7 mm, p < 0.10). No significant change was seen in the ECG as regards electrical axis deviation, QT interval, QT dispersion and thrombolysis between both groups. No patients had new left or right bundle branch block after thrombolysis in both groups. Only 16 (15%) patients in group I and nine (20%) patients in group II had persistent ST segment elevation > 2 mm at time of transfer to chest hospital for coronary angiography (p < 0.13).

**Coronary angiography**

There were 61 (58%) patients in group I who had dominant right coronary artery versus 29 (65%) patients in group II (p = NS) and there were 44 (42%) patients who had dominant circumflex coronary artery in group I versus 16 (35%) patients in group II (p = NS). There was no significant difference in the residual coronary stenosis of the infarct related artery in patients from both groups (60.9 ± 15.1% versus 65.4 ± 12.2%, p < 0.05).

There was a significant decrease in the number of patients with single vessel disease in patients of group I than those of group II (26 (25%) versus 30 (66%), p < 0.05) but there was a significant increase in number of patients who had two vessel disease and those who had three vessel disease in patients of group I than those of group II (50 (48%) versus 12 (27%), p < 0.05 and 29 (37%) versus 3 (7%), p < 0.05 respectively). There was a significant coronary artery lesion of the non-infarct region in patients from group I than those of group II (75.2 ± 4.52% versus 62.5 ± 5.31%, p < 0.05). As regards coronary collaterals, there was a non-significant difference in the percentage of the patients between both groups (35 (33%) versus 11 (24%), respectively, p = NS, Table 1).

<table>
<thead>
<tr>
<th>Table 1: Coronary angiography in both groups of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Culprit lesion of infarct related artery n (%)</td>
</tr>
<tr>
<td>Proximal left circumflex artery n (%)</td>
</tr>
<tr>
<td>Proximal right coronary artery n (%)</td>
</tr>
<tr>
<td>Single vessel disease n (%)</td>
</tr>
<tr>
<td>Two vessel disease n (%)</td>
</tr>
<tr>
<td>Three vessel disease n (%)</td>
</tr>
<tr>
<td>Residual coronary stenosis-IRA (%)</td>
</tr>
<tr>
<td>Coronary artery at non-infarct region (%)</td>
</tr>
<tr>
<td>Coronary collaterals n(%)</td>
</tr>
</tbody>
</table>

**Echocardiography and Doppler study**

There was a non-significant difference as regards the left ventricular end-systolic dimension and left ventricular ejection fraction in patients of both groups (44.2 ± 3.2 versus 46.1 ± 2.6 mm, p = NS and 50.3 ± 3.6 versus 55.7 ± 5.3%, p = NS), respectively. But there was a significant decrease in left ventricle segmental wall motion score index in patients from group I than those of group II (1.92 ± 0.31 versus 1.31 ± 0.43, respectively, p < 0.05).

**Reference group**

The median value (± SD) of Sm of TDI was 9.8 ± 1.23 cm/sec, median value of Em = 11.63 ± 1.14 cm/sec, median value of Am = 7.88 ± 0.69 cm/sec and Em / Am ratio = 1.47 ± 0.21. The pulsed-Doppler derived mitral valve diastolic flow velocities indicated that the median value of E velocity was 158.41 ± 23.12 cm/sec, the median value of A velocity = 89.58 ± 21.35 cm/sec and the median value of E / A ratio = 1.76 ± 0.54.

**Study group**

The cut-off value of Sm was < median-2SD = < 7.37 cm/sec, Em was < median - 2SD = < 9.35 cm/sec, Am was > median + 2SD = > 9.26 cm/sec and Em / Am ratio was < median - 2SD = 1.05.

There was a significant decrease in Em velocity, Em / Am ratio and systolic contraction velocity (Sm) in
the patients from group I than those of group II (6.82 ± 1.3 versus 11.2 ± 2.4 cm/sec, 0.57 ± 0.09 versus 1.34 ± 0.16 and 7.2 ± 1.5 versus 9.8 ± 0.6 cm/sec, respectively, p < 0.01), but there was a significant increase in Am velocity in patients of group I than those of group II (11.9 ± 2.4 versus 8.6 ± 1.6 msec, p < 0.05, Table 2).

Out of 79 patients in group I who had significant coronary artery disease supplying the non-infarcted region, there were 70 (88.6%) patients who had impaired TDI versus nine (11.4%) patients who had normal TDI (p < 0.01). But out of 26 patients in group I who had normal coronary artery in the non-infarcted region, there were three (11.6%) patients who had impaired TDI versus 23 (88.4%) patients who had normal TDI (p < 0.01). Out of 15 patients in group II who had significant coronary artery disease, there were 11 (73.3%) patients who had impaired TDI versus four (26.7%) patients who had normal TDI (p < 0.05). Out of 30 patients in group II who had normal coronary artery in the non-infarcted region, there were eight (27%) patients who had impaired TDI versus 22 (73%) patients who had normal TDI (p < 0.05, Fig. 1).

Out of 48 patients who had ST depression in V1-V3, there were 38 (79%) patients who had impaired TDI in the non-infarcted region versus nine (21%) patients who had normal TDI (p < 0.05), and out of 30 patients who had ST segment depression in V3-V5, there were 10 (33%) patients who had impaired TDI versus 16 (67%) patients who had normal TDI, (p < 0.05). But out of 27 patients who had ST segment depression in V5-V6, there were 21 (77%) patients who had impaired TDI versus six (23%) patients who had normal TDI (p < 0.05, Fig. 2).

There was a non-significant decrease in systolic velocity of TDI at the infarcted region as compared with systolic velocity (Sm) of TDI at the anterior non-infarcted region in patients of group I (5.9 ± 1.2 versus 7.3 ± 1.5 cm / sec, respectively, p = NS), but there was a significant decrease in systolic velocity of TDI at the infarcted region as compared with systolic velocity of TDI at the anterior non-infarcted region in patients of group II (6.2 ± 1.4 versus 9.7 ± 0.6 cm / sec respectively, p < 0.05). There was a non-significant difference between systolic velocity (Sm) of TDI at the infarcted region between both groups (5.9 ± 1.2 versus 6.2 ± 1.4 cm / sec respectively, p = NS).

There were no patients in both groups who developed mechanical complications such as pericardial effusion, cardiac tamponade, ventricular septal defect or intracardiac thrombus.

Forward stepwise logistic analysis:

Multivariate analysis revealed that impaired TDI-derived variables at anterior non-infarcted region after acute IMI are significantly associated with the +10 year increment in the age of the patients (p < 0.05), the site of ST segment depression (V1-V4 and V5-V6, p < 0.05), left circumflex coronary artery dominance (p < 0.05), persistence of ST segment depression (> 12 hour

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Table 2: Parameters of pulsed-TDI of mitral valve annulus in both groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 105</td>
<td>N = 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Em (cm/sec)</td>
<td>6.8 ± 1.3</td>
<td>11.2 ± 2.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Am (cm/sec)</td>
<td>11.9 ± 2.4</td>
<td>8.6 ± 1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Em/Am ratio</td>
<td>0.57 ± 0.09</td>
<td>1.34 ± 0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sm (cm/sec)</td>
<td>7.2 ± 1.5</td>
<td>9.8 ± 0.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Em: Two distinct signals in early diastole; Am: Two distinct signals in late diastole; Sm: Single systolic signal

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Fig. 1: Impaired and normal tissue Doppler imaging in patients of both groups as regards the presence or absence of coronary artery disease (CAD) at the anterior non-infarcted region.

Fig. 2: Impaired and normal tissue Doppler imaging in patients of group I as regards ST depression in the chest leads
Table 3: Stepwise logistic multivariate analysis of patients with Vs without impaired TDI of mitral valve annulus corresponding to non-infarcted region as regards independent variables

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Coefficient</th>
<th>p-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year increment</td>
<td>0.0629</td>
<td>NS</td>
<td>0.598</td>
<td>0.174 - 1.031</td>
</tr>
<tr>
<td>10-year increment</td>
<td>0.1232</td>
<td>&lt; 0.05</td>
<td>1.653</td>
<td>1.051 - 2.287</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.0629</td>
<td>NS</td>
<td>0.732</td>
<td>0.204 - 1.331</td>
</tr>
<tr>
<td>Female</td>
<td>0.0654</td>
<td>NS</td>
<td>0.728</td>
<td>0.121 - 1.215</td>
</tr>
<tr>
<td>Diabetes mellitus status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.0629</td>
<td>NS</td>
<td>0.624</td>
<td>0.170 - 1.134</td>
</tr>
<tr>
<td>No</td>
<td>0.0754</td>
<td>NS</td>
<td>0.516</td>
<td>0.121 - 1.082</td>
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<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.0218</td>
<td>NS</td>
<td>0.878</td>
<td>0.125 - 1.417</td>
</tr>
<tr>
<td>No</td>
<td>0.0429</td>
<td>NS</td>
<td>0.539</td>
<td>0.192 - 1.088</td>
</tr>
<tr>
<td>Residual IRA coronary stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>0.0713</td>
<td>NS</td>
<td>0.628</td>
<td>0.141 - 1.196</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>0.0553</td>
<td>NS</td>
<td>0.831</td>
<td>0.122 - 1.574</td>
</tr>
<tr>
<td>Coronary artery dominance pattern</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RCA dominance</td>
<td>0.0342</td>
<td>NS</td>
<td>0.518</td>
<td>0.129 - 1.091</td>
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<tr>
<td>LCX coronary artery dominance</td>
<td>0.3171</td>
<td>&lt; 0.05</td>
<td>1.692</td>
<td>1.276 - 2.293</td>
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<tr>
<td>Site of ST segment depression</td>
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<tr>
<td>V1-V4</td>
<td>0.1581</td>
<td>&lt; 0.05</td>
<td>1.743</td>
<td>1.182 - 2.390</td>
</tr>
<tr>
<td>V3-V5</td>
<td>0.0821</td>
<td>NS</td>
<td>0.552</td>
<td>0.195 - 1.129</td>
</tr>
<tr>
<td>V5-V6</td>
<td>0.1497</td>
<td>&lt; 0.05</td>
<td>1.511</td>
<td>1.059 - 2.088</td>
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<tr>
<td>Persistence of ST depression</td>
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<td></td>
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<tr>
<td>&lt; 12 hour after thrombolysis</td>
<td>0.0523</td>
<td>NS</td>
<td>0.638</td>
<td>0.147 - 1.211</td>
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<tr>
<td>&gt; 12 hour after thrombolysis</td>
<td>0.3723</td>
<td>&lt; 0.05</td>
<td>1.655</td>
<td>1.041 - 2.207</td>
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<tr>
<td>ST depression &gt; 2 mm</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>0.1607</td>
<td>&lt; 0.05</td>
<td>1.753</td>
<td>1.243 - 2.567</td>
</tr>
<tr>
<td>No</td>
<td>0.0363</td>
<td>NS</td>
<td>0.712</td>
<td>0.167 - 1.289</td>
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<tr>
<td>Coronary collaterals status</td>
<td></td>
<td></td>
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<tr>
<td>Present</td>
<td>0.2057</td>
<td>&lt; 0.05</td>
<td>1.599</td>
<td>1.205 - 1.912</td>
</tr>
<tr>
<td>Absent</td>
<td>0.0628</td>
<td>NS</td>
<td>0.876</td>
<td>0.139 - 1.487</td>
</tr>
<tr>
<td>SWM Score Index</td>
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<td></td>
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<tr>
<td>0.1 score index increment</td>
<td>0.0674</td>
<td>NS</td>
<td>0.753</td>
<td>0.159 - 1.429</td>
</tr>
<tr>
<td>0.2 score index increment</td>
<td>0.1862</td>
<td>&lt; 0.05</td>
<td>1.599</td>
<td>1.196 - 1.953</td>
</tr>
</tbody>
</table>

Number of observations = 150, IRA = infarct related artery; RCA = right coronary artery; LCX = left circumflex; SWM Score Index = segmental wall motion score index

after thrombolysis, p < 0.05), ST segment depression > 2 mm, p < 0.05), presence of coronary collaterals (p < 0.05), the +0.2 increment in the segmental wall motion score index (p < 0.05). The analysis also revealed that diabetes mellitus status (yes or no), hypercholesterolemia (yes or no), residual stenosis of infarct related coronary artery (> 50% or < 50%), the site of ST segment depression (V3-V5), persistence of ST segment depression (< 12 hour after thrombolysis), ST segment depression < 2 mm and the right coronary artery dominance pattern are not associated with impaired TDI-derived variables at anterior non-infarcted region after acute IMI (p = NS, Table 3).

Table 4: Agreement of the coronary angiogram and the systolic velocity of TDI at mitral valve annulus corresponding to anterior non-infarcted region as regards the prediction of significant coronary artery stenosis supplying the non-infarcted region

<table>
<thead>
<tr>
<th>Significant coronary artery stenosis (&gt; 50%)</th>
<th>Coronary artery stenosis &lt; 50% or normal coronary</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved systolic velocity of TDI</td>
<td>81</td>
<td>11</td>
</tr>
<tr>
<td>Normal systolic velocity of TDI</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>56</td>
</tr>
</tbody>
</table>

Kappa Coefficient value (k) = 0.741

Agreement and reliability

Table 4 shows that there was an agreement between angiographically documented coronary artery stenosis and systolic velocity of TDI with Kappa coefficient (K) = 0.741. The predictive indices showed that impaired systolic velocity of TDI is valid for prediction of patients with significant coronary artery disease supplying the non-infarcted region as sensitivity was 86%, specificity 80%, accuracy 84%, positive predictive value 88% and negative predictive value 77% (Table 5).

Receiver operating characteristic (ROC) curve

The best cut-off value of Sm velocity to predict significant coronary artery disease was 7.1 cm/sec at 86% sensitivity and 83% specificity (the maximum sensitivity and maximum specificity near to the left diagonal), with 32% probability of error at 100%
sensitivity and the area under curve was 0.849 (Fig. 3). The ideal cut-off value of Em and Am velocities to predict significant coronary artery disease was 6.2 cm/sec at 85% sensitivity and 82% specificity and 12.3 cm/sec at 75% sensitivity and 73% specificity, with 42 and 48% probability of error at 100% sensitivity and the area under curve was 0.832 & 0.764, respectively (Fig. 4). The ideal cut-off value of Em / Am ratio to predict significant coronary artery disease was 0.54 at 81% sensitivity and 78% specificity, with 44% probability of error at 100% sensitivity and the area under curve was 0.809 (Fig. 5). Table 6 showed that the positive likelihood ratio of Sm variable was higher than other variables (4.78 versus 4.382, 2.70 & 3.69 respectively) and the negative likelihood ratio of Sm variable was lower than other variables (0.160 versus 0.189, 0.358 & 0.262 respectively).

Reproducibility

There was no significant difference in inter-observer variability and intra-observer variability as regards the measurement of systolic and diastolic velocities of TDI (p = NS) and there was a good agreement between measurements of TDI parameters by both observers.
artery disease. These observations support the active
(Am) had no significant correlation with the coronary
but we have shown that the TDI-derived velocity
velocities (Sm and Em) at the non-infarcted region
of motion results in wastage of energy developed in
myocardium as asynchronous and opposite direction
imposed by the ischemic myocardium on the normal
receptor density. There is a mechanical disadvantage
of myocytes and the myocardial beta-adrenergic
and lusitropic states at rest and with exercise
an important role in regulating the myocardial inotropic
function. It is also dependent on the adrenergic nervous
and hypoxia may alter systolic and diastolic myocardial
flow. Pislaru et al reported that systolic myocardial velocity
and Edvardsen et al reported that myocardial velocities could estimate the
myocardial perfusion and therefore, is valid in the
situation of ongoing ischemia.

Regional function is dependent on the number of
normally functioning myocytes and is reduced with
myocyte necrosis and replacement fibrosis. Ischemia
and hypoxia may alter systolic and diastolic myocardial
function. It is also dependent on the adrenergic nervous
system and the circulating catecholamines, which play
an important role in regulating the myocardial inotropic
and lusitropic states at rest and with exercise. Shan
et al reported that systolic myocardial velocity
and Em are strongly dependent on both the number of
myocytes and the myocardial beta-adrenergic
receptor density. There is a mechanical disadvantage
imposed by the ischemic myocardium on the normal
myocardium as asynchronous and opposite direction
of motion results in wastage of energy developed in
the normal region.

We found a significant inverse correlation between
the coronary artery stenosis and DTI-derived velocities (Sm and Em) at the non-infarcted region
but we have shown that the TDI-derived velocity
(Am) had no significant correlation with the coronary
artery disease. These observations support the active
ventricular myocardium contribution to Sm and Em
and suggest that Am is perhaps reflective of passive
ventricular motion or maybe more dependent on atrial
myocardium function.

Plazak et al, found that wall motion score index
was normal both before PTCA, after PTCA and during
re-stenosis, but re-stenosis in patients after PTCA was
manifested by renewed decrease of systolic myocardial
velocity in ischemic segments. Smiseth et al concluded that TDI can be recommended for clinical
use for diagnosis of coronary artery disease. Lin et al concluded that pulsed wave TDI technique provides
objective quantitative information for identification of
multi-vessel or left circumflex coronary artery stenosis
(>50%) in patients with chest pain but without apparent
wall motion abnormalities on echocardiography.

We found that there were 11 patients who had
normal coronary angiogram of the arteries supplying
the anterior non-infarcted region with impaired TDI
at the same region. This is explained by a mechanical
disadvantage imposed by the ischemic myocardium
on the normal myocardium as the asynchronous and
opposite direction of motion results in wastage of
energy developed in the normal region and possibly
impairment in coronary blood flow reserve.

Our results revealed that a subgroup of patients in
group I with ST depression in V3-V5 had less impaired
TDI-derived Sm as compared with other subgroups of
patients. Most patients from this subgroup (27 out of
30 patients, 90%) had RCA dominance and logistic
analysis revealed that RCA dominance and the site
of ST depression in V3-V5 are not associated with
impaired TDI-derived Sm.

Previous investigators have put forth a number
of explanations for precordial ST segment depression
during an MI. Researchers have proposed that
precordial ST segment depression is purely an ECG
consequence of ST segment elevation in the inferior
limb leads, without physiological importance. Others
have proposed that precordial ST segment depression during MI signifies anterior wall ischemia
and thus is a marker of left anterior descending
coronary artery or multi-vessel disease.

Methodological consideration
The method used in this study provides reliable,
non-invasive and a valid technique to diagnose
patients with multiple vessel disease after acute myocardial infarction, and it can be reproduced. This is in agreement with the results of Moladoust et al[31]. However, Gjesdal et al[32] and Becker et al[33], found that ultrasound speckle tracking is valid for the detection of ischemic and reperfused myocardial regions. Derumeaux et al[34], reported that strain rate imaging study is a reliable method to determine myocardial alterations in senescent mice.

Confounding factors
With regards to coronary collaterals, there was a significant increase in the number and percentage of patients in the group I compared with those of group II, and this may confound the results. The reperfusion injury after thrombolytic therapy in successful revascularization may also confound the results.

Limitations of this study
- Relatively small number of patients.
- Echocardiography study was done after thrombolytic therapy. Therefore, it is difficult to study the effect of thrombolysis on TDI at infarcted and non-infarcted regions.
- Evaluation of percentage coronary stenosis should have been done quantitatively and not qualitatively, specifically, for most of the patients with > 50% lesions.
- Myocardial contrast echocardiogram was not done as it detects myocardial blood flow and perfusion.
- Body weight was not assessed. Therefore, it is difficult to study the effect of obesity on TDI-derived variables at the non-infarcted regions.
- Tumuklu et al., reported that obesity is associated with subclinical changes in left ventricle which can be detected by strain and strain rate imaging even without overt heart disease[35].

CONCLUSION
Inspite of limitations and confounders, we propose that the TDI can be helpful to identify patients with likelihood of significant coronary artery stenosis supplying the non-infarcted region. This may help one to consider these patients for a coronary angiogram in the early post-infarction period.

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Original Article

Return to Work Following Cardiac Rehabilitation in Patients Undergoing Cardiac Procedures with an Approach to Patient’s Viewpoints and Attitude

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Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran


ABSTRACT

Objectives: To estimate the rate of return to work (RTW) after cardiac rehabilitation and determine the relationship between RTW and clinical and socio-demographic factors with an approach to patient’s attitude

Design: Prospective follow-up study

Setting: Tehran Heart Center, Iran

Subjects: Two hundred and forty six consecutive patients undergoing different types of cardiac procedures between May and September 2007 were studied.

Intervention: A checklist was completed for patients according to medical history and physical examination recorded in medical files. A complementary interview was also carried out by phone.

Main Outcome Measures: Rate of RTW after cardiac rehabilitation and the relationship between RTW and clinical and socio-demographic factors

Results: Two groups were matched for gender, age, occupation type and the type of cardiac procedures. Rehabilitated patients in comparison with control group had higher rates of RTW three month (55.4 Vs 26.2%) and eight months (94.7 Vs 81.0%) after the time of cardiac rehabilitation. Positive attitude toward RTW was observed more in rehabilitated patients three month and eight months after cardiac procedures. Cardiac rehabilitation programs (OR: 3.507, p = 0.027), preoperative functional class (OR: 6.541, p < 0.001), experience of regular physical activity at home before RTW (OR: 3.836, p = 0.004) and job support programs (OR: 4.050, p = 0.022) were main predictors for RTW eight months after cardiac procedures.

Conclusion: Patients undergoing cardiac procedures benefit from cardiac rehabilitation to preserve work status. The need for appropriate supportive protocols can guarantee RTW after cardiac rehabilitation and improve patients’ attitude toward continuing their jobs.

KEY WORDS: acute coronary syndrome, cardiac rehabilitation, cardiac surgery

INTRODUCTION

In the early years of cardiac surgeries, candidates for surgical intervention usually consisted of relatively young patients with limited coronary artery disease (CAD), favorable left ventricular function and few co-morbid conditions. Today, the surgical population, especially in developing countries, has evolved into a young group of patients with more extensive coronary involvement and more left main disease. Furthermore, there are considerably increased numbers of patients with risk factors for CAD. Despite the increasing risk profile of this population, outcome of cardiac events has generally remained stable or has improved[1]. However, researches have shown that the results of these events can mainly influence return to work (RTW) in this population, especially in the younger group.

According to these findings, RTW has been variable, ranges between 35 and 80 percent and has been as high as 80% in those who were employed prior to undergoing cardiac surgeries. Some factors have been known to adversely affect the prospects of patients for RTW including advanced age, postoperative angina, job satisfaction prior to surgery, and a period of unemployment or disability before surgery[2]. However, some other studies showed that clinical postoperative complications may not negatively influence patients’ RTW[3]. However, few studies are available about the rate and determinants of RTW after supportive programs such as cardiac rehabilitation especially in patients who underwent different types of cardiac procedures.

The main purpose of the present study was to estimate the rate of RTW in cardiac rehabilitated and non-rehabilitated patients and determine the association between RTW after cardiac rehabilitation and clinical and socio-demographic factors in an Iranian population. We also considered patients’ attitude towards RTW.

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SUBJECTS AND METHODS
In a historical cohort study, two hundred and forty six patients who underwent different types of cardiac procedures including coronary artery bypass surgery, percutaneous coronary intervention or valve surgeries in Tehran Heart Center between May and September 2007 were consecutively entered into the study. Among studied patients, 114 patients undergoing complete protocol of cardiac rehabilitation were designated as the study group while others who underwent routine follow-up assessment acted as the control group. Patients with any physical or psychiatric disease that would interfere with participation in the program were excluded. Patients who underwent cardiac rehabilitation program incompletely were also excluded. The rehabilitation program comprised of 24 exercise sessions, scheduled over eight weeks. Each session took 30 - 45 min; beginning with a 3 - 5 min warm-up followed by 30 - 45 min aerobic exercise, and was terminated with a 3 - 5 min cool-down. The exercise was done under electrocardiographic monitoring if the patient was at high risk.

A checklist was completed for the patients according to medical history and physical examination recorded in medical files by trained general practitioners and nurses. The criterion of patient’s RTW rate three and eight months after cardiac procedures program was evaluated by a self-completed questionnaire sent to the patients. Data were also collected in the control group at the same times. If no response was received, a complementary interview was carried out by phone. This questionnaire consisted of 18 items covering different aspects of patient’s usual employment status and main occupation and also their attitude towards RTW after cardiac procedures.

Informed consent was obtained from all patients. The study was approved by the local ethical committee.

Results were reported as mean ± standard deviation (SD) for the quantitative variables and as percentages for the categorical variables. The groups were compared using the Student’s t-test for the continuous variables and the chi-square test, one-way analysis of variance (ANOVA) test or Fisher’s exact test for the categorical variables. Univariate analysis was first used (p-values < 0.1) to estimate the strength of association between individual predictors and RTW after six months. In the subsequent analysis, all predictors were simultaneously considered in a multiple logistic regression analysis to screen for independent significant factors. p-values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 for windows (SPSS Inc., Chicago, IL, USA).

RESULTS
The mean age of all studied patients was 58.52 ± 9.93 (range = 36 to 86 years) and 72.4% out of them were male. The study and control groups were well matched for gender (p = 0.472), age (p = 0.707), occupation type (p = 0.387) and the type of cardiac procedures (p = 0.785) (Table 1). In the first group, the time interval between cardiac procedures and cardiac rehabilitation program was 33.16 ± 22.82 days. Time interval between cardiac procedure and the beginning of personal activities in rehabilitation group was significantly shorter in the study than the control group. However, time interval between these procedures and RTW were similar between the two groups. Among men, 97.4% in rehabilitation group and 93.8% in another group were employed before cardiac procedures (p = 0.283) such that 44.0 and 58.4% of them worked in the two shifts, respectively. Among women, 3.3% in rehabilitation group and 7.1% in control group worked out of the house (p = 0.212) whereas others were housewives. The minority of all studied patients advantaged from job consultation programs such that only 5.3% of men used job consultation programs whereas none of the women advantaged from these programs. Job support from workplace or society was found more in the non-rehabilitated group (Table 1).

Table 1: Demographic characteristics and clinical data of studied patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rehabilitation group* (n = 114)</th>
<th>Control group* (n = 132)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>70.2</td>
<td>74.2</td>
<td>0.472</td>
</tr>
<tr>
<td>Age (year)</td>
<td>58.78 ± 9.23</td>
<td>58.29 ± 10.35</td>
<td>0.707</td>
</tr>
<tr>
<td>Occupation status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>46.5</td>
<td>55.3</td>
<td>0.387</td>
</tr>
<tr>
<td>Housewife</td>
<td>27.2</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>26.3</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>Type of cardiac procedure:</td>
<td></td>
<td></td>
<td>0.785</td>
</tr>
<tr>
<td>PCI</td>
<td>50.4</td>
<td>54.0</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>42.5</td>
<td>38.1</td>
<td></td>
</tr>
<tr>
<td>Other procedures</td>
<td>7.1</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Time interval between cardiac procedure and personal activities (days)</td>
<td>26.15 ± 26.08</td>
<td>34.66 ± 29.00</td>
<td>0.018</td>
</tr>
<tr>
<td>Time interval between cardiac procedure and returning to work (days)</td>
<td>52.98 ± 38.14</td>
<td>62.06 ± 42.41</td>
<td>0.102</td>
</tr>
<tr>
<td>Experience of regular physical activity before returning to work</td>
<td>60.0</td>
<td>52.5</td>
<td>0.313</td>
</tr>
<tr>
<td>Use of job consultation before returning to work</td>
<td>3.8</td>
<td>4.2</td>
<td>0.92</td>
</tr>
<tr>
<td>Job support from workplace or society</td>
<td>79.2</td>
<td>61.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Anti-anxiety drug administration</td>
<td>37.6</td>
<td>71.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data presented as mean ± SD or percentages
In the rehabilitation group, 55.4 and 94.7% of patients returned to work after three and eight months after the cardiac procedure, respectively, whereas these rates in the control group were 26.2 and 81.0, respectively. Rates of RTW after the two above time points were higher in the rehabilitation group in comparison with the control group (Fig. 1 and 2). Majority of patients in both the groups had to modify their preoperative jobs, three months after the procedure. Also, eight months after the operation, rehabilitated men and women continued their modified jobs, whereas other patients needed to continue their job modification (Tables 2 and 3).

Regarding RTW following different cardiac procedures, considerable number of patients undergoing coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) returned to their work three months and eight months after each procedure (Table 4).

Multivariate logistic regression analysis (Table 5) showed that the cardiac rehabilitation programs (OR: 3.507, p = 0.027), preoperative functional class (OR: 6.541, p < 0.001), experience of regular physical activity at home before RTW (OR: 3.836, p = 0.004) and job support programs (OR: 4.050, p = 0.022) were main predictors for returning to work eight months after cardiac procedure.

We also studied the frequency of positive attitude toward returning to work in rehabilitated and control groups. The positive attitude toward returning to work was also observed more in rehabilitation group three month and eight months after cardiac procedure. Furthermore, positive relationships were found between the rate of positive attitude toward RTW and the time interval between cardiac procedure and follow-up time in both groups (Table 6).
DISCUSSION

Some of the previous studies have shown clear beneficial effects of myocardial revascularization procedures on different aspects of health, especially patient’s quality of life and even employment over several years\[4,5\]. The ability to work are considered important components of quality-of-life analyses for persons with disabilities and this ability is linked to personal financial security, life satisfaction, and better quality of life in general\[6-8\]. However, a few studies are available about the impact of non-invasive supportive procedures such as cardiac rehabilitation on ability to RTW. Besides, Iran’s population is one of the youngest populations among developing countries and therefore, unemployment of young individuals can lead to a heavy economic burden. The economic burden on the nation could be substantially decreased, if fewer working-age adults were unable to work because of impairment\[9\]. Thus, assessment of RTW after each cardiac procedure in our young population is necessary. In the present study, we firstly determined the main predictors of RTW in patients undergoing cardiac rehabilitation after different types of cardiac interventions and then assessed their positive attitude towards RTW. We showed that the rate of RTW eight months after cardiac rehabilitation in rehabilitated and non-rehabilitated patients was 94.7 and 81.0%, respectively and it was significantly higher in the first group. Also, in our study, the time interval between cardiac procedure and personal activity was shorter in rehabilitated group. Although, the time interval between cardiac procedure and RTW was numerically shorter in rehabilitated group, this difference was not significant between the two studied groups. However, it seems that the cardiac rehabilitation program can successfully shorten the time interval between cardiac procedure and RTW, because in some previous studies, 80.2% of patients who did not undergo cardiac rehabilitation had returned to work one year later\[10\]. Also, in a study by Boudrez et al RTW within a one year follow-up was observed in 83.3% patients\[11\].

In the present study, the parameter of job support programs was the main predictor for returning to work after cardiac rehabilitation. Predictive value of this factor has been previously described. Brines et al indicated that the relationships with employers and co-workers and financial pressures have been associated with the rate of RTW\[12\]. Also, Smith and O'Rourke found that the employment-related physical activity and perception of health status were the only significant predictors of RTW\[13\]. Varaillac also found that of the socio-professional factors, only difficulties related to the patients’ work such as modification or change of job were associated with a more delayed RTW\[14\]. We believe that the main cause of discontinuing the job and confining oneself at home is the absence of job support from employers such as insurance support. Therefore, the use of adaptive devices or a redesign of the job description to allow the person to perform the job is necessary.

In our study, we focused on the patients’ attitude towards RTW after cardiac rehabilitation, because we suppose that their attitude and perception has a major effect on RTW. The patient’s perception of his or her illness, particularly the belief that the illness would last a long time and have serious consequences, has been associated with slower RTW\[15\]. Mittag et al

<table>
<thead>
<tr>
<th>Table 5: Multivariate analysis for determination of the predictors for return to work (RTW) eight months after cardiac procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors for RTW</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cardiac rehabilitation program</td>
</tr>
<tr>
<td>Experience of regular physical activity</td>
</tr>
<tr>
<td>Job support from workplace or society</td>
</tr>
<tr>
<td>Anti-anxiety drug administration</td>
</tr>
<tr>
<td>Functional class</td>
</tr>
</tbody>
</table>

Hosmer-Lemeshow goodness of fit test: chi-square = 0.131; p = 0.936; RTW = return to work

<table>
<thead>
<tr>
<th>Table 6: Positive attitude toward returning to work after cardiac procedure in men and women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive attitude</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>On admission day to rehabilitation ward</td>
</tr>
<tr>
<td>Three month after cardiac rehabilitation</td>
</tr>
<tr>
<td>Eight months after cardiac rehabilitation</td>
</tr>
<tr>
<td>p-value</td>
</tr>
</tbody>
</table>

*Data presented in percentage
showed that the patients’ viewpoint on RTW after myocardial infarction is based on their former job status, job satisfaction, and negative incentives for RTW[16]. We found that the cardiac rehabilitation programs improved the patients’ attitude towards RTW because within rehabilitation process, the use of education programs and psychological consultations can enhance their viewpoints towards RTW.

The present study has some limitations. First, we did not consider general risk factors for CAD as predictors for RTW because of missing data from the files. However, some previous studies have confirmed that medical variables such as cardiac status had little relevance to re-employment[16]. But, we recommend assessing the influence of these parameters on resuming the job and even on attitude toward RTW in future studies. Also, we did not find relationship between the type of cardiac procedures and RTW. Other investigations are also recommended to study these relationships with a greater sample size.

CONCLUSION

Patients undergoing cardiac procedures can benefit from cardiac rehabilitation programs to preserve working status. CAD is common in the working age population and appropriate supportive protocols can guarantee RTW after cardiac rehabilitation and improve patients’ attitude toward their continuing the job.

REFERENCES

Original Article

Perceptions and Attitude towards Lumbar Puncture (LP) among Parents in Kuwait

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ABSTRACT

Objective: To assess the knowledge, understanding and acceptance of lumbar puncture (LP) among parents of pediatric patients in hospitals
Design: Questionnaire-based cross sectional survey
Setting: Department of Pediatrics in three hospitals in Kuwait, namely, Al-Amiri, Al-Adan and Al-Jahra hospital
Subjects: Three hundred and fifty-eight parents of children admitted with various underlying diagnoses
Intervention: A self-administered questionnaire.
Main Outcome Measures: Rate of acceptance of LP, characteristics of parents accepting and refusing LP, reasons for rejecting LP and means to improve LP acceptance among parents in Kuwait
Results: A total of 358 parents responded to the questionnaire. Only 15.3% agreed for LP, 42.5% did not agree and 42.2% preferred taking a second opinion. Relationship to the child, nationality and educational level of the parent were significantly associated with acceptance of LP (p < 0.05). The majority (79.1%) answered that LP is unsafe because it might cause complications like paralysis (46.2%), pain (16.6%), infertility (17.2%), and deterioration of child’s health (12.8%). Out of the parents who did not accept LP, 67.0% said that they might have changed their mind, if the procedure was fully explained by a doctor with the use of a diagram. Another group (66.0%) felt that the media can help to increase the acceptance of LP among parents.
Conclusion: Parent’s refusal of LP is a common problem among parents in Kuwait. The main reasons are lack of knowledge and the misconception that this is a harmful procedure. There is a great need to educate parents about the safety of LP in children.

INTRODUCTION

Lumbar puncture (LP) is a diagnostic and at times therapeutic procedure that is performed in order to collect a sample of cerebrospinal fluid (CSF) for biochemical, microbiological, and cytological analysis, or rarely, to relieve increased intracranial pressure. The most common purpose for a lumbar puncture is to collect cerebrospinal fluid in a case of suspected meningitis, but it can also be performed to diagnose other neurological conditions such as subarachnoid hemorrhage, hydrocephalus and benign intracranial hypertension. It is a safe procedure, if performed in the absence of increased intracranial pressure. Post-LP headache is the most commonly described complication in adults, but is rare in children[1].

Despite the fact that LP is a procedure with a great diagnostic and therapeutic value, many parents are refusing LP to be performed on their children. In a study in Malaysia, 25% of the parents refused LP[2]. In a previous study of meningitis in Kuwait, it was noticed that the refusal rate of this important diagnostic procedure was 15 - 20% and could reach up to 40% in some hospitals[3]. This has resulted in an underestimation of the number of laboratory confirmed cases of meningitis and the overuse of antibiotics in cases of suspected meningitis.

This study was carried out to determine the extent of the LP refusal, evaluate the reasons for refusal of LP and explore the possible ways to improve the rate of LP acceptance among parents in Kuwait.

SUBJECTS AND METHODS

In order to assess the knowledge, attitude, and behaviour of parents in Kuwait towards LP performance, a questionnaire-based study was performed. The questions were self administered in both Arabic and English languages. The study was undertaken between September and December 2006
in three hospitals; in the capital city, the northern and the southern areas of Kuwait to represent various ethnic groups of the population. The questionnaire was offered to all parents of admitted children with various diagnoses, including those for whom LP was not indicated also. We used only the fully answered questionnaires in the final analysis and disregarded incomplete questionnaires.

The questionnaire had five components: the first; focused on the parents’ personal data such as age, nationality, education and area of residence. The second component included questions about the child such as age and gender. The third component questioned the parent’s acceptance of LP procedure on their children. It also included questions to evaluate the knowledge of parents about LP like the reason for requesting LP, whether there are other alternatives, when LP is performed and by whom. The fourth component discussed the parents’ knowledge about the safety of the procedure, its complications and from where they derived their information about these complications. The final component requested the parents’ suggestions to improve the acceptance of the procedure.

To assess the parents’ knowledge about LP, we have created an LP ‘knowledge score’ based on the seven questions in the third component which were: the reason for the procedure, if there is an alternative, by whom performed, when, how the sample is taken, the quantity and the age at which LP can be performed safely. One point was given for every correct choice and nil for the wrong choice. Those who scored from 0 to 3 were considered as having poor knowledge of LP procedure and those with score from 4 to 7 were considered knowledgeable.

This study was approved by the hospital ethical committee.

The collected data was processed using Statistical Package for the Social Sciences, SPSS (16.0). Basic statistical parameters were calculated and included frequency, mean and proportions. Chi-square test \((\chi^2)\) was used to test the association between the knowledge and refusal or acceptance of LP. A p-value of \(\leq 0.05\) was considered significant.

RESULTS

A total of 555 questionnaires were distributed during the period of the study. Only 358 (64%) questionnaires were complete and were included in the final analysis. There were 273 (76.9%) mothers and 82 (23.1%) fathers. The median age of the respondents was 31.0 ± 7.0 years (range 19 - 57 years). The characteristics of the participating parents and their children are shown in Table 1. Out of the surveyed parents, only 55 (15.3%) accepted LP, 152 (42.5%) rejected the procedure and 151 (42.2%) preferred taking a second opinion.

Knowledge of parents about LP

Majority of the parents (57.1%) answered that diagnosis is the main reason for performing this procedure while 22.1% did not know why doctors ask permission for this procedure. When asked about other tests that will give the same yield as LP; 24.4% of parents chose CBC, 23% chose physical examination and 17% chose CT scan of the head. Only 15.5% answered that there is no alternative test for LP. Majority of the parents (76.7%) answered that consultants and senior doctors perform this procedure while 18.3% said that any doctor is capable of performing LP. A high proportion (42%) did not know when this procedure should be performed during hospitalization. However, 30% answered that it should be done when the child is not improving on treatment. When asked about the age at which LP can be done safely, 57% answered that the procedure can be done safely at any age.

A majority (79.1%) of the parents felt that the LP is an unsafe procedure while 14.2% felt that it is safe and 6.4% were not sure about the safety of this procedure. The respondents who felt that LP is not safe believed that it may induce paralysis (49.2%), pain (16.6%), infertility (17.2%), deterioration of child’s health (12.8%) and 7.2% did not know what complications were likely to occur. Seventy percent of the parents knew about these complications from relatives and neighbours while 14% of the parents had this knowledge from reading books or newspapers. The audiovisual media was the source of the knowledge about LP complications in 8% of parents who answered the questionnaire.

| Table 1: General Characteristics of the parents and their children |
|-----------------|-----------------|-----------------|
| Characteristics                  | Percentage |
|-----------------|-----------------|-----------------|
| Relation to patient                  |                |
| Mother                    | 76.9           |
| Father                   | 23.1           |
| Nationality                |                |
| Kuwaitis            | 88.2           |
| Arabs                    | 7.8            |
| Non- Arabs              | 4.0            |
| Level of education       |                |
| Primary school   | 17.5           |
| High-school              | 29.0           |
| Post high-school        | 53.5           |
| Residence                |                |
| Capital                   | 31.0           |
| North                     | 36.0           |
| South                     | 33.0           |
| Gender of the child       |                |
| Male                                | 58.0           |
| Female                               | 42.0           |
| Age of the child          |                |
| Neonate                   | 12.5           |
| Infant                    | 49.0           |
| Preschool                 | 25.2           |
| School                    | 13.3           |
Factors associated with LP acceptance
Twenty-seven percent fathers said that they will accept LP as compared to 10.6% mothers (p < 0.0001). Non-Arab nationalities accepted LP (36%) more often compared to Arabs (29%) and Kuwaitis (13%, p = 0.01). More parents with post-high-school education accepted LP (19%) than high-school education (9%) and primary education (8%, p = 0.02). Parents with knowledge score ≥ 4 accepted LP more frequently when compared to parents with score < 4 (30 Vs 10%, Fig. 1).

Improvement of LP acceptance among parents
Among the suggestions given by parents to improve LP acceptance were the utilization of the media (66%), and education by the doctor (28%). An overwhelming majority (80%) of the parents, who initially refused LP or said that they would take a second opinion, would be willing to change their mind and agree on LP based on various factors. Such factors include: full explanation by the doctor using a diagram (78%), meeting a child who underwent LP (11.6%) and talking to parents whose child had LP (7%).

DISCUSSION
Lumbar puncture (LP) is an important and safe procedure to diagnose underlying central nervous system problems, mainly meningitis. Many parents often regard LP as anxiety provoking even if the experience was repeated[4]. Unfortunately, few studies have addressed the attitudes and acceptance by parents of lumbar puncture in children[2,5]. This issue might not be of great importance in the industrialized countries, but the refusal of LP in some countries has resulted as an impediment to the diagnosis of intracranial infections and its management[3].

Our study shows a high proportion of LP refusal among parents in Kuwait reaching up to 80%. There are few studies that address the issue of LP refusal in medical practice. Only one out of 20 (5%) adult patients refused LP in a study of Lyme disease in the United States of America[6]. In another study from Denmark five out of 68 (7%) patients refused LP[7]. Contrary to these low figures of refusal in the United States and Europe, two studies from Malaysia on children with febrile convulsions showed a refusal rate of 29[3] and 24%[2].

Knowledge is one of the important factors that influenced parents’ decisions to accept or refuse LP. This was supported in our study by the increased acceptance rates among parents with high knowledge score and those with post high-school education. The ethnic group was the other factor influencing acceptance of LP decision. Local citizens (Kuwaitis) were more likely to refuse LP when compared to non-nationals. A similar finding was reported in Malaysia where the local Malay ethnic group were more likely to refuse lumbar puncture (p = 0.01)[3]. This may be a result of certain cultural beliefs, or feeling more empowered in front of the health system. Further studies need to be done to determine the role of cultural beliefs in influencing the decisions of parents in accepting LP on their children.

It is crucial to educate parents to increase their knowledge about the safety of this procedure. Half of
the parents in our study thought that LP will result in paralysis of the child. Paralysis and death with LP were concerns of parents in other Asian countries\textsuperscript{[5]}. Since majority of the parents had acquired their erroneous information from non-medical friends, we feel it is important to educate the public through mass media or health campaigns. Increasing the knowledge can be done also with proper explanation by the doctors using visual aids. Similar successful education process was performed to improve compliance to asthma medications\textsuperscript{[8]}

The primary limitation of this study is that the data represent self-reported LP acceptance and refusal based on hypothetical situation. It is likely that the refusal rates would be lower, if parents were actually in a real situation where their child would need an LP. The finding that acceptance rates were significantly higher among those with higher education and knowledge score supports our inference that greater knowledge will translate to greater acceptance rates.

CONCLUSIONS

LP refusal is a common problem in the local setting and is a hindrance to proper management of patients with intracranial pathology. Appropriate measures must be carried out to educate the public about the safety and usefulness of this procedure. This will go a long the way in avoiding unnecessary treatment with antibiotics and prolonged hospitalization of those with suspected bacterial meningitis not confirmed by LP.

ACKNOLEDGMENT

This study was approved by the Ministry of Health Research Committee

REFERENCES

INTRODUCTION

More than 30 years ago, Marton and Saljo[1] used the terms deep and surface level processing to describe the different levels of processing they identified in their research. Later, Entwistle et al contended that the term “processing” to describe the deep and surface level phenomenon under study was inadequate and the term “approach” came to be preferred to describe the differences in these two learning forms.[2]

Students using deep strategy read widely, gather more information, relate to other areas of interest and discuss with others. They study a topic in order to form their own conclusions. These students continue to study most of the suggested readings until they have abstracted the problem solving conclusions. On the other hand, students using surface strategy study just enough to get a pass mark from assessments. Their extrinsic motivation causes premature closure of their study with minimal effort within a short period.[3,4]. Some students may intend to get highest scores from the assessments organizing their time and effort. Entwistle explored the concept of strategic or achieving approach for this type of learning.[5]. In a later study, Kember et al reported that students’ approaches to learning could be described by a model consisting of two main factors namely deep and surface regardless of intermediate approaches[6].

Biggs et al clustered students’ previous learning strategies and motivation together and called them “preferred approaches to learning” which they described as another student related factor[7]. Preferred learning approaches which are associated with student related presage factors can be influenced by other presage factors, learning-focused activities and extrinsic motivation causes premature closure of their study with minimal effort within a short period[8,9].

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learning outcomes and they can affect ongoing learning approaches during the study process[7]. Apart from student-related presage factors, other presage factors are related to the teaching context. Teaching context presage factors include objectives of the learning session, assessment method, classroom climate, teaching method[8] and institutional procedures[9]. In summary, a student’s approach to learning as one of the presage factors may be changed by prior knowledge, abilities, curriculum (including assessment, course structure and content), teaching method, learning climate, and learning outcomes.

This study was designed to reveal learning approaches of undergraduate students at different medical schools with different curricula in Turkey. Furthermore, we compared these different curricula; Hybrid, Integrated and Problem Based Learning (PBL) in terms of the differences of students’ approaches to learning (SAL) if there were any.

Approval of the institutional ethics committee was obtained in 2008.

**SUBJECTS AND METHODS**

To reveal learning approaches of medical students in Turkey, the Revised Two-Factor Study Process Questionnaire developed by Biggs et al in 2001 was chosen[7]. This questionnaire is unidimensional for each subscale and the subscales are internally consistent[7]. It asks 20 items about students’ attitudes to studying and ways of studying. To calculate a student’s deep approach score, the scores of items related to the 1st, 2nd, 5th, 6th, 9th, 10th, 13th, 14th, 17th and 18th questions are added. The sum of the remaining items’ scores provides the surface approach score. Odd number questions probe and score motivation and even number questions probe and score strategy. The maximum possible score is 50 for each of deep or surface approaches consisting of motivation and strategy scores equally whereas the minimum possible score is ten for each approach. The Revised Two-Factor Study Process Questionnaire was translated into Turkish at first in order to solve language problem for participants.

Apart from this, the questionnaire for demographic characteristics consisting of four questions asking student’s gender, high school, parents’ graduation and living area was established and applied in order to see any association between learning approaches and these characteristics.

Three medical schools were chosen. They all accept students achieving high scores from Central Admission Test (CAT) as the only selection criterion. The lowest score to be accepted by Medical School of Pamukkale University was 356,491, whereas it was 358,422 and 361,520 for Akdeniz and Ege university respectively[10]. Learning aims of these three medical schools include graduation of competent doctors in terms of medical knowledge, clinical reasoning and professional skills. During the first half of the six-year program, students attend lectures, laboratory lessons, small group activities and professional skill classes such as development of communication skills and clinical reasoning ability. Apart from these learning activities, medical students at Pamukkale University are at four-hour PBL sessions three times per fortnight during the first three years. Students sit for Multiple Choice Question (MCQ) at the end of each module and each block. At Akdeniz University, the integrated program consists of five thematic blocks in the first two years. Applying Hybrid curriculum, the first week of each block is allocated to PBL modules. Students are assessed by MCQ and Clinical Objective Reasoning Examination (CORE). At Ege University, organ system based themes in 10 blocks are formed by many different disciplines. Additionally, small group activities and simulated patient problem sessions are designed. Students here are assessed by the questions requiring short answers in each block and by MCQ, simulated patient problems, assignments and portfolio at the end of each block. The student / teacher ratio is 2 : 5 for the Medical School at Pamukkale University, 3 : 2 and 3 : 9 for those at Akdeniz University and Ege University, respectively. After institutional ethics approval was obtained, all of Year I and Year II students (n = 1038) at these three medical schools were invited to fill out the questionnaires in late 2008. At that time, 128 of 1038 students in Year I and Year II were at Pamukkale University, 363 at Akdeniz University, and 547 at Ege University.

Statistical analyses were done by using SPSS 13.0. Chi-square test was used for the analysis of the data.

**RESULTS**

Nine hundred and sixty-six out of 1038 (93%) students filled out the questionnaires. Three hundred

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<table>
<thead>
<tr>
<th>Curriculum</th>
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<th>Surface approach</th>
<th>Total students</th>
<th>Statistical analysis</th>
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*Total number (N = 966) is less than total number of students (N = 1038) because of the participation rate.
and thirty-six out of them were in the medical school with Hybrid curriculum, and 514 and 116 were with the Integrated and PBL curricula, respectively. Different numbers of students were caused by the admission intake proportion of universities\(^\text{[10]}\). A total of 72 students did not fill the questionnaires. Twenty-seven out of them were from Akdeniz University, 33 from Ege University and 12 from Pamukkale University respectively.

Table 1 depicts the differences between Hybrid, Integrated and PBL curricula in terms of students’ approaches (\(\chi^2 = 14.349, p = 0.00\)). Learning approaches of the participants in Year I and Year II are shown in Table 2. More participants in Year I have approached their learning activities deeply than those in Year II (\(\chi^2 = 16.417, p = 0.00\)). The results shown in Table 3 importantly reveal that only at the medical school applying PBL more participants in Year II have deep approach than those in Year I (\(\chi^2 = 9.983, p = 0.00\) for Year I and \(\chi^2 = 16.263, p = 0.00\) for Year II, Fig. 1). The significant difference at Year II between students at different schools has been mainly caused by the students at the medical school applying PBL, whereas in Year I, for the students at the medical school with Integrated curriculum.

Looking at the demographic characteristics, we found that there is no association between these characteristics except gender and learning approaches (Table 4).

**DISCUSSION**

Students with a deep approach gather new ideas and organize them within the structure established by previous knowledge in order to deal with real-life problems effectively. On the other hand, students who adopt a surface approach focus on distinct signs in order to memorize easily and fail to relate concepts with real life experiences or to distinguish principles and evidence\(^\text{[11]}\). Furthermore, higher examination scores are highly correlated with a deep approach and lower scores with a surface approach\(^\text{[4,12,13]}\). Tertiary institutions try to develop intrinsic motivation and deep strategies and discourage the use of the surface approach because of these characteristics of learning approaches mentioned above\(^\text{[14]}\). In spite of these efforts students increasingly turn to surface approaches in many institutions\(^\text{[9,15,16]}\). Similarly, 42.8% of the participants in Year II in our study have adopted

<table>
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<th>Student category</th>
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<td>12.8</td>
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*Total number (N= 966) is less than total number of students (N = 1038) because of the participation rate*
a surface approach whereas 30.2% of the participants in Year I have done so (Table 2).

Johnston has shown that learning approaches could change within six months[17] although some authors previously claim that approaches to learning are not changeable[18,19]. Preferred learning approaches of the students participating to the current study could be adopted in previous years at high-school. They might influence the learning strategies of students, particularly in the first year. Richardson reports that first year students in different schools changed their preferred learning approaches after they started at their universities[20]. Furthermore, Presage Process Product model developed by Biggs explains the changeability as well as the significance of learning approaches in the learning process[14]. According to these investigations, looking at the difference between Year I and Year II students would be enough to see, if there is a change in their learning approaches. Actually, the results of the current study have revealed a significant change. In addition, we have planned to follow up these students’ learning approaches a year later, in order to get a clear evidence.

Newble and Jaeger found that the assessment method has a crucial effect on learning processes in medical curricula[21]. Changing both the assessment method and the curriculum could certainly be expected to impact on students’ approaches to learning. By comparing a traditional curriculum and PBL curriculum, Newble and Clarke found that the traditional curriculum was associated with a surface approach whereas PBL fosters a deep approach[22,23]. In our study, we similarly observed statistically significant association between PBL and deep approach. Other previous and recent studies also emphasized that PBL was associated with deep approach[22,23]. They did not compare PBL with Hybrid and Integrated curricula together. Hybrid and Integrated curricula were associated with a surface approach in this study (Table 3). It might be caused by different assessment methods and/or other factors related to the curriculum. We did not include these factors in the current study.

Yan and Kember studied the learning behaviours of students working in groups[24]. They interviewed 57 university students in Hong Kong and found a parallel between student behaviour in groups and learning approaches. Students who engaged in group activities have similar characteristics to deep learners while those who avoided group interaction had surface approach characteristics. Students at the medical school applying PBL mostly study in a small teaching group environment. At the medical school applying PBL in the current study, only seven or eight students and their facilitator meet together for PBL sessions 12 hours fortnightly. At these sessions, they approach their learning topic together. The facilitator is responsible for making each of them engage in group activities.

Most of the researchers consider students’ motivations and strategies as core elements of learning approaches. Hence factors affecting motivation and strategy are expected to impact on their learning approach. Factors such as interest in the topic[25,26], pleasure in the task and self-directed learning are expected to promote intrinsic motivation and therefore, a deep approach to learning[27-29]. Early encounters with clinical problems at PBL might increase interest, pleasure, and accordingly self-directed learning of the participants in our study. An earlier study found that self-directed learning was related to a deep approach while lack of self-directed learning was associated with a surface approach[30].

<p>| Table 4: A comparison of learning approaches and demographic characteristics of all participants* |
|--------------------------------------------------|--------------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Deep approach | Surface approach | Total students | Statistical analysis |</p>
<table>
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<th>%</th>
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<td>0.188</td>
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</table>

*Total numbers are less than 966 due to lack of related information
**Accepting students without any examination score as entering criterion
***Accepting students with high scores on high school selection examination
Watkins reported that unsupportive learning environments with boring classes and extensive pressure promoted a surface approach. It is expected that learning in a small group is less boring than attending a lecture in the big class. The structure of PBL sessions as mentioned above formed more supportive and friendly learning environment at the medical school applying PBL than those at the other schools in the current study. It includes teaching small group sessions and accordingly requires more teachers. Increasing number of teachers decreases student/teacher ratio. Small enrolment size is another reason of low student/teacher ratio at the medical school applying PBL in our study. Low student/teacher ratio is expected at schools applying PBL because more students require more teachers in order to learn in small groups.

Trigwell and Prosser reported that freedom in learning was associated with a deep approach. The students at the medical school applying PBL chose their learning materials without any pressure caused by their lecturers. They shared their own knowledge with their group members in a friendly environment. Establishing a friendly environment is one of the responsibilities of all PBL session facilitators as well as forming an interactive and motivating session. Kember and Gow reported that good teaching sessions were related to a deep approach.

All or some of these factors impacting SAL may affect our findings. Interestingly, all figures relate to Hybrid curriculum implementing PBL. Fifteen percent of all classroom sessions were found between the figures related to Integrated and PBL curricula (Table 1 and 3). This supports the idea that PBL curriculum directs students to adopt a deep approach. Additionally, similar demographic characteristics of the participants may support this idea (Table 4). The difference between learning approaches of male and female students occurring in our study does not ignore this idea because the number of male students is bigger than that of female students at each school and the gender distribution in these three medical schools is similar ($\chi^2 = 1.445, p = 0.485$). If there is an impact of the gender on learning approaches of students, this impact would be similar at these three different schools.

CONCLUSION

We conclude that the application of PBL curriculum is more helpful for developing a deep learning approach than that of Hybrid and Integrated curricula. Looking at the first two years of a traditional six-year undergraduate program is not enough to conclude that Hybrid and Integrated curricula make students adopt a surface approach. Some factors affecting SAL such as encounters with clinical problems will occur often and/or lately in these curricula. Accordingly, measurement of SAL at later years would provide stronger evidence to our claim and will be beneficial for our students.

ACKNOWLEDGEMENT

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REFERENCES

Original Article

Allergic Sensitization in Healthy School Children in Kuwait: An Emerging Public Health Concern

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ABSTRACT

Objective: To determine the current level of sensitization in healthy school children in Kuwait
Design: Prospective cross-sectional study
Setting: Al-Rashid Allergy Center, Kuwait
Subjects: Healthy school-children between the ages of 8 -15 years
Intervention: Skin prick test (SPT) and measurement of serum specific IgE levels

Main Outcome Measures: Skin wheal diameter (> 3 mm) and IgE levels (> 0.35 KIU/l)
Results: 47% of children showed positive specific IgE levels and 38% showed a positive SPT to at least one allergen. Polysensitization was common in the population (IgE 32%, SPT 20%). One in three (31%) children showed sensitization to Bermuda Grass (IgE); around one in five showed sensitization to Prosopis juliflora tree (20% IgE); grass mix (19% SPT); to cockroach (18% IgE, 12% SPT) and just slightly less to cat (15% IgE and SPT). One in 10 healthy children were sensitized to dog (11% IgE, 10% SPT); few to house dust mite (D pteronyssinus) (IgE 8%, SPT 4%); ascars (IgE 7%). The lowest rates of sensitization were to Alternaria alternata (IgE 4%, SPT 2%); aspergillus (SPT 4%); and cladosporium (SPT 2%). Frequent, severe sensitization (Classes 3 - 6 for specific IgE) was found for Bermuda Grass (16%), prosopis tree (6%) and cat allergen (5%).

Conclusion: Kuwait may be an example of conflict between two aspects of public health endeavour in a desert environment. Practices that make the desert habitable, viz, aorestation and air-conditioning may be the same ones that encourage exposure to allergens, allergic sensitization and allergic disease.

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Allergic diseases such as asthma, allergic rhinitis (hay fever) and atopic eczema are now among the most prevalent diseases in the world[1-4].

However, population levels of allergic sensitization have been far less well studied than levels of allergic diseases. Therefore, the current study is a useful contribution to the literature. The study also adds importance to the few but rapidly increasing number of studies of allergic disease and allergic sensitization in the Arab World where possible associations between sensitization and allergic disease resulting from rapid modernization and environmental change may provide valuable lessons that can be generalized to many other situations worldwide.

We report on a study of allergic sensitization in normal healthy Kuwaiti school children, which investigates frequency of sensitization to particular allergens, frequency of mono and polysensitization,
levels of IgE and total IgE. Other possible environmental associates in this modern desert environment are also discussed[6].

**SUBJECTS AND METHODS**

To study the prevalence of sensitization among healthy children, three hundred and three healthy children (303) were enrolled. These healthy children were selected mainly from schools (n = 281); a few (n = 22) were selected from health clubs. The study was conducted in Kuwait from October 2006 to May 2007.

Permission for the study procedure and the recruitment of the school pupils was sought from and agreed by the Ministry of Health, the Ministry of Education and its regional directors. It was agreed that the best way to recruit healthy children would be to send a request to the parents of all children asking their permission to enrol their child in the study. If the study procedures were acceptable to the parents/guardian of the child, then the parent/guardian was asked to sign a consent form which included the name, age and address of the student including the telephone number. Screening questions were included asking parents to identify, if the child was suffering from any current or chronic disease.

In total, 10,000 copies of the request form were prepared and distributed to the children’s parents of four schools in each of the five educational district areas. It was assumed that parents (n = 8620) who did not return the form were unwilling for their child to participate in the study. Out of all the forms sent out, 1380 forms were returned with 730 giving permission for the study.

The forms received were first reviewed for parental consent, age limit (i.e., 9-15 years old) and to exclude any children suffering from any chronic disease. A total number of four hundred and six (n = 406) children were within the inclusion criteria with parental consent but only two hundred and eighty-one healthy children (n = 281) from schools were able to participate.

When arranging appointments with each family, confirmation was made with each parent/guardian that the child was not suffering from a) any chronic/persistent respiratory disease, b) any illness contraindicated by the study procedures (i.e., severe allergic reaction), c) any illness that might lead to erroneous results and d) was not taking medication that could affect any of the study measures (e.g., anti histamines). These points were cleared with each parent/guardian of the child.

The Allergy Center in Kuwait was the base for the study (laboratory, parents waiting area and three clinic rooms). As required by the hospital authorities, there was an emergency arrangement at the site at all times (i.e., availability of a medical doctor, oxygen, a nebulizer, salbutamol inhaler, adrenaline and hydrocortisone injection).

All study participants underwent the following procedures: Assessment of IgE mediated sensitization by: SPT and Specific serum IgE. In addition, a family and environmental questionnaire enquired about smoking at home, current and past pet ownership and pet contact outside home, home air conditioning, type of cooking fuels at home, type of home and its age, floor covering in bedrooms and living rooms; family history of atopy, history of breast feeding, history of allergic diseases and immunizations and demographic characteristics: (age, sex, and place of birth of the child).

All the 303 healthy children were skin tested with nine allergens (cat, dog, grass mix, Aspergillus, cockroach, house dust mite, trees mix, Cladosporium, Alternaria alternata) and a positive and negative control. A wheal diameter of 3 mm or more was considered as positive test[6,7].

Blood (10 ml) was obtained from 285 healthy children. The remaining, (18 children) refused to have a blood test, either due to panic at the time of blood sampling or lack of parental consent for blood tests. Serum was separated from the whole blood by centrifuging the blood within 30 - 60 minutes of collecting the blood. The whole cells were discarded and serum was kept in the freezer (at -20 °C) in the hospital. The serum was assayed for both total and specific IgE. Allergen-specific IgE determinations were made with the CAP-RAST test. This is a fluorenyl-monochromatization of the conventional RAST[8]. The assay was calibrated against the WHO IgE reference serum 75/502. The working range of the assay was 0.35 - 100 KIU/l. In both tests, serum samples and standards were incubated with allergen CAPs and the bound antibody after washing was reacted with enzyme-labeled anti-IgE antibody. Specific IgE was tested for Bermuda grass, Prosopis juliflora, dog, Alternaria alternata, house dust mite, cockroach and Ascaris.

All SPT and IgE results and responses to the questionnaire were coded and entered into SPSS and all were triple checked to ensure there were no entry transcription errors.

**RESULTS**

The study showed that a large proportion (nearly half, 47%, 133/285) of the normal healthy school children showed positive specific IgE to at least one allergen from the eight tested, and over a third (38% 114/303) showed positive SPT to the nine allergens tested by this method (Table 1).

Polysensitization was apparent in one third of this population measured by detectable specific IgE (32%, 90/285), which was two thirds of those showing any IgE sensitization (90/133, 68%). SPT measurement
showed 20% (61/303) with polysensitization present in half (61/114, 54%) of those showing positive SPT sensitization (Table 1).

High levels of more severe sensitization (Classes 3 - 6 for specific IgE) was found for Bermuda Grass in half (53%, 46/87) of those sensitized to it; only slightly fewer (42%, 5/12) of those sensitized to Alternaria alternata; in a third (33%, 14/43) of those sensitized to cat, and in a quarter (28%, 16/58) of those sensitized to Prosopis Juliflora tree. Only around 17% showed severe IgE classes 3 - 6 for cockroach (8/50, 16%), for house dust mite (4/24 17%) and for Ascaris (4/22, 18%). Out of those sensitized to dog very few showed severe sensitization (1/30, 3%) (Table 2).

Frequencies of sensitization to specific allergens are shown in Table 2 (specific IgE) and Table 3 (SPT). One in three (31%) children showed sensitization to Bermuda Grass (IgE); around one in five showed sensitization to Prosopis Juliflora tree (20%, IgE); to grass mix (19%, SPT); to cockroach (18% IgE, 12% SPT); and just slightly less to cat (15%, IgE and SPT). One in 10 healthy children were sensitized to dog (11% IgE, 10% SPT); and slightly fewer to house dust mite (IgE 8%, SPT 4%); Ascaris (IgE 7%). The lowest rates of sensitization were to Alternaria alternata (IgE 4%, SPT 2%); aspergillus (SPT 4%); and Cladosporium (SPT 2%).

**DISCUSSION**

The monosensitization, the polysensitization rate and the total IgE suggest that there is a large pool of children, age 8 – 15 years (nearly half, i.e., 47% on IgE measures, 38% SPT) sensitive to one allergen or more, and a considerable number with multiple and/or a severe level of sensitization. This is the first study solely on a healthy child population in Kuwait. There has been one healthy young adult epidemiological survey of allergic sensitization in Kuwait, in which, half were found to be already sensitized to one or more inhalant allergens, and total IgE level was somewhat lower at GM 66 KU/1 [19].

Total IgE in normal healthy children in the current study with a geometric mean of 92 KU/l (CI 170 - 277) is higher than a number of other studies in children in the USA [10]. An earlier study of adults in Kuwait found very much lower rates of sensitization in healthy adults of GM 44 U/l (CI 11.7 - 162.2) [11], and a similar rate (132 KU/l) in one very small Kuwait study with 33 healthy adults [12]. Interestingly the only two studies so far found with a similar high level of total IgE in healthy children of similar age
Normal healthy children 8-15 years of age in Kuwait are considered unfavorable for the development and increase in allergic diseases such as asthma. The prevalence of allergic diseases appears to have dramatically increased within the general population, with rates ranging from 15 - 44%. Asthma (wheezing) among school children has been recorded at 26%. A study among 13-14 year-old school children in Kuwait showed that asthma admissions to hospital increased from 9 to 15% over the period of 1982-85. This increase is attributed to the development and symptomatic expression of allergic diseases, which is well documented in adults who claimed never to have had any allergic disease or symptoms.

It seems that allergic diseases were rare in Kuwait until around the mid-1950s, and the first concrete evidence of a rapid increase in allergic disease in Kuwait was the study of Strannegard and Strannegard[20], who showed that within a period of three years (1982 - 1985), asthma admissions to hospital among Kuwaiti children had increased from 9 to 15% of all emergency admissions. A study among 13-14 year-old school children has found a prevalence of asthma (wheezing) to be as high as 26%[21]. Kuwait is thus at the upper end of prevalence rate of allergic disease worldwide, with rates ranging from 15 - 44% of the general population[3,8]. Overall, the prevalence of allergic diseases appears to have rapidly increased in Kuwait, ominously in parallel with urbanization and development[20,22]. The harsh climatic conditions found in Kuwait are considered unfavorable for the availability of airborne allergens such as house dust mite, pollen, and mould[23].

A number of studies have now firmly established that some of the most prevalent sensitizing allergens are pollen of local plants, especially Mesquite (Prosopis), Bermuda grass, Chenopodium, Eucalyptus, Acacia and Date palm[9,22,24]. These are horticultural plants, intended to either provide shade/aesthetics or to bind sand. This involved a massive importation of non-native plants, and cultivation of others that are native to the Arabian desert. Incidentally, many of these plants have turned out to be sources of potent sensitizing pollens. In the current study, the highest rates of severe sensitization in healthy school children were found for Bermuda grass and Prosopis tree. Recent data has shown sensitization to pollens by specific IgE measurement or SPT detected in 87 - 92% of patients with allergic rhinitis and/or asthma[24,25]. Reassuringly, the government has responded to these findings by initiating a program of systematic replacement of many of the flowering plants with non-flowering alternatives.

Development has also affected the indoor environment with a significant impact on the availability of indoor allergens. The extensive use of air-conditioners has dramatically altered the indoor environment. House dust mites which could not tolerate the high ambient temperatures and low humidity, now thrive. Thus, unlike 20 years ago, when sensitization to house dust mite was found only in 1.5% of allergic patients[23], today the rate is in the range 24 - 35%. Cockroaches and moulds probably followed the same pattern[24,25].

There is also the issue of pollution arising from emissions from automobiles as well as from the petroleum industry activities in the country. The role of fossil fuel combustion products as an immunological adjuvant in allergen sensitization and as risk factors for the development and symptomatic expression allergic diseases is well documented[26,27].

### Table 3: Sensitization rates in healthy children 8-15 years by SPT

<table>
<thead>
<tr>
<th>Sensitization agent</th>
<th>Normal healthy children 8-15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass mix</td>
<td>(56/303) 19%</td>
</tr>
<tr>
<td>Cat</td>
<td>(46/303) 15%</td>
</tr>
<tr>
<td>Cockroach</td>
<td>(35/303) 12%</td>
</tr>
<tr>
<td>Dog</td>
<td>(32/303) 10%</td>
</tr>
<tr>
<td>Trees mix</td>
<td>(15/303) 5%</td>
</tr>
<tr>
<td>House dust mite</td>
<td>(13/303) 4%</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>(12/303) 4%</td>
</tr>
<tr>
<td>Cladosporium</td>
<td>(7/303) 2%</td>
</tr>
<tr>
<td>Alternaria alternata</td>
<td>(6/303) 2%</td>
</tr>
</tbody>
</table>

The current prevalence of mono-sensitization among healthy children, aged 9 - 15 years (18% by SPT and 15% by serum specific IgE) is consistent with previous results showing a high prevalence of atopy in Kuwait[15-17] and is in agreement with data from other studies[18,19].

It seems that allergic diseases were rarely found in Kuwait until around the mid-1950s[10]. The first concrete evidence of a rapid increase in allergic disease in this environment was the study of Strannegard and Strannegard[20], who showed that within a period of three years (1982 - 85), asthma admissions to hospital among Kuwaiti children had increased from 9 to 15% of all emergency admissions. A study among 13-14 year-old school children has found a prevalence of asthma (wheezing) to be as high as 26%[21]. Kuwait is thus at the upper end of prevalence rate of allergic disease worldwide, where rates range from 15 - 44% of the general population[3,8]. Overall, the prevalence of allergic diseases appears to have rapidly increased in Kuwait, ominously in parallel with urbanization and development[20,22]. The harsh climatic conditions found in Kuwait are considered unfavorable for the availability of airborne allergens such as house dust mite, pollen, and mould[23].

A number of studies have now firmly established that some of the most prevalent sensitizing allergens are pollen of local plants, especially Mesquite (Prosopis), Bermuda grass, Chenopodium, Eucalyptus, Acacia and Date palm[9,22,24]. These are horticultural plants, intended to either provide shade/aesthetics or to bind sand. This involved a massive importation of non-native plants, and cultivation of others that are native to the Arabian desert. Incidentally, many of these plants have turned out to be sources of potent sensitizing pollens. In the current study, the highest rates of severe sensitization in healthy school children were found for Bermuda grass and Prosopis tree. Recent data has shown sensitization to pollens by specific IgE measurement or SPT detected in 87 - 92% of patients with allergic rhinitis and/or asthma[24,25]. Reassuringly, the government has responded to these findings by initiating a program of systematic replacement of many of the flowering plants with non-flowering alternatives.

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There is also the issue of pollution arising from emissions from automobiles as well as from the petroleum industry activities in the country. The role of fossil fuel combustion products as an immunological adjuvant in allergen sensitization and as risk factors for the development and symptomatic expression allergic diseases is well documented[26,27].

## CONCLUSION

With 15 - 44% of the general population known to be allergen sensitized in various parts of the world[3,8], and the current study showing nearly half the children aged 8 - 15 years in Kuwait sensitized to at least one inhalant allergen, it needs to be acknowledged that allergen sensitivity has become a serious public health problem for children. Allergic diseases are bound to exacerbate in these individuals, (i.e., children and adults) exist in this population. Although not all atopic individuals eventually develop allergic disease, they represent a particularly high-risk group, given the close association between the prevalence of allergic diseases such as asthma and rhinitis and polysensitization (atopy)[15-17].

The current prevalence of mono-sensitization among healthy children, aged 9 - 15 years (18% by SPT and 15% by serum specific IgE) is consistent with previous results showing a high prevalence of atopy in Kuwait[15-17] and is in agreement with data from other studies[18,19].

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the way sensitization influences the development of allergic diseases. Work is also needed to study ways of improving self-management of allergic disease when it does occur, and to study further possible protective factors that may reduce the incidence of sensitization.

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Original Article

Violence against Medical Staff: Prevalence and Effects of Violence against Psychiatrists in Kuwait

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ABSTRACT

Objectives: To determine the prevalence and effects of violence against psychiatrists in Kuwait

Design: Questionnaire-based study

Settings: Hospital for Psychological Medicine, Kuwait

Subjects: All the consenting psychiatrists working in the only psychiatric hospital in the country were administered two questionnaires; a 12-item frequency-weighted questionnaire to measure the rates, frequency, and severity of violence and another 5-item, duration-weighted questionnaire to measure the effects of violence.

Main Outcome Measures: 1) The frequency and the type of the violent incidents and 2) the after effects of violence on the victim, over the past one year

Results: Fifty-three (69%) out of 77 psychiatrists completed and returned the questionnaires. Fifty-one (96%) psychiatrists reported having experienced one or another kind of violent incident; twenty-three (49%) experienced physical violence involving a single act of violence and another nineteen (36%) were subjected to physical violence involving multiple assaults or use of a weapon or a gun. The consequences of violence, in order of frequency, included flashbacks (53%), taking time off (41%), fearfulness (32%), and sleeplessness (26%).

Conclusions: The prevalence and severity of violence against psychiatrists are higher than the emergency department (ED) doctors but after-effects of violence were more severe amongst the ED doctors. Introduction of formal protocols, documentation of violent incidents, prosecution of offenders, and organizational support are some of the measures likely to help bring safety at workplace. In view of the small sample size, firm conclusions are difficult to draw.

KEY WORDS: doctors, emergency department, psychiatrists, violence

INTRODUCTION

Workplace violence is increasingly being recognized as a serious health problem in the medical field. Formal reports of violence against health staff are on the increase and the healthcare providers have expressed their concern about the safety of the medical staff at work. The Department of Health in UK has launched a Zero Tolerance Zone Campaign and sent a clear message to the public that aggression, violence, and threatening behavior would no longer be tolerated in the National Health Service. The Department of Health in UK has launched a Zero Tolerance Zone Campaign and sent a clear message to the public that aggression, violence, and threatening behavior would no longer be tolerated in the National Health Service. The consequences of violence against the medical staff have variously been described to include traumatic flashbacks of the incident, sleep and appetite disturbances, feelings of depression, low morale, deterioration in the service delivered to the patients, and rapid staff turnover.

True incidence of aggression against doctors is difficult to determine from the literature. The reported incidence of violence has varied from 54 to 79%. Among the hospital doctors, those working in psychiatry, accident and emergency departments (ED), and obstetrics and gynecology have been reported to carry the highest risk of violence. Widespread variation in rates between doctors working in different areas and among different groups of patients has been reported. The severity of incidents recorded varies in different studies as do the definitions of what constitutes violence. Lastly, considerable underreporting of violence has been described as many doctors, for a variety of reasons, may not see any point in reporting violent incidents and even expect to encounter it as part of their normal work.

Health and Safety Executive defined violence as, any incidence in which an employee is threatened or assaulted by a member of the public in circumstances arising out of the course of his or her employment. Verbal abuse and threats were, as identified by health and safety executive, the commonest types of
incidents. We decided to use this operational definition of violence since its comprehensiveness encompasses verbal and physical assault on the one hand, and manifest and imminent, on the other.

Although some reports of violence against doctors and nurses in general hospitals, and accident and emergency departments have been published during the last decade[9-12], no data exist about violence against psychiatrist, a high risk area, in Kuwait. Kuwait is an Arab country with mid-year population of 3,399,637; 30.75% are Kuwaitis and expatriates, mainly from the Asian subcontinent (39%) and other Arabs (30.25%) make up rest of the population[13]. The psychiatric services are hospital based with once weekly clinics in the six regional general hospitals. The psychiatric hospital has 691 beds and provides outpatient services on a daily basis and runs an emergency walk-in clinic round the clock. In addition, it has a drug addiction treatment facility with 225 beds. The hospital is staffed by 77 psychiatrists, 61 psychologists, seven social workers, and 451 nurses[14]. The objectives of this study were to determine the prevalence, degree and the effects of violence on all doctors serving in the Hospital for Psychological Medicine in Kuwait.

SUBJECTS AND METHODS

Sampling

The sample consisted of all doctors working in the hospital. Following approval from the ethical committee, a written consent was obtained from each of the participants. The questionnaires were distributed among the participants and retrieved during the next four weeks.

Instruments

Violence Indices Scale: A 12-item, frequency-weighted questionnaire was used to measure rates, frequency, and severity of violence. The questionnaire, devised and validated by the authors[9], had previously been used to study violence against doctors[9-12]. The items are arranged in the order of severity of acts of violence beginning with minor verbal insults to more serious acts like shooting with firearms. Each question is weighted by the frequency of occurrence during the past year and the response format includes six choices: once, twice, thrice, 3-5 times, 6-10 times, 11-19 times, 20 or more times. The internal reliability of the questionnaire was tested using Cronbach’ Alpha.

Violence Effects Scale: A five-item, duration-weighted questionnaire was used to measure the effects of violence at work. The items have been derived from the most commonly reported after-effects by the staff subjected to violence incidents. The five related items selected included reliving experience (flashbacks), sleeplessness, depression, fearfulness, and time taken off work. The response format consists of six choices; up to 1 week, 1-2 weeks, 2-3 weeks, 3-4 weeks, and 4 weeks or more. The internal reliability of the questionnaire was tested using Cronbach’ Alpha.

The prevailing practices and the views of the nurses on violence was measured through a five-item questionnaires. The questions related to their concern about violence, any training that they might have received to deal with violent or potentially violent patients, any hospital policy regarding reporting of such incidents, and if the police had charged any offenders following aggressive incidents. Lastly, they were asked if they thought training to deal with potentially violent situations would be useful.

Procedures

Categorization of violence: The items on the 12-item questionnaire were arbitrarily divided into three parts:

A. Responses to items 1-4, involving verbal insults or gestures implying imminent acts of violence, are regarded as mild.
B. Items 5-8 involving single acts of physical violence unlikely to result in serious injury are considered to indicate violence of moderate severity.
C. Items 9-12 entailed multiple acts of violence or the use of a knife or a gun likely to cause a serious or fatal injury has been classified as severe in type.

Computation of violence indices: The violence indices can be expressed as either rates or scales. The rates are binary variables and the scales are continuous variables. The incidence rate has the advantage of unambiguous meaning and the ease of understanding by the general public. The rates, however, do not reflect the degree of violence. For this reason frequency of violence in each of the three categories, mild, moderate, and severe, was also computed. The frequency reported for each violent incident, being a continuous variable, was computed by taking midpoints from the choice format: 3-5 = 4, 6-10 = 8, 11-19 = 15, 20 or more = 22.5. Both sets of data expressing rates as well as frequency are presented. The data was analyzed on SPSS.

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

RESULTS

Fifty three (69%) out of 77 doctors (excluding those on leave abroad) completed the questionnaires. The male: female ratio was 38: 2 and the age ranged from 27 - 63 years (mean = 46.94; SD = 9.02). The Cronbach’s Alpha value, based on standardized items, for the ‘Violence indices’ and the ‘Effects’ scales were 0.825 and 0.750, respectively.
Prevalence of violence

Fifty-one (96%) psychiatrists reported having experienced one or more violent incidents during the last year. Twenty-six (49%) psychiatrists experienced both mild and moderate degrees of violence; and nineteen (37%) reported all three; mild, moderate, and severe forms of violence. In the mild form of violence, verbal insults (93%), threatening to hit (76%), smashed or kicked something (70%), in that order, were the most commonly reported incidents. Amongst the incidents involving physical assaults, ‘hit with something’ (42%), ‘pushed or grabbed’ (40%), and ‘threatened with knife/gun’ (26%), were the most frequently reported (Table 1).

Out of the total number of estimated incidents, more than three quarter (78%; n = 529) were mild (verbal insults or threats of violence), 16% (n = 111) were moderate (involving single act of violence unlikely to cause serious injury) and 6% (n = 38) were severe (involving multiple physical assaults or the use of knife or gun likely to result in serious or fatal injury, Table 2).

Effects of violence (Table 3)

About half of the doctors suffered from ‘flashbacks’; one third became ‘depressed’; a quarter experienced sleeplessness and a similar number took time off. Flashbacks and fearfulness persisted in four doctors beyond four weeks and one doctor took off for more than a month as an aftermath of experiencing violence at work.

Comparison with the previous study (Table 5)

Comparison with a similar study carried out in the ED of all the six general hospitals eight years ago showed that the estimated number of incidents involving single act of violence (moderate) and also those involving multiple acts or use of a weapon or gun (severe) are much higher amongst psychiatrists.
Comparison with doctors working in emergency
department (ED)

<table>
<thead>
<tr>
<th>Violence</th>
<th>Psychiatrists N = 53</th>
<th>ED doctors N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>51 (96)</td>
<td>87 (86)</td>
</tr>
<tr>
<td>Moderate</td>
<td>26 (49)</td>
<td>22 (21)</td>
</tr>
<tr>
<td>Severe</td>
<td>19 (36)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flashbacks</td>
<td>26 (49)</td>
<td>51 (50.5)</td>
</tr>
<tr>
<td>Sleeplessness</td>
<td>14 (26)</td>
<td>49 (48.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>17 (32)</td>
<td>59 (58)</td>
</tr>
<tr>
<td>Fearfulness</td>
<td>2 (3.7)</td>
<td>44 (43.6)</td>
</tr>
<tr>
<td>Time off</td>
<td>14 (26.4)</td>
<td>32 (31.7)</td>
</tr>
</tbody>
</table>

* This study had reported that 86% of the ED doctors experienced verbal insults, 28% physical attacks, and 7% repeated physical assaults likely to cause serious or fatal injury. 86% of those exposed to violence suffered from one or more of the symptoms consisting depression, flashbacks, insomnia, and taking ‘time off’[10].

Higher rates of violence against our psychiatrists[23], some authors argue[24] that violence may be associated with ‘sick’ organization, overcrowded wards, and unsuitable environmental conditions for patients rather than patient psychopathology. The psychiatric services in Kuwait are grossly inadequate: for a mid-year population of 3,399,637, there are 0.29 psychiatrists, 0.17 psychologists, 0.02 social workers, and 1.32 psychiatric nurses per 100,000 population[25]. The community psychiatric services are virtually non-existent. The services are restricted to the main psychiatric hospital with some outpatient clinics in general and specialty hospitals. The provision of services at primary health and community level is absent[25]. Lastly, like in any other developing country, the stigmatizing connotations associated with, and limited awareness about, psychiatric illnesses in the country, may have played some role in the higher rates of violence found in our group of psychiatrists[26].

Although the rates and severity of violence were lower in the ED doctors, the effects of violence were more severe in them. More ED doctors suffered from after-effects and also, the effects lasted longer in them (Table 5). This may partly be explained by the very nature of the work in the two groups: the psychiatrist may perceive aggressive behavior as one of the possible symptoms of the psychiatric disorders, accepting it as ‘part of the job’. Moreover, by virtue of their own training, psychiatrists may be better equipped to cope with, and work through, consequences of violent incidents at workplace. It may be that the common factor linking staff who are victims of violence in psychiatric setting is the belief that they can cope and are coping, whatever the circumstances. The illusion of coping may be a weak point in their professionalism[19].

Most (92.5%; n = 46) of our psychiatrists regarded training to deal with violence as ‘useful’; a substantial number (81%; n = 42) remained worried about violence at workplace; twenty-one (39%) had received training to deal with violence at work and a similar number had been advised to report violent incidents. Interestingly, in 139 possible cases involving physical violence, the offender was charged only twice. This may perpetuate under-reporting of violent incidents at work. The introduction of formal protocols to document violent incidents, obligatory recording of such incidents, and prosecution of the offender by the service provider rather than the victim, may help alleviate some of the concerns of psychiatrists regarding safety at workplace[10].

The management of health care workers is an important issue which merits far more attention than it seems to be receiving at the present. Lack of respect for and trust in local organization of care, among others, has been identified as an important determinant of mental health professionals’ vulnerability to violence
at workplace[27,28]. The management ought to take initiative in helping individuals by providing them with easy access to experienced supervisors who could help them reflect on their work. It promotes a sense of being valued, assists them to develop reflective skills, and ensures that they receive proper training with positive impact of service on clients, colleagues, and the working environment[15].

It is important to mention some limitations of this study. Firstly, our sample size was small which makes it difficult to draw firm conclusions. Secondly, the responses to our questionnaires were subject to recall bias. And lastly, the measures used to determine the after-effects of violence did not include standardized instruments. However, our sample constituted all the consenting psychiatrists working in the only hospital in the country, and the severity of violence was measured both in terms of frequency as well as the type of violent incidents directed against psychiatrists. Our findings have important implications for the service providers. Further prospective studies, to define the degree of workplace violence and its psychological consequences, using formal psychiatric interview or the standardized instruments, are needed.

CONCLUSION

The prevalence and severity of violence against psychiatrists are higher than the emergency department doctors, whereas the after effect of violence were more severe amongst the emergency doctors.

ACKNOWLEDGMENT

This study was supported by the Ministry of Health Research Committee, Kuwait

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Case Report

McKusick-Kaufman Syndrome: A Rare Case Report with Review of Literature

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ABSTRACT

Hydrometrocolpos (HMC), postaxial polydactyly (PAP) and congenital heart disease (CHD) are well documented features of the McKusick Kaufman Syndrome (MKKS). This is a rare autosomal recessive disease which may be associated with other multiple malformations. MKKS is an extremely rare cause of non-immune hydrops with only one case reported in the literature. We report the first case of MKKS in Kuwait who presented with non-immune hydrops.

KEY WORDS: hydrometrocolpos, McKusick Kaufman syndrome, non-immune hydrops, polydactyly

INTRODUCTION

McKusick-Kaufman syndrome (MKKS, OMIM #236700) was first reported by McKusick in 1964[1] as a triad of hydrometrocolpos (HMC), postaxial polydactyly (PAP) and congenital heart disease (CHD), in an Old Order Amish sibship. Ever since, more than 90 cases have been reported in the literature[2]. MKKS is allelic to Bardet Biedl syndrome (BBS, with over 500 cases reported in the literature). BBS consists of retinitis pigmentosa (hallmark), mental retardation, hypogonadism, obesity and renal anomalies[2]. Hydrocolpos and PAP may also be present. MKKS was linked to a mutation on chromosome 20p12 by Stone in 1998[3]. The gene was cloned by Stone in the Amish population[4]. For non-Amish females without a family history, HMC with distal vaginal agenesis or a transverse vaginal septum and PAP are considered sufficient clinical evidence to diagnose MKKS at birth[5]. BBS type 6 also has a mutant MKKS gene (5-10% of BBS cases). Prognosis for mental development in MKKS is favorable[6]. Non-immune hydrops usually carries a poor prognosis and in 75% of the cases an etiology can be found with full genetic and pathological evaluation[6].

CASE REPORT

An eight-day-old female neonate (gestational age 30 weeks) was transferred to our hospital. Her mother was a 28-year-old para 2 + 0 Kuwaiti lady. The parents were first cousins with no family history of any illness. Antenatal ultrasound at 29 weeks gestation showed fetal ascites, anhydraminos, distended urinary bladder, hydrenephrosis and a large cystic mass adjacent to the bladder. An ascitico-amniotic shunt was placed to drain the ascites in utero. Four days later the mother developed antepartum hemorrhage with placental abruption and was delivered by an emergency Cesarean section.

Our patient had a birth weight of 2.1 kg and an Apgar score of 3 and 6 at one and five minutes respectively. She had generalized edema, hydrops, low set ears, depressed nasal bridge, downward slanting eyes, postaxial polydactyly in all limbs (Fig. 1 and 2), marked abdominal distension (Fig. 3) and a single perineal orifice. She was intubated and ventilated. She had an obstructive uropathy (serum urea 30 mmol/l, creatinine 275 μmol/l). Two urinary catheters (suprapubic and perineal) were placed. Paracentesis was done with the ascitic fluid showing white cell count of 158/mm³ (neutrophils 32%, lymphocytes 68%), red cell count of 600/mm³, protein 35g/dl, LDH 228 IU/l, creatinine 288 μmol/l and culture no growth. The edema subsided and the abdominal distension resolved gradually but worsened on removing both catheters. Therefore, the perineal catheter was re-inserted.

Serial abdominal ultrasounds showed resolving hydrenephrosis. Genitogram and cystoscopy showed an urogenital sinus. Magnetic resonance (MRI) of the abdomen showed hydrometrocolpos (Fig. 4) and brain computerized tomography (CT) was normal. Echocardiogram showed atrial septal defect. Karyotype was 46XX and fluorescent in situ hybridization (FISH) was normal. Retinal exam was normal. The renal functions improved. The patient had a urinary infection with sepsis and was treated with antibiotics. Renal function gradually normalized.

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Vaginostomy was done at 60 days of life draining 100 ml of mucinous fluid with urine. The patient was discharged at 73 days of life on full feeds with a normal abdominal girth. She was seen in the outpatient clinic twice and was gaining weight with appropriate development for corrected age.

DISCUSSION

MKKS consists of HMC (70% in Amish cases, 95% in non-Amish cases), PAP (60% in Amish cases, 98% in non-Amish cases), CHD (15% in both groups) as per Stone et al.[3]. MKKS gene is mutant in Amish patients[4]. This gene is bounded by markers D20S894 and D20S175. This gene encodes a protein similar to chaperonin family suggesting its role in limb, cardiac and reproductive system development. It is related to the JAG 1 gene which is mutant in Alagille 1 syndrome. FISH is done to detect mutations using bacterial artificial chromosome 255F12, 19H8 and 57P3 from chromosome 20p12 as probes[4].

HMC is caused by distal vaginal atresia or a transverse vaginal septum leading to accumulation of cervical secretions due to maternal hormones. Other genitourinary anomalies were reported, such as urogenital sinus (36%), ectopic urethera, absent vaginal or uretheral openings, genitourinary tract fistulae in females and prominent scrotal raphe with glandular hypospadias in males[2].

Polydactyly is usually postaxial, in the hands (commonest 29%), the feet or all four limbs. Polydactyly may be heptadactyly. Syndactyly, brachydactyly and mesoaxial polydactyly are less common[2]. CHD includes common atrioventricular canal, atrial and ventricular septal defects, tetralogy of Fallot, left hypoplastic heart and patent ductus arteriosus. Gastrointestinal anomalies include Hirschsprung disease[5], imperforate anus and tracheosophageal fistula[7].

Renal involvement may include hydronephrosis, hydroureter, cortical cysts, atrophy and corticomедullary dysplasia but without chronic renal failure[2]. There were no cases of retinitis pigmentosa[2]. Development was normal[5]. One 16-year old female patient gave birth to male child[8]. Craniofacial dysmorphology is rare and inconsistent[2] including cleft palate, bifid manubrium, albinism and hearing impairment.
Non-immune hydrops with MKKS as in our case was reported by Rosen in 1991[9]. The patient had HMC with urogenital sinus. Antenatal ultrasound showed polyhydraminos (due to partial or intermittent urinary obstruction) and a persistent full bladder which eventually turned out to be the HMC, stressing the importance of considering HMC, if there is a persistent bladder-like mass on serial antenatal ultrasounds.

Due to the phenotypic overlap between MKKS and BBS, it is important to follow the patients up to five years of age for final diagnosis. This is due to the fact that retinitis pigmentosa, obesity and mental retardation in BBS are age dependent with cone/rod dystrophy starting after the first year of life as detected by electroretinogram. BBS can be diagnosed in infancy, if there is hypoplasia of ovaries, uterus and fallopian tubes. David et al reported nine cases diagnosed as MKKS in infancy which turned out to be BBS during follow up in childhood[10]. Faraj and Teebi reported the incidence of BBS in Kuwaiti Bedouins to be one in 13,500, but MKKS has never been reported from Kuwait to the best of our knowledge[11].

Other differential diagnosis of MKKS include Pallister Hall syndrome (hypothalamic hamartoblastoma, polydactyly, hydrocolpos, imperforate anus) as reported by Unsinn[12], Ellis Van Creveld syndrome (PAP, CHD, natal teeth, long narrow chest, acromelia), Varadi syndrome (polydactyly, short stature, cleft palate, mental retardation) and Mayer Rokitansky Syndrome (mullerian fusion defect, tetralogy of Fallot, PAP and renal anomalies)[13].

Prognosis is favorable for vision and development but complications may occur such as urinary infections, incontinence, obstruction, renal tubular acidosis, hypertension or vaginal re-stenosis. Follow up of MKKS patients with growth, development, blood pressure, renal function and ERG should continue into childhood to rule out BBS. Head MRI is needed to detect a silent hamartoma[13].

CONCLUSION

Our case report highlights the importance of considering the diagnosis of MKKS in any patient with HMC / PAP but the diagnosis should not be finalized before the age of five years so as to rule out BBS. Hypoplasia of the upper female genital tract may help in differentiating the two conditions.

It is important to consider HMC, if serial antenatal fetal ultrasounds show a persistent full fetal bladder as early intervention can prevent obstructive uropathy.

REFERENCES

Case Report

Tuberculosis of the Shoulder: An Unusual Presentation

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ABSTRACT

There is a recent increase in the incidence of musculoskeletal tuberculosis, especially among the homeless, the immigrant population, the immunocompromised and also due to emerging multidrug-resistant strains of *Mycobacterium tuberculosis*. Osteoarticular tuberculosis poses a diagnostic dilemma to the clinician. Advanced disease closely mimics other granulomatous diseases, infections and even malignancy. Unfortunately, delayed diagnosis of tuberculous infection in the extra-axial skeleton leads to progressive joint deformity and destruction. Radiological imaging while not being specific, can map the extent of the disease to arrive at the earliest possible diagnosis. In this report, we present the unusual radiological findings of tuberculous infection of the shoulder.

KEY WORDS: magnetic resonance imaging, shoulder, tuberculosis

INTRODUCTION

Tuberculosis (TB) can affect virtually any organ system in the body with devastating effects, if left untreated[1]. More than three quarters of the world’s cases are found in south and east Asia and sub-Saharan Africa[2]. Skeletal involvement occurs in 1-3% of patients with TB, with the spine being the single most commonly affected osseous site in 50% of cases[3]. Articular manifestations are second in frequency of presentation, most commonly affecting the knee and the hip, followed by the sacroiliac joint, shoulder, elbow and the ankle in order of frequency[2,4]. TB of the shoulder joint is unusual, the incidence being 1 - 2.8%[3]. In the adult, *caries sicca* or dry TB is more common. Concomitant pulmonary TB is seen in about 30% of cases[6]. In this report we present the magnetic resonance imaging (MRI) features in an unusual case of the fulminant variety of TB of the shoulder in a young adult with pulmonary and abdominal TB. The fulminant variety is usually more common among children and the elderly. Review of literature revealed very few instances of reported cases of tuberculous infection of the shoulder, especially with the complex combination of MRI findings described here, making this case a rare entity.

CASE REPORT

A 23-year-old Southeast Asian lady presented with a one month history of painful left shoulder. She denied any significant past or family history, and was not immuno-compromised. Her hemogram revealed a raised total white blood cell count and an ESR of 65 mm/hr. She had been diagnosed as a case of pulmonary TB two months prior and had been on a four-drug anti-tubercular treatment (ATT) regime. Abdominal CT done in the initial month had revealed diffuse lymphadenopathy in the periportal, peripancreatic, splenic hilum, para-aortic and para-iliac regions. A 2 x 1.2 cm abscess was identified in the left iliopsoas muscle. The aspirate from this abscess was negative for acid fast bacilli (AFB). Two weeks after initialization of the ATT, her sputum became negative for AFB.

Clinical examination revealed tenderness on palpation over the scapula. There was restriction of movement in flexion, extension and abduction of the shoulder. There was neurological deficit. Plain radiograph of the shoulder (Fig. 1) revealed cortical erosion of the greater tuberosity and osteoporosis of the humeral head and proximal metaphysis with a moth-eaten appearance. The joint space and glenoid architecture appeared relatively preserved.

MRI of the left shoulder was performed with a dedicated shoulder coil on a 1.5T GE scanner. Plain and post contrast gadolinium enhanced images were obtained in the sagittal, axial and coronal planes. The anteromedial aspect of the humeral head, the greater tuberosity and posterolateral aspect of the metaphysis showed multiple ring enhancing abscesses. There were areas of cortical disruption with spillover and formation of abscesses in the rotator cuff muscles involving the supraspinatus, subscapularis, infraspinatus and teres minor. The lateral aspects of the subscapularis and supraspinatus were seen to
be separated from their insertions on the humerus by the collection distending the gleno-humeral joint and the inferior axillary recess (Fig. 2 a, b and Fig. 3 a - e). The biceps tendon sheath was distended by the abscess. The imaging findings were suggestive of osteomyelitis with secondary arthritis. Multiple rim enhancing lymph nodes were seen in the left axilla. There were no fistulae or sinus tracts Fine needle aspiration of the abscess revealed AFB. The patient subsequently chose to return to her native country for further management.

DISCUSSION

Tuberculous osteomyelitis is usually due to hematogeneous spread from an active pulmonary, meningeal or lymphatic focus\(^6\). The infection can then erode through the cortex to form a paraosseous mass or collection, or much later through the articular surface to involve the joint\(^7\). There is usually a fortnight’s delay between infection and clinical presentation due to an insidious pathologic process. Isolated tuberculous osteomyelitis, in the absence of tuberculous arthritis is rare and affects mainly the femur, tibia and small bones of the hands and feet\(^8\).

Plain film findings of tuberculous osteomyelitis in the extra-axial skeleton include monostotic involvement, osteopenia, and minimal or absent sclerotic reaction in a periarticular lesion. MRI can demonstrate the intraosseous involvement earlier than with other modalities and is being increasingly employed as the primary or even sole imaging method in osseous and articular infections due to its lack of ionizing radiation, multiplanar capability and optimal soft tissue contrast. MRI is extremely sensitive in giving an accurate anatomical map of the infection in terms of early soft-tissue changes as well as the presence and extent of joint effusion. However, the imaging findings are non-specific, and fine-needle aspiration or bone biopsy is mandatory to establish the diagnosis\(^9\). Chronic untreated infection may lead to sinus tract formation.

Fig. 1. Oblique radiograph of the left shoulder showing cortical erosions and mottled destruction of the medullary bone

Fig. 2: Sagittal (a) and axial (b): Fat-suppressed non-enhanced T1W MRI images of the left shoulder showing the osseous cortico-medullary (thick black arrow) and soft tissue abscesses (thin black arrow)
Tuberculous arthritis results from the hematogenous spread of an active pulmonary or lymphatic focus of tuberculosis to the synovium; rarely, direct spread from an adjacent focus of osteomyelitis can occur. Radiographic findings of articular TB include monoarticular involvement, soft-tissue swelling, joint effusions, periarticular osteopenia and marginal erosions. The articular cartilage is preserved until late in the disease. This latter triad of abnormalities is called the Phemister triad.

If left untreated, bone sequestration and sinus formation can develop. Complete joint obliteration with fibrous ankylosis ensues. The mimics of this entity include pyogenic, fungal, rheumatoid arthritis and rarely neoplasm when involving the epiphysis. Factors favoring the diagnosis of tuberculosis include insidious onset, significant osteoporosis, minimal sclerosis, relative absence of periosteal reaction and bone proliferation, and relative preservation of joint space till late in the disease.

In this case, it is likely that the extensive shoulder pathology developed even when the patient was on ATT, because of non-compliance with the therapy.

CONCLUSION

The diagnosis of musculoskeletal TB is difficult for the clinician by virtue of its rarity. However, management whether conservative or surgical, depends on diagnostic efficacy. While imaging findings are atypical in this process, the radiologist...
must be aware of the obscure manner of presentation of this disease and aim to reduce morbidity.

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REFERENCES
Case Report

AIDS Encephalopathy in a 14-Year-Old Girl

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ABSTRACT

Human immunodeficiency virus (HIV) syndrome encephalopathy is a known clinical entity, but it is not a common presenting feature in HIV infected children. It is usually associated with a long illness history and low CD4 counts. We report a young patient who had many rare features at presentation. She had acquired HIV infection vertically from her mother. The other rare feature she had was gross hepatomegaly due to extensive fatty infiltration proved by liver biopsy to be exclusively due to HIV infection.

KEY WORDS: fatty liver, HIV, HIV encephalopathy, opportunistic infections

INTRODUCTION

Globally, there has been a rise in the incidence of human immunodeficiency virus (HIV) infection over the past decade. Organ-involvement in HIV has been well described. However, the diagnosis of HIV-encephalopathy is made uncommonly. Progressive and static encephalopathy with cognitive, behavioral and motor manifestations has been described in HIV infected children[1]. Fatty liver has been described commonly in HIV either due to HIV virus itself, associated with hepatitis B and C virus co-infections or due to treatment with anti-retroviral agents[2].

CASE REPORT

A fourteen year-old girl was admitted with a history of fever and tonic-clonic seizures of one-day duration. She had her first seizure four months previously, which was associated with difficulty in walking and performing daily activities and gradual cognitive decline. She also lost weight.

General examination on admission showed a febrile patient with cachexia, mild pallor, no icterus or lymphadenopathy with normal hemodynamics in post-ictal state. Neurologically, she was stuporous with normal cranial nerves except fundus examination which showed optic atrophy. There was generalized hypotonia, brisk reflexes and bilateral extensor plantars. There was no neck stiffness. Abdominal examination revealed firm non-tender hepatomegaly extending up to the right iliac fossa. The rest of the systemic examination was normal. The patient was shifted to intensive care unit to control her seizures and for assisted ventilation as she developed hypoxia due to status epilepticus.

Her blood investigations showed lymphopenia, low platelets, normocytic normochromic anemia and raised liver enzymes. Serum alkaline phosphatase (ALP) was 261 IU/l, gamma glutamic transferase (GGT) was 320 IU/l, aspartate amino transferase (AST) was 128 IU/l and alanine amino trasferase (ALT) was 110 IU/l with normal bilirubin levels. Her serum calcium, phosphorus and magnesium levels were normal as also were her renal functions. Computed axial tomography (CT) scan of brain showed brain atrophy. Cerebrospinal fluid examination showed increased proteins (0.99 g/l) with normal cell count and sugar. Electroencephalography (EEG) was grossly abnormal with diffuse slowing of the basic activity. Magnetic resonance imaging (MRI) of the brain showed global white matter changes with no features suggestive of toxoplasmosis, lymphoma or cryptococcus. There were bilateral basal ganglia calcification and ventricular dilatations and the posterior fossa showed thinning of brain stem and cerebellum (Fig. 1). Ultrasound and CT abdomen showed massive hepatomegaly (Fig. 2). Hepatitis screen for hepatitis A, B and C was negative. Liver biopsy revealed changes of diffuse, severe, mixed macrovesicular and microvesicular (predominantly macrovesicular) steatosis (Fig. 3). Special stain for copper did not reveal increased deposit within hepatocytes and there were no inclusion bodies. Mantoux test and brucella agglutination test were negative. Investigations done to rule out hemolytic anemias proved negative. Metabolic disorders screening for Wilson’s disease and hemochromatosis as well as lysosomal and glycogen storage diseases were negative. Her thyroid function tests were
normal. HIV test was positive by enzyme linked immunosorbent assay (ELISA) and Western blot. Subsequently, she was investigated for opportunistic infections and was positive for cytomegalovirus, Epstein Barr virus, JC virus and Cryptosporidium but was negative for Pneumocystis jirovecii and Mycobacterium avium intracellulare. She was screened for latent tuberculosis The CD4 count was 5 and the CD4:CD8 ratio was inverted. Tracheal aspirate for Pneumocystis carini and virology were negative. Blood was also sent for Mycobacterium avium intracellulare, malaria, JC virus. Patient developed muco-cutaneous herpes simplex (perioral, anogenital) and in tracheal secretions (Fig. 4). Our diagnosis was AIDS, opportunistic infections and AIDS encephalopathy. After anti-retroviral treatment (HAART), patient developed CMV and polyoma virus in urine and blood, Candida septicemia, Pseudomonas in ETT and grew MRSA in nasal swabs.

On reviewing family history, it was found that the patient’s mother died of leukemia and her father died at age of 40 years from supposedly severe pneumonia. We suspected vertical transmission and screened her twin brother as well after appropriate counseling and he was detected to be HIV positive with no manifestation of AIDS. The patient expired in spite of adequate and aggressive management.

**DISCUSSION**

AIDS is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the HIV. The later stages of the disease leave the individual prone to opportunistic infections and tumors. HIV infection is transmitted through direct contact with a mucous membrane or the blood stream with bodily fluid containing HIV such as blood, semen, vaginal fluid, fluids and breast milk. The vertical transmission is the predominant route of transmission in children and accounts for 85% of pediatric HIV infections. In 2005 alone AIDS claimed 2.4 - 3.3 million lives out of which more than 570,000 were children. The symptoms of AIDS are primarily the result of conditions that do not normally develop in individuals with healthy immune systems. Most of these conditions are infections caused by bacteria, viruses, fungi and parasites. Opportunistic infections in AIDS patients affect nearly every organ system. People with AIDS
also have increased risk of developing various types of cancers such as Kaposi sarcoma, cervical cancer and lymphomas.

The true incidence of central nervous system involvement is not known, although it is thought to occur in most HIV infected children. It is at least three times more than that in adults. The diagnosis of HIV encephalopathy is made uncommonly in HIV infected children as progressive and static encephalopathy with cognitive, behavioral and motor manifestations. The risk of HIV encephalopathy is correlated directly with the severity of HIV-related symptoms and depression of CD4 count and P 24 antigen level in the mother[4]. Most children will have their encephalopathy in the early years of their lives. The diagnosis of HIV encephalopathy is based on CDC-revised classification system: presence of one or more progressive neurological finding for at least two months (in the absence of other identifiable causes) from amongst the following:

1. Failure to attain or loss of milestones or of intellectual ability, verified by standard developmental scale or neuropsychological tests
2. Impaired brain growth or acquired microcephaly as demonstrated by head circumference measurements or brain atrophy on CT scan or MRI with serial imaging in children less than two years
3. Acquired symmetric motor deficits with paresis, pathological reflexes, ataxia and/or gait disturbance[1]

The virus probably enters the CNS through infected macrophages. The neurological manifestations may result from the direct effects of the virus or through cells of macrophages lineage and toxic cytokines. Although most affected children do not have an identifiable pathogen other than HIV in presentation (as our patient), other CNS process like opportunistic infections, inflammatory diseases, vascular or neoplastic process can cause encephalopathy and must be searched for. Imaging of brain will show diffuse cortical atrophy, attenuation of white matter and inter-cerebral calcification especially in basal ganglia.

Presence of hepatomegaly, splenomegaly (as in our patient) and increased viral load increase the likelihood of development of HIV encephalopathy.[2]. Being a manifestation of advanced disease, the median survival rate in patients with HIV encephalopathy is about 11 month from the diagnosis. Hepatomegaly is a common manifestation of pediatric HIV infection. It might be due to HIV infection itself, metabolic derangements, chronic inflammation, hepatitis co-infection and treatment with certain nucleoside reverse transcriptase inhibitors. Our patient presented with fatty liver with no obvious predisposing factors. There is increasing concern that patients with chronic HIV infection may be at increased risk of non-alcoholic fatty liver disease (NAFLD), which may evolve into non-alcoholic steatohepatitis (NASH) and cirrhosis[6]. The cornerstone of management of HIV-associated fatty liver is currently to treat the predominant underlying condition.

CONCLUSION

We present this case in view of the rare presenting features of HIV in this patient and the long time interval for HIV encephalopathy to appear and the associated fatty liver. HIV is a global disease. It should be suspected in this area as well and age is no barrier.

REFERENCES

Case Report

Child Survived with Complete Neurological Recovery after Prolonged Out-of-Hospital Cardiac Arrest due to Electric Shock

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ABSTRACT

The mortality and neurological morbidity in children secondary to out-of-hospital cardiac arrest due to electric shock is very high. Poor prognosis is related to lack of cardiopulmonary resuscitation in the field, long duration between cardiac arrest and hospital arrival, absent pulse on presentation, need for many doses of epinephrine and relatively long duration of resuscitation in the emergency room. We present a nine-year-old girl who sustained an electric injury outside the hospital. She had no cardiopulmonary resuscitation in the field, presented to the emergency room after 20 minutes with cardiopulmonary arrest, pulseless, asystole rhythm, fixed dilated pupils and needed four doses of epinephrine and ten defibrillation shocks to revert to normal sinus rhythm. Although optimal pediatric defibrillation doses are unknown and 2 joules/kg is thought to be suboptimal, she needed two doses of 7 joules/kg and eight doses of 12 joules/kg to revert to sinus rhythm. However, our patient had perfect neurological outcome on follow-up after six months from the event.

KEY WORDS: cardiac arrest, defibrillation, electric shock, neurological outcome

INTRODUCTION

In children the outcome of cardiac arrest outside the hospital has been poor, with very high rates of mortality¹,². Several studies have demonstrated that cardiac arrests and longer periods of cardiopulmonary resuscitation (CPR) were associated with worse neurological outcomes. Schindler et al¹ demonstrated that out of 80 patients with cardiac arrest, six (8%) survived to hospital discharge, and at one year follow-up three had moderate deficits, two were in a persistent vegetative state, and one died. They also demonstrated that no survivors with good neurological outcome received more than three boluses of epinephrine or more than 30 minutes of resuscitation.

We report a case of a nine-year-old girl who was a victim of electrical injury and presented to emergency room (ER) after 20 minutes in cardiopulmonary arrest (CPA), pulseless, asystolic rhythm and fixed dilated pupils. She needed four doses of epinephrine and ten shocks for secondary ventricular fibrillation and remarkably survived with complete neurological recovery on follow up after six months.

CASE HISTORY

A nine-year-old previously healthy girl, presented to our ER 20 minutes after sustaining an electric shock. The electric current passed through her lips while drinking from a water cooler and she was thrown away. She lost her consciousness, became unresponsive and apneic. She was brought by car to the hospital. No CPR was done on the way to the hospital.

On arrival to ER she was in complete CPA with fixed dilated pupils and a temperature of 34.4 ºC. The inlet was mucous membrane of lips and the outlet was the second toe of right foot (Fig. 1 a, b). Initial blood gases, after intubation showed severe metabolic acidosis; pH 6.9, PCO2 6.7 kPa, PO2 15.3 kPa, HCO3 10.3 mmol/l, BE -21mmol/l. The patient was intubated and connected to a mechanical ventilator. As the monitor showed asystole, external cardiac compression (ECC) was started. The patient received initially two doses of epinephrine (1 mg) until the rhythm converted to ventricular fibrillation (VF) after four minutes. The patient was in pulseless VF. Therefore, cycles of defibrillation with epinephrine were started. She received a total of 10 shocks; two
shocks at 200 J, then eight shocks at 360 J. Two more doses of epinephrine (1 mg) and one dose of lignocaine 30 mg were given. After 10 minutes of resuscitation the rhythm was converted to normal sinus rhythm with recovery of spontaneous circulation (Fig. 2a, b). On arrival to the pediatric intensive care unit (PICU) the patient was hypotensive (BP 85/40 mmHg) and was started on dopamine. She developed generalized tonic convulsions and was started on phenytoin infusion. Glasgow Coma Scale (GCS) was 6/15 and pupils were 3 mm with sluggish reaction. She had generalized hypotonia and hyporeflexia. Laboratory investigations showed evidence of myocardial injury (Troponin I 9.4 mcg/l (0.0-0.03) creatinine kinase CK: 32,469U/l (20-270), CKMB 272 mcg/l (0.6-6.3). Repeated cardiac enzymes were 1.86, 4,854 and 28.8 respectively. This could be a complication of repeated shocks causing muscle injury. Electrocardiogram (ECG) showed ST elevation and T wave inversion in V2-V4. Echocardiogram showed good left ventricular size and function, hypokinetic septum, trivial mitral regurgitation and mild tricuspid regurgitation. Initial results of renal function, liver function and coagulation profile were normal. No evidence of other organ damage was detected.

The patient showed remarkable improvement in the PICU; she did not have any arrhythmias afterward. She was extubated on the second day and dopamine stopped on the fourth day. Neurologically; level of consciousness started to improve within 24 hours and she was back to normal after 72 hours without any focal neurological signs. CT – brain showed normal brain with no hypoxic changes. The patient was discharged after seven days from PICU to the general ward in good general condition. The patient was discharged home after 10 days. Her speech, vision and hearing were normal and there was no neurological deficit. She was seen after six months and her neurological examination was unremarkable with normal cognitive function.

**DISCUSSION**

We report the case of a nine-year-old girl who sustained an electrical shock from household electrical equipment. Electrical injury affects the heart through two mechanisms; direct necrosis of the myocardium or cardiac dysrhythmia. Asystole and VF are the most serious of the cardiac complications of electrical injury[3,4]. Several factors such as voltage, tissue resistance, tissue susceptibility, type of current, current pathway, site, and duration of electrical contact determine the severity and distribution of the injury[5]. In our case the current passed through a low resistance area, the mucous membrane of the lip, passed through the heart to the right foot. The current was low voltage (220 - 240V, alternating current 50-60 Hz) used in household electrical equipment which can cause sudden death, usually from VF[5,6].

One striking point in our case was the perfect neurological outcome after out-of-hospital cardiac arrest. The outcome of cardiac arrest in children outside the hospital has been poor, with very high rates of mortality and neurologic morbidity. Many survivors remain in a persistent vegetative state[1,2]. A...
collective review of 44 articles published from 1970 to 1997 on pediatric cardiac arrest found that overall survival after out-of-hospital cardiac arrest was poor at 8.4%[7]. In studies of the neurologic outcome of out-of-hospital cardiac arrests in children, all survivors of arrest had serious neurologic disabilities[1,2,8]. Several studies attempted to identify predictors of survivals in pediatric out-of-hospital cardiac arrest. First, early effective bystander CPR and witnessed arrest are crucial to increasing the chances of survival[7]. The presence of pulse on arrival to the hospital is a very important predictor of survival. Studies showed that children with a respiratory arrest who still had a palpable pulse had a better outcome than those with a cardiac arrest[9,10]. This is because children usually have an arrest secondary to hypoxia. If the hypoxic insult has been of sufficient duration and severity to stop the heart, the severe anoxia undergone by the central nervous system often precludes a neurologic recovery except in the setting of hypothermia[1]. The initial cardiac rhythm has been increasingly recognized to be an important factor of survival in pediatric cardiac arrest. Cardiac arrest in children is typically due to asystole or pulseless electrical activity, whereasVF and pulseless ventricular tachycardia (VT) namely, shockable rhythms, are relatively rare[1]. In the collective review approximately 10% of the pediatric cardiac arrest patients were in VF or VT and 30% of them survived to discharge from hospital in comparison to 5% survival only in patients with asystole.[7].

Another important predictor of survival to hospital discharge is the duration of resuscitation in the ER and the doses of epinephrine given. Most studies have shown that resuscitation of more than 20 to 30 minutes and the use of more than two doses of epinephrine are associated with poor prognosis[1,11,12].

Our patient obviously had many predictors of poor survival and neurological outcome; she arrived to ER after 20 minutes, no CPR was done on the way, arrived pulseless, first recorded rhythm was asystole with secondary VF and needed four doses of epinephrine. The only good predictor for survival was the duration of resuscitation which did not exceed 10 minutes.

The other remarkable point in our case is the number and energy doses of defibrillation the patient received to treat her VF. The patient needed 10 shocks. She received starting dose of 200 J (7 J/kg) for two doses followed by 360 J (12 J/kg) for the rest of the CPR. Fortunately, she responded within seven minutes with recovery of spontaneous circulation. She did not show any long term evidence of cardiac dysfunction or neurological deficit as a result of this high dose. The optimal defibrillation dose in children is unknown; recommended energy doses for children are derived from limited animal studies[13], from case series with few patients[14], and from extrapolation of adult doses. Studies that prospectively evaluate the effectiveness of current recommendations for pediatric shock doses are lacking, and the data obtained from pediatric animal models and from a case series[13] indicate that a 2 J/kg dose is at least suboptimal. It has been suggested that high shock doses are effective and well tolerated by pediatric hearts[16]. In this sense, the European Resuscitation Council’s new guidelines recommend 4 J/kg as the first energy dose for defibrillation in children[17].

Experimental data on the myocardial injury provoked by electric shocks are also non-conclusive, with some studies demonstrating an absence of deleterious effects of high doses of biphasic energy[18] and other studies suggesting myocardial damage and worse neurological outcome in piglets treated with adult biphasic doses[19,20].
Our patient showed excellent recovery on follow up; her cardiac enzymes were back to baseline and echocardiography showed normal ventricular function. Neurologically the patient did not have any neurological deficit with Pediatric Cerebral Performance Category Scale at six months after arrest.

CONCLUSION

Despite the poor outcome of cardiac arrest in children outside the hospital, some cases may survive with good neurological outcome. This may be attributed to many factors of which the cause of the arrest, electrical shock in our case, can be an important factor. This point should be further investigated and patients with favorable etiologies may deserve more prolonged and aggressive resuscitation. We suggest using a higher start shock doses for defibrillation in pediatric arrest, it is well tolerated by pediatric heart and may be more effective in an arrest situation.

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Case Report

Gyrate Atrophy of the Choroid and Retina with Hyperornithinemia: Report of Three Cases and Review of Literature

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ABSTRACT

Hyperornithinemia associated with gyrate atrophy of the choroid and retina is a rare, autosomal recessive disorder resulting from a deficiency of the mitochondrial matrix enzyme, ornithine d-aminotransferase (OAT). This enzyme catalyses the pyridoxal phosphate-dependent transamination of ornithine and a-ketoglutarate to D'-pyrroline 5-carboxylic acid and glutamic acid. Over 150 biochemically documented cases have been reported out of which one-third are Finnish.

We report three cases of this metabolic disorder in one family who was investigated for high myopia associated with degenerative changes in the fundus. The diagnosis was made on clinical, electrophysiological and biochemical features. Since this disorder can present in the pediatric age with myopia, children presenting with degenerative myopia need to be investigated for this disorder.

KEY WORDS: Gyrate atrophy (GA), Ornithine d-aminotransferase (OAT)

INTRODUCTION

Gyrate atrophy (GA) of the choroid and retina was first described by Fuchs in 1896[1]. Human hereditary deficiency of ornithine aminotransferase (OAT) activity is transmitted as an autosomal recessive trait[2] and results in 10 to 20-fold increased level of plasma ornithine and is shown to be associated with GA[3]. The initial complaint of decreasing visual acuity and night vision is followed by the appearance of sharply demarcated, circular areas of chorioretinal atrophy with hyperpigmented margins in the midperiphery of the fundus[3].

This appears through the first three decades of life and leads to blindness in the fourth to seventh decades. Myopia, posterior subcapsular cataracts, and vitreous opacities may also be present[4].

OAT is a mitochondrial nuclear encoded pyridoxal phosphate enzyme that catalyzes the interconversion of ornithine glutamate and proline. GA is a genetic disorders with increased frequency in the Finnish population with an incidence of one case per 50,000 individuals in Finland[4].

Valle in a review in 2001 revealed that amongst the over 150 biochemically documented cases of GA, about one third of them were from Finland and only seven of them (less than 5%) had been responsive to therapy with Vitamin B6 dietary supplementation[5].

CASE REPORT

Three children (two boys, 9 and 7 years old and one girl, 11-year-old) of second-degree consanguineous parents were involved. The girl child presented with a two-year history of deterioration in vision. The initial complaint of decreasing visual acuity and night vision is followed by the appearance of sharply demarcated, circular areas of chorioretinal atrophy with hyperpigmented margins in the midperiphery of the fundus[3].

Myopia, posterior subcapsular cataracts, and vitreous opacities may also be present[4].

OAT is a mitochondrial nuclear encoded pyridoxal phosphate enzyme that catalyzes the interconversion of ornithine glutamate and proline. GA is a genetic disorders with increased frequency in the Finnish population with an incidence of one case per 50,000 individuals in Finland[4].

Valle in a review in 2001 revealed that amongst the over 150 biochemically documented cases of GA, about one third of them were from Finland and only seven of them (less than 5%) had been responsive to therapy with Vitamin B6 dietary supplementation[5].
Fig. 1: Fundus view of the right eye showing central part of the retina with spared macula

Fig. 2: Fundus view of the left eye showing central part of the retina with spared macula

Fig. 3: Sharply demarcated, circular areas of chorioretinal atrophy in the mid-periphery with hyperpigmented margins (girl)

Fig. 4: Sharply demarcated, circular areas of chorioretinal atrophy in the mid-periphery with hyperpigmented margins (girl)

Fig. 5: Sharply demarcated, circular areas of chorioretinal atrophy in the mid-periphery of the retina (elder boy)

Fig. 6: Sharply demarcated, circular areas of chorioretinal atrophy in the mid-periphery with hyperpigmented margins (elder boy)

Fig. 7: Sharply demarcated, circular areas of chorioretinal atrophy in the mid-periphery of the retina (younger boy)

Fig. 8: Sharply demarcated, circular areas of chorioretinal atrophy in the mid-periphery of the retina (younger boy)
Screening for all the family revealed two of her brothers having the same fundus picture (Fig. 5-8) with myopia between (-3.0 Ornithine d-aminotransferase (OAT) Sp/-2Cyl) to (-4.5 Sp/-3.0 Cyl). Visual acuity improved to 6/12 with glasses. The color vision was normal.

The routine blood chemistry including liver and renal function tests and muscle enzymes were within normal limits. The blood ammonia was 51 µg / dl (reference range 25-93 µg/dl). Quantitative analysis of plasma and urinary amino acids were carried out by gradient elution high-performance liquid chromato-graphy (HPLC) using a C18 octadeceylisilyl (ODS), 5 µm particle column after pre-column derivatization with ophthalaldehyde.

A massive increase in the concentration of ornithine in plasma and urine, between 721-864 µmol/l (reference range 24 -112 µmol/l), mild hypo-lysinemia 54 - 83 µmol/l (reference range 107 - 244 µmol/l) and lysinuria was noted. The d-lactam of ornithine was detected in their urine. No other abnormal amino acids were detected. In view of the ophthalmological findings associated with increased blood ornithine without hyperammonemia or homocitrullinuria, a diagnosis of hyperornithinemia associated with GA of the choroid and retina, was made.

The patients were started on pyridoxine 30 mg/ day orally and arginine restricted diet with plenty of gelatin which is a rich source of proline. They were advised to come for a follow up after six months to monitor their blood ornithine levels. After six months blood ornithine level decreased only in the female patient and it was 390 umol/l. However, the patients were not compliant and were lost to follow up. Electroretinogram (ERG) showed an extinguished response in all the siblings. Electrooculogram (EOG) was subnormal as were the values of dark adaptation thresholds. This, to the best of our knowledge, is the first documentation of hyperornithinemic gyrate atrophy (HOGA) from Kuwait.

DISCUSSION

The majority of cases of myopia in children are variants in the frequency curve of axial length and curvature. Pathological axial myopia is a degenerative and progressive condition which is essentially a disturbance of growth on which is imposed degenerative phenomenon. The clinical manifestations of degenerative myopia are the same as those of simple myopia except that the visual acuity may not be corrected to normal with any lenses. Thus, myopia of a mild degree may show marked degenerative changes while high myopia may show no changes. An inborn error of ornithine metabolism resulting in hyperornithinemia, as in these cases, leads to degenerative myopia.

Hyperornithinemia occurs in two types of genetic disease. In GA of the choroid and retina associated with hyperornithinemia, plasma ornithine concentration is increased 10 - 20 fold and there is no hyperammonemia or homocitrullinuria[6]. Hypolysinemia occurs due to increased renal clearance of lysine. Plasma glutamic acid concentrations are sometimes reduced. A deficiency in the activity of OAT can be demonstrated in cultured fibroblasts and phytohemagglutinin (PHA)-stimulated lymphocytes. In another disorder, the hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH syndrome), a defect in the transporter that mediates ornithine entry into the mitochondria results in increased plasma ammonium and glutamine concentrations particularly after ingestion of a protein load. Urinary excretion of orotic acid is increased in HHH individuals.

The human OAT gene has been cloned and mapped (10q26), and more than 60 mutations causing the disease have been identified[6].

GA of the choroid and retina begins in childhood and leads to blindness in the fourth to seventh decade of life[7]. The affected individuals develop axial myopia in early childhood and most have impaired peripheral and night vision by the first decade. Sharply demarcated, circular areas of chorioretinal atrophy are observed in the periphery of the retina on fundoscopy. There is concentric reduction of the visual fields leading to tunnel vision and eventually blindness. Posterior capsular cataracts have been reported in nearly all patients. The standard tests of visual function become abnormal at an irregular rate, with periods of rapid progression interspersed with periods of relatively stable function.

The ERG, which may be normal initially, eventually diminishes in amplitude and usually is totally extinguished well before the chorioretinal atrophy becomes complete. A few patients have been reported to have mild proximal muscle weakness. Tubular aggregates in type 2 skeletal muscle fibres and ultrastructural abnormalities in the mitochondria of the skeletal muscle and liver have been described[8]. Despite clinical, biochemical and molecular characterization of GA, the exact pathophysiologic mechanism of the progressive retinal degeneration is unknown and several hypotheses have been proposed. Sipila and coworkers[9] have proposed that deficiency of creatine and creatine phosphate may account for both the histologic abnormalities in muscle and chorioretinal degeneration. They have suggested that the high ornithine concentrations inhibit glycine transaminidase thereby reducing creatinine synthesis and causing a reduction in total body creatine and creatine phosphate. The well-
documented sensitivity of glycine transaminidase to ornithine in vitro and the observations that fasting plasma guanido-acetate, creatine and creatinine are all reduced in patients with GA as compared to normals provide evidence for this hypothesis[8].

Another hypothesis for the pathophysiology of GA involves the deficient synthesis of D1-pyrroline-5-carboxylate owing to the deficiency of OAT and to inhibitory effects of ornithine on D1-pyrroline-5-carboxylate synthase, the enzyme that catalyses the formation of D1-pyrroline-5-carboxylate from glutamate. The observation that D1-pyrroline-5-carboxylate synthase is inhibited in vitro by near-physiological concentrations of L-ornithine and that ornithine is toxic to cells lacking OAT supports this hypothesis[10].

No form of therapy has been reported to be unequivocally effective in patients with this rare disorder. Pyridoxine, the precursor of the co-factor, pyridoxal phosphate, has been administered in pharmacological doses in an attempt to stimulate any residual OAT activity. A significant reduction in plasma ornithine has been reported in seven patients with this therapy[11-13]. Fibroblast OAT in six of these patients responded in vitro to high concentrations of pyridoxal phosphate in the assay mixture. One patient described by Valle and co-workers[10] had an in vivo response without an in vitro response while Kennaway et al[14] described a patient with an in vitro response without an in vivo response. The B6-responsive patients of Weleber and co-workers[12] showed a biochemical response as indicated by a decrease in blood ornithine levels, even to low doses of pyridoxine (18 - 30 mg/day). Clinical improvement was observed with high doses (600 mg/day) of this vitamin. However, the two pyridoxine-responsive patients of Hayasaka and co-workers[15] had some progression of their chorioretinal degeneration over two years despite lowering of their blood ornithine levels while on 120 mg and 600 mg of this vitamin. Hence the possibility remains that pyridoxine therapy may not produce clinical improvement even if it produces a biochemical response. However, the rate of progression of the disease may be slowed by this therapy. Lowering of plasma ornithine has also been achieved by dietary restriction of arginine and by lowering protein intake to 0.2 g/kg/day[16].

Dietary arginine restriction limits the source of ornithine. The long-term reduction of ornithine accumulation by an arginine-restricted diet has slowed the progression of the chorioretinal atrophy[17]. Promotion of the renal excretion of ornithine by administration of pharmacological doses of lysine and α-aminoisobutyric acid have been attempted. Although these compounds increase ornithine excretion, the long-term efficacy of this therapy is not known.

Creatine supplementation has been tried for therapy by some workers[18] because of the hypothesis that GA may be due to a deficiency of creatine and creatine phosphate. Although creatine supplementation has resulted in improvement in histologic abnormalities in the skeletal muscle there was a continued progress of the chorioretinal lesions in 13 patients at a 5-year follow-up[19]. These results however indicate that creatine depletion does play a role in muscle abnormalities.

Based on a hypothesis that a deficiency of proline in the retina and choroid may produce atrophies in the affected patients despite normal serum proline levels, supplemental proline has been administered. Proline therapy has been reported to minimize the progression of the disease in one patient and halt the progression in two of the four patients of Hayasaka and coworkers[15]. Thus, the outcome of this therapy is mixed. In conclusion, no single therapy has been shown to halt the progression of this disease in all affected patients. Genetic counseling of the family members and evaluation of their blood ornithine levels which are elevated even in the presymptomatic stage when all other standard visual function tests may be normal, forms an important part of management of these cases. Recently, a microradiographic method for assay of OAT has been reported indicating a potential for prenatal diagnosis by the first trimester chorionic villus sampling[20].

CONCLUSION

Myopia in a child may be due to the rare, inherited metabolic disorder ‘hyperornithinemia’ associated with GA of the choroid and the retina.

Although treatment with pyridoxine, dietary restriction of arginine, and supplementation with creatine and proline have been attempted in previously reported cases, no form of therapy is found to be unequivocally effective.

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Case Report

Double Aneuploidy: Down Syndrome Associated with Klinefelter Syndrome

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ABSTRACT

The occurrence of double aneuploidy, i.e., the existence of two meiotic non-disjunction events is relatively rare. Although the association between double autosomal trisomy, such as trisomy 21 and 18 is extremely unusual, rare cases of combination between Down syndrome and gonosomal trisomy have been reported.

We report the case of an Indian boy with Down and Klinefelter syndrome. The patient’s condition resulted from de novo trisomy-21 with extra X-chromosome (48, XXY, +21). He was born normally with birth weight, length and head circumference of 2590 gram, 45 cm and 31 cm respectively.

INTRODUCTION

The occurrence of double aneuploidy, i.e., the existence of two meiotic non-disjunction events is relatively rare. Multiple non-disjunction has been observed in non-viable trisomy causing spontaneous abortion[1]. Reported cases of live born double aneuploidy usually involve acrocentric autosomes and sex chromosomes, the commonest being between Down syndrome and gonosomal trisomy[2].

CASE REPORT

The patient was an Indian boy born on 18-03-1992 at term by spontaneous vaginal delivery. The pregnancy was complicated by hypertension and gestational diabetes, but the mother was not on any medications. Birth weight, length and head circumference were 2590 gram (5th centile), 45 cm (3rd centile) and 31 cm (< 3rd centile) respectively. Apgar score was 8 and 9 at one and five minutes after birth. At birth, the patient had features of Down syndrome with imperforate anus. He had colostomy on the second day of life and later total surgical correction was performed. The mother was 31 years and father was 32 years old at the time of delivery.

He had dysmorphic features of Down syndrome with an imperforated anus, severe mental retardation, small phallus and bilateral undescended testicles but no congenital heart disease. The weight and height were on the 3rd centile while the head circumference was below the third centile. The patient developed hypothyroidism by the age of six years and was maintained on L-thyroxin. Testosterone level was pre-pubertal and failed to rise after human chorionic gonadotropin (HCG) stimulation test.

The development milestones were delayed. He had his social smile at five months, crawl at two years and he walked when he was two and half years old. The speech was delayed but the hearing and vision were normal. He is mentally retarded but has no behavioral disturbance and attends a special school for the mentally handicapped. The patient developed hypothyroidism by the age of six years and was maintained on L-thyroxin.

Physical examination revealed a weight and height at 3rd centile while head circumference below 3rd centile. He had facial features of Down syndrome including hypertelorism, depressed nasal bridge, upslant palpebral fissures, epicanthic folds, small mouth, geographical tongue and flat occiput. There were no brush field spots and eye examination was normal (Fig. 1). The hands were short and broad with bilateral simian creases and clinodactyl of the fifth fingers (Fig. 2). The feet showed a gap between hallux and second toe (Fig. 3). The phallus was small with bilateral undescended testicles and no signs of puberty. Cardiac examination was normal. Neurological examination showed generalized hypotonia and the joints were hyperflexible.

The karyotype was 48, XXY, +21 (Fig. 4), TSH 11.0 uIU/ml (0.25 - 4.99), free T4 4.4 pmol/l (6 - 24.5)
and testosterone 0.07 nmol/l raised to only 0.5 nmol/l after human chorionic gonadotropin (HCG) test. Echocardiogram is normal.

**DISCUSSION**

The purpose of meiosis is to achieve reduction from diploid state of gonadal stem cell \((2n = 46)\) to haploid complement of normal gametes. In meiosis I, the primary gametocyte (oocyte or spermatocyte) gives rise to two secondary gametocytes, each with 23 chromosomes. In meiosis II, the secondary gametocyte separate into their component chromatides, each gamete contains a haploid set of chromosomes. The diploid complement is restored at conception with the union of two haploid gametes.

Non-disjunction is the failure of homologous chromosome to segregate symmetrically at cell division. In non-disjunction in meiosis I, pair of homologous chromosomes fail to separate, while non-disjunction in meiosis II, the chromatides fail to separate. Each defect will produce a disomic and a nullisomic cell \((2:0\) segregation\). This ends with trisomic or monosomic conceptus. Angel *et al.*\(^3\) proposed three events as a mechanism for non-disjunction. The first is failure of homology to pair during meiosis I, so that they exist in two separate univalent instead of bivalents. The
second event, the univalent provide the separation of the two chromatides. In the third event, the separated chromosomals segregate at random to either the oocyte or to the polar body.

For the acrocentric chromosomes (13, 14, 15, 21 & 22), the proportion of cases of paternal origin was similar among the five trisomies: 12% for trisomy 13, 17% for trisomy 14, 12% for trisomy 15, 9% for trisomy 21 and 11% for trisomy 22. The stage of non-disjunction was also similar among the five trisomies, with the majority of cases of maternal origin being due to non-disjunction at meiosis I, whereas for paternally derived cases, non-disjunction occurred primarily at meiosis II. 55% of 47, XXY and 90% of 47, XXX syndromes are due to maternal non-disjunction, in which 68% arise during meiosis I.

Double aneuploidy is the result of either a double event on non-disjunction resulting in one abnormal gamete, or less likely separate events in gametogenesis in both parents. The higher occurrence of 48, XXY, +21 may be due to greater accessibility of disomic ovum to Y-carrying sperm, and promotion of non-disjunction in ovum by Y-bearing sperm. 48, XXY, +21 was found to be age-dependent, as the proportion of mothers and fathers over age 35 was increased in the general population. This is in contrast to the apparently age-independent 48, XYY, +21.

Microsatellite polymorphisms and cytogenetic heteromorphisms determined that both aneuploidies of a terminated pregnancy with 48, XXX, +21 arose as a result of non-disjunction in maternal meiosis II.

While another case report of 48, XXY, +21 have shown that the origin of the extra X chromosome was the result of paternal non-disjunction at meiosis I and the extra chromosome 21 derived from maternal meiosis II non-disjunction. Cases of multiple non-disjunction of sex chromosomes are reported due to segregation error on one parent even with multiple X chromosomes.

The simultaneous occurrence of two events of non-disjunction is probably more frequent than it would be expected by chance. Double aneuploidy has repeatedly been found in spontaneous abortions with an incidence of 2.18%. Live born double trisomies mostly involve acrocentric autosomes and sex chromosomes. Only few cases reported non-mosaic trisomy 21 in combination with other aneuploidy, usually sex chromosomes, the most frequent being XXY (Klinefelter syndrome) with one case report of a twin with 48, XXY, +21. Other associations include XXX, XYY, XO (Turner syndrome) and trisomy 18. A combination between trisomy 13 and trisomy 18 with extra sex chromosomes were reported in less frequency.

CONCLUSION

The findings in our patient support the hypotheses that a segregation defect at a cellular level may cause non-disjunction involving more than one chromosome. DNA study with microsatellite markers is required to determine the cause and the nature of these events in our patient. This is in order to improve our understanding of the mechanism of non-disjunction.
REFERENCES


Case Report

Cutaneous Tuberculosis (Scrofuloderma) in a Five Year-Old Boy: Case Report

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ABSTRACT

Cutaneous tuberculosis (CTB) is a rare form of extra-pulmonary TB in our region. The incidence of CTB seems to be increasing in some countries. CTB continues to be one of the most elusive and difficult diagnoses to make for dermatologists practicing in developing countries. We report the case of a five-year-old boy with an infected discharging ulcer on his face referred to our hospital in Gorgan, north of Iran. After physical, pathological and radiological examination, the diagnosis of CTB was confirmed. The condition improved after standard antitubercular regimen.

INTRODUCTION

Tuberculosis (TB) is still a serious problem in both developing and developed countries[1]. The incidence of TB registered an upward trend even in developed countries with the advent of HIV infection[2] and chemotherapy[3]. Cutaneous TB (CTB) is a rare form of extra pulmonary TB primarily occurring in developing countries[4] and accounts for 1 - 2% of extra-pulmonary cases. It is often confused with various cutaneous disorders both clinically and histopathologically[1,2,5]. In such a situation, it is crucial to recognize the different clinical features of CTB to prevent missed or delayed diagnoses[5]. The incidence of CTB seems to be increasing in some countries like Tunisia[6]. Lupus vulgaris and TB verrucosa cutis remain the most common forms of CTB, and erythema induratum of bazin is the most common tuberculid[7,8]. In Lupus vulgaris the usual sites of involvement are head and neck[8]. In the whole spectrum of CTB, there are a proportion of patients with disseminating involvement, who are of great epidemiological significance as they require a change in the standard therapeutic regimens recommended for CTB[9,10]. CTB is a rare form of extra-pulmonary TB in our region (Middle East). This form should be more extensively studied because it may be suggestive of visceral forms of TB.

CASE PRESENTATION

A five-year-old boy was referred to our dermatology clinic with a suppurative discharging ulcer in the periauricular region. It had developed over the last eight months before admission as a painful red swelling of periauricular region which then ruptured to form a fistula after three months with suppurative discharge (Fig. 1). The patient had a history of productive cough, anorexia and night sweats since one year. A diagnosis of dermatophytosis with superadded bacterial infection was made, which was unsuccessfully treated with different drugs such as systemic antibiotics (penicillin, cepazolin, erythromycin, cloxacillin, cephalexin) and antifungal drugs (griseofulvin, terbinafin). His vital signs were normal. On physical examination, an ulcerative nodule was seen in the periauricular region with tenderness and induration. Retro-auricular and cervical lymphadenopathy was seen. Smears and cultures were negative for dermatophytosis and the smear was negative for Leishman bodies. Smears of sputum and the lesion were positive for acid-fast bacillus (AFB). Pathological and histological findings of skin biopsy specimen were as follows: ulcerated skin tissue with multiple granuloma formation in the dermis composed of epitheloid and multinucleated giant cells (Langhans type) surrounded by chronic inflammatory cells (lymphocytes and plasma cells) (Fig. 2). A consolidation was seen on chest X-ray, in the upper lobe of the right lung obliterating the right border of the upper mediastinum and hilum of the right lung (silhouette sign). An air-bronchogram was apparent in the lesion (Fig. 3). Based on the above mentioned clues, the diagnosis of CTB was established and the standard regimen was prescribed for a period of six months. Subsequently, improvement was noted on his face (Fig. 4) and in his chest X-ray.

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DISCUSSION

CTB is a rare infection, with an incidence of 3.5% reported among patients with organ TB\(^3\). The clinical presentation of CTB may vary depending upon host immunity, infection route and previous exposure\(^3,11\). Unexpected areas such as the trunk, extremities, periocular and perianal regions might be involved instead of the conventional regions such as the head and neck, especially the nose, the cheek, and the ears\(^8,11\).

Generally CTB is classified to two groups: the first group is CTB with actual invasion of bacillus into the skin and the second group is tuberculoids or hypersensitivity reactions accompanied with primary foci in other sites. The most common form of CTB is different depending on geographical areas. The majority of investigators believe that lupus vulgaris is the most common clinical form of CTB\(^12\).

The characteristic lesion is a plaque, composed of nodules of an ‘apple-jelly’ colour, which extend irregularly in some areas, and when they ulcerate, they heal by scarring causing considerable tissue destruction over many years\(^13\). Although scrofuloderma is one of the most common forms of CTB as reported in some series\(^14\), most cases develop from an infected lymph node, and less commonly as a result of an infected bone, joint\(^15\) and infection of the lacrimal system\(^16\).

This case highlights scrofuloderma arising from underlying lymph node involvement. Other diagnoses that need to be considered include carbuncle, deep mycotic infections, leishmaniasis, atypical mycobacteriosis, tertiary syphilis and cutaneous malignancies. Although a positive culture remains the gold standard for diagnosis of TB, PCR may actually have a higher sensitivity than culture. A further advantage for PCR is the possibility for early diagnosis and institution of treatment in these patients\(^17\). Our patient had a suppurative discharging ulcer in the periauricular region eight months before admission and a history of productive cough, anorexia and night sweats since one year. Smears of sputum and the lesion were positive for AFB. Pathological and histological findings of skin biopsy were as follows: ulcerated

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Fig 1: A case of cutaneous tuberculosis with ulcerated nodules in preauricular area with infective discharge

Fig 2: Scrofuloderma (low magnification). There are several tubercles (×100)

Fig 3: Chest X-ray with consolidation in the right upper lobe with air bronchogram appearance

Fig 4: Atrophic scars after antitubercular treatment
skin tissue with multiple granuloma formation in the dermis composed of epitheloid and multinucleated giant cells (Langhans type) surrounded by chronic inflammatory cells (lymphocytes and plasma cells) (Fig. 2). A consolidation was seen in the chest X-ray, in the upper lobe of the right lung which obliterated the right border of upper mediastinum and hilum of right lung (silhouette sign). An air-bronchogram was apparent in the lesion (Fig. 3). Based on the above mentioned clues, the diagnosis of CTB was established and the standard regimen was prescribed for a period of six months. Subsequently, clinical improvement was noted on his face (Fig. 4) and on his chest X-ray. A six-month regimen including four drugs in the initial two months (rifampicin, isoniazid, pyrazinamide plus ethambutol or streptomycin), followed by rifampicin and isoniazid in the four-month continuation phase is highly effective in patients with fully sensitive organisms. This standard six-month regimen is now recommended by the British and American Thoracic Societies. For osteoarticular TB, the American Thoracic Society recommends six-to-nine-month duration of therapy for patients with drug sensitive disease\[18\].

CONCLUSION
It is very important to consider the diagnosis of CTB in chronic lesions, especially when there is a chronic infection. Unusual cases of CTB are not uncommon and a high index of clinical suspicion is one of the most important factors in making a correct diagnosis.

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Identification of Mycobacterium Tuberculosis-Specific Genomic Regions Encoding Antigens Inducing Protective Cellular Immune Responses

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Comparative genomic studies have identified 11 regions of difference (RD1, RD4, RD5, RD6, RD7, RD9, RD10, RD11, RD12, RD13 and RD15) in Mycobacterium tuberculosis genome which are absent in all vaccine strains of M. bovis BCG. The proteins encoded by genes predicted in these RDs could be useful as protective vaccines and/or exacerbate the disease process by inducing cellular immune responses involved in protection and pathogenesis of tuberculosis. In our studies, by using pools of overlapping synthetic peptides covering the sequence of putative proteins encoded by genes predicted in each RD, we have determined the cellular immune responses in relation to antigen-induced proliferation and secretion of the protective Th1 cytokine IFN-gamma and the pathologic Th2 cytokine IL-10 by peripheral blood mononuclear cells of tuberculosis patients and healthy humans. It has been observed that peptides of RD1pool induced the highest antigen-induced proliferation and IFN-gamma responses, whereas the peptides of RD12pool and RD13pool induced the highest IL-10 responses. Furthermore, addition of RD12pool and RD13pool to peripheral blood mononuclear cells (PBMCs) cultures inhibited the RD1pool-induced secretion of IFN-gamma by PBMCs of healthy humans. These results suggest the relevance of RD1-encoded proteins in protection and RD12- and RD13-encoded proteins in pathogenesis of tuberculosis.

Solitary Rectal Ulcer Syndrome: A Clinicopathological Study of 13 Cases

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Background/Aims: Solitary rectal ulcer syndrome (SRUS) is a rare disorder that has a wide spectrum of clinical presentation and variable endoscopic findings. To further characterize the clinical and pathological features, a retrospective, hospital-based clinicopathological study was conducted.
Material and methods: All cases of SRUS diagnosed at Farwania Hospital, Kuwait, between 2002 and 2007 were retrieved from the computerized filing system. The histological slides were reviewed by two authors to confirm the diagnosis. Immunohistochemical stain for smooth muscle actin (SMA) was performed. The clinical files were reviewed for clinical features and endoscopic findings.
Results: Thirteen cases were identified: 8 males and 5 females. The age range was 15-85. Rectal bleeding, constipation, and abdominal pain were the most common presenting symptoms and were seen, either alone or in various combinations, in 12 of the 13 cases. Rectal ulceration was the most common endoscopic finding, being seen in 9 of the 3 cases; 3 of these cases had multiple ulcerations. Two patients had rectal polyps, with one of them having multiple polyps. The histological examination revealed surface serration, fibromuscular obliteration of the lamina propria, and crypts’ distortion in all the cases. Seven of the cases
Long-Term Follow-Up of 100 High-Risk Renal Transplant Recipients Converted from Calcineurin Inhibitors to Sirolimus: A Single Center Experience


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Transplant Proc 2009; 41:1666-1670

While conversion of stable renal transplant recipients (RTR) from calcineurin inhibitors (CNI) to sirolimus (SRL) is safe and effective, it is still under investigation for recent, high-risk cases. We studied the long-term effects of conversion of high-risk subjects maintained on a CNI, mycophenolate mofetil, plus steroid regimen to SRL, mycophenolate mofetil, plus steroid on graft and patient outcomes. We retrospectively reviewed the first 100 RTR converted to SRL treatment over approximately 5 years. The main indications for conversion were biopsy-proven acute rejection (BPAR), CNI toxicity, CNI elimination, and acute-tubular necrosis (ATN). Exclusion criteria were limited to bone marrow suppression. The overall mean +/- SD age was 38.5 +/- 15.6 years, including pediatric and geriatric age groups. Mean +/- SD body mass index (BMI) was 28.99 +/- 8.0 and 40% had a BMI > 30. There were 40% RTR from deceased donors and 60% showed 4 to 6 HLA mismatches. Preconversion total BPAR and steroid-resistant rejection incidences were 35% and 14%, respectively. Mean +/- SD time to start of SRL was 11.9 +/- 22.8 months posttransplantation. Proteinuria > 2 g/d, leukopenia, and hyperlipidemia increased significantly after conversion (P = .001, P = .0003, and P = .0001, respectively). Patient and graft survivals were 95% and 90%, respectively. There was significant improvement in graft function postconversion (P < .0001). There was a high incidence of side effects and cases of SRL discontinuation. Multivariate analysis demonstrated the influence of bone marrow suppression, obesity, hyperlipidemia, nutritional status, proteinuria, and graft function on graft and patient outcomes. We concluded that conversion from CNI to SRL was effective among high-risk RTR, but with a high incidence of adverse events during long-term follow-up.

Recent Advances in the Diagnosis and Treatment of Multidrug-Resistant Tuberculosis

Ahmad S, Mokaddas E

Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

Respir Med 2009 Aug 4 [Epub ahead of print]

Tuberculosis (TB) is a major infectious disease killing nearly two million people, mostly in developing countries, every year. The increasing incidence of resistance of Mycobacterium tuberculosis strains...
Health-Related Quality of Life of Kuwaiti Women with Breast Cancer: A Comparative Study using the EORTC Quality of Life Questionnaire

Alawadi SA, Ohaeri JU
Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait
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BMC Cancer 2009; 9:222

Background: The Kuwaiti perspective on quality of life (QOL) in breast cancer is important because it adds the contribution from a country where the disease affects women at a relatively younger age and seems to be more aggressive. We used the EORTC QLQ - C30 and its breast-specific module (BR-23) to highlight the health-related QOL of Kuwaiti women with breast cancer, in comparison with the international data, and assessed the socio-demographic and clinical variables that predict the five functional scales and global QOL (GQOL) scale of the QLQ - C30.

Methods: Participants were consecutive clinic attendees for chemotherapy, in stable condition, at the Kuwait Cancer Control Center.

Results: The 348 participants were aged 20-81 years (mean 48.3, SD 10.3); 58.7% had stages III and IV disease. Although the mean scores for QLQ - C30 (GQOL, 45.3; and five functional scales, 52.6% - 61.2%) indicated that the patients had poor to average functioning, only 5.8% to 11.2% had scores that met the < or = 33% criterion for problematic functioning, while 12.0% to 40.0% met the >66% criterion for more severe symptoms. Most (47.8% - 70.1%) met the >66% criterion for “good functioning” on the BR-23 functional scales. The mean scores of the QLQ - C30 indicated that, despite institutional supports, Kuwaiti women had clinically significantly poorer global QOL and functional scale scores, and more intense symptom experience, in comparison with the international data (i.e., < or = 10% difference between groups). For the BR-23, Kuwaiti women seemed to have clinically significantly better functional scale scores, but more severe symptoms, especially systemic side effects and breast symptoms. Younger women had poorer HRQOL scores. In regression analysis, social functioning accounted for the highest proportion of variance for GQOL.

Conclusion: The relatively high number that met the criterion for good functioning on the functional scales is an evidence base to boost national health education about psychosocial prognosis in cancer. In view of the poor performance on the symptom scales, clinicians treating Kuwaiti women with breast cancer should prepare them for the acute toxicities of treatment and address fatigue. The findings call for the institution of a psycho-oncology service to address psycho-social issues.
Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy


6th Annual International Pediatric Orthopaedic Symposium presented by POSNA and AAOS
Dec 02 - 06, 2009
Lake Buena Vista, FL, United States
Contact: American Academy of Orthopaedic Surgeons
Phone: 847-823-7186; Fax: 847-823-8125
E-Mail: meeting@aaos.org

Update on Cervical Diseases
Dec 03 - 05, 2009
New York, NY, United States
Contact: American College of Obstetricians and Gynecologists, 409 12th St., S.W., PO Box 9692
Phone: 202-638-5577
E-Mail: coding@acog.org / meetings@acog.org

27th Annual Infectious Disease Seminar for the Practicing Physician
Dec 04 - 06, 2009
Naples, FL, United States
Contact: Julie Embick
Phone: 330-325-6575 or 877-325-1212
Fax: 330-325-5929
E-Mail: ce@neoucom.edu

The 8th International Symposium in Ocular Pharmacology and Therapeutics
Dec 03 - 06, 2009
Rome, Italy
Contact: Hila Vakrat
Phone: 41-0-225-330-948 Fax: 41-0-225-802-953
E-Mail: oishay@isopt2009.com

40th Union World Conference on Lung Health
Dec 03 - 07, 2009
Cancun, Quintana Roo, Mexico
Contact: Conference Unit
Phone: 33-143-299-087; Fax: 33-153-108-554
E-Mail: cancun2009@theunion.org

10th Congress of the Slovak Society of Aesthetic and Cosmetic Dermatology with International participation
Dec 03 - 05, 2009
Slovakia
Contact: Ms Lenka Cuperova
Phone: 421 55 68 06 261; Fax: 00-421-556-806-156
E-Mail: lenka.cuperova@progress.eu.sk

Asian Cardiology Summit 2009 (ACS 2009)
Dec 04 - 06, 2009
Singapore, Singapore
Contact: Amilyn Ang
Phone: 65-63-490-249
E-Mail: AM.Ang@elsevier.com

The First Persian Gulf Congress on Rhinology and Facial Plastic Surgery
Dec 04 - 06, 2009
Kish Island
Contact: Mrs. Maryam Dehghan: Rhinology Research Society
Phone: 982-188-758-705; Fax: 982-188-741-343
E-Mail: info@rhinologysociety.org

Mayo Clinic 4th Annual Practical Course in Dermoscopy & Update on Malignant Melanoma
Dec 04 - 06, 2009
Scottsdale, AZ, United States
Contact: Meeting Organiser
Phone: 480-301-4580; Fax: 480-301-8323
E-Mail: king.staci@mayo.edu

Pain Management Conference Cruise
Dec 05 - 12, 2009
Honolulu, HI, United States
Contact: Continuing Education, Inc.
Phone: 1-800-422-0711; Fax: 727-522-8304
E-Mail: Sandra@continuingeducation.net

The British Medical Ultrasound Society (BMUS) 2009 Annual Scientific Meeting and Exhibition (EUROSON 2009)
Dec 06 - 08, 2009
Edinburgh, Scotland, United Kingdom
Contact: Meeting Organiser
E-Mail: office@bmus.org

XXI World Allergy Congress
Dec 06 - 10, 2009
Buenos Aires, Argentina
Contact: Mariu Denovi
Phone: 541-147-779-449; Fax: 541-147-711-536
E-Mail: info@worldallergy2009.com
2009 Annual Meeting of the American College of Neuropsychopharmacology
Dec 06 - 10, 2009
Hollywood, FL, United States
Contact: American College of Neuropsychopharmacology, 545 Mainstream Drive Suite 110, Nashville TN 37228
Phone: 615-324-2360; Fax: 615-324-2361
E-Mail: acnp@acnp.org

8th International Scientific Meeting of Obstetrics and Gynaecology
Dec 07-09, 2009
Middle East, United Arab Emirates
Contact: Synovetics
Phone: 971-0-26-673-418; Fax: 971-0-26-673-389
E-Mail: rcog@synovetics.com

26th Annual Advances in Heart Disease
Dec 11-13, 2009
San Francisco, CA, United States
Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 94118
Phone: 415-476-4251 / 415-476-5808; Fax: 415-476-0318 / 415-502-1795
E-Mail: info@ocme.ucsf.edu

Rheumatology for the Primary Care Physician
Dec 12-20, 2009
Fort Lauderdale, FL, United States
Contact: Eileen Tener, ACC Phone: 813-333-6878
E-Mail: ETener@CruisersParadise.com

Orthopaedics for the Primary Care Physician
Dec 20-27, 2009
Port Canaveral, FL, United States
Contact: Eileen Tener, ACC
Phone: 813-333-6878
E-Mail: ETener@CruisersParadise.com

53rd All India Congress of Obstetrics and Gynaecology
Jan 09 - 12, 2010
Guwahati, India
Contact: Congress Secretariat
E-Mail: fogsi@bom7.vsnl.net.in

Keystone Symposia: HIV Biology and Pathogenesis (A6)
Jan 12-17, 2010
Santa Fe, NM, United States
Contact: Keystone Symposia Meeting Organiser
Phone: 1-800-253-0685 / 1-970-262-1230; Fax: 1-970-262-1525
E-Mail: info@keystonesymposia.org

Conference of Congenital Heart Diseases from fetal life to childhood
Jan 13-16, 2010
Dar Salwa Hall, Kuwait
Contact: Dr. Amira AAH Al Hay, Head of Conference Organizing Committee
Phone: +965 25660607; Office tel. and fax: +965 24829613;
Mobile: +965 99494093
website: www.pecfek.com;
Email: amira_alhay@hotmail.com

World Cardiology, Metabolism and Thrombosis Congress (WCMTC)
Jan 20-23, 2010
Sao Paulo, Brazil
Contact: Iris Lev
Phone: 41-22-533-0948 Fax: 41-22-580-2953
E-Mail: ilev@paragon-conventions.com

ICAD & 3rd ECAA: International Congress of Aesthetic Dermatology
Jan 21-23, 2010
Bangkok, Thailand
Contact: Catherine Decuyper
Fax: 33-0-1-568-637-805
E-Mail: emc@euromedicom.com

68th AIOS Annual Conference
Jan 21-24, 2010
Kolkata, India
Contact: Parminder Singh
Phone: 1-800-102-2220
E-Mail: confsales@saharaglobal.in

The Society of Thoracic Surgeons 46th Annual Meeting
Jan 25-27, 2010
Fort Lauderdale, FL, United States
Contact: The Society of Thoracic Surgeons, 633 N. Saint Clair Street, Suite 2320, Chicago, IL 60611
Phone: 312-202-5800; Fax: 312-202-5801
E-Mail: sts@sts.org

13th International Congress of the Egyptian Hepato-Pancreato-Biliary Society
Jan 27-30, 2010
Cairo, Egypt
Contact: Ms. Fifi Erian
Phone: 20-2-2453-2916 or 20-2-2453-2917; Fax: 20-2-2453-3515
E-Mail: alfa@alfamedical.org

2nd International Conference on Drug Discovery & Therapy
Feb 01-04, 2010
Dubai, United Arab Emirates
Contact: Atif Hussain
Phone: 97-165-571-132; Fax: 97-165-571-134
E-Mail: marketing@icddt.com
9th International Conference on New Trends in Immunosuppression and Immunotherapy
Feb 04 - 07, 2010
Prague, Czech Republic
Contact: KENES International
Phone: 41-229-080-488; Fax: 41-229-069-140
E-Mail: immuno@kenes.com

10th Annual International Symposium on Congenital Heart Disease
Feb 06 - 09, 2010
St. Petersburg, FL, United States
Contact: Suzanne Anderson
Phone: 727-767-8584 Fax: 727-767-8601
E-Mail: cme@allkids.org

3rd International Gulf Group for the Study of Diabetes Conference
Feb 09 - 11, 2010
Jeddah, Saudi Arabia
Contact: Ms. Shieila
Phone: 966-2-614-3137; Fax: 966-2-614-3136
E-Mail: info@pediatricians.org.sa

Society of Laparoendoscopic Surgeons AsianAmerican MultiSpecialty Summit IV
Feb 10 - 13, 2010
Honolulu, Hawaii, United States
Contact: Conference Coordinator
Phone: 800-446-2659; Fax: 305-667-4123
E-Mail: conferences@sls.org

26th Annual Computed Body Tomography 2010: The Cutting Edge
Feb 11 - 14, 2010
Baltimore, MD, United States
Contact: Johns Hopkins University School of Medicine, Thomas B. Turner Building, 720 Rutland Avenue, Room 20, Baltimore, Maryland 21205-2195
Phone: 410-502-9634
E-Mail: cmenet@jhmi.edu

Obs-Gyne Middle East Meeting
Feb 14 - 16, 2010
Dubai, United Arab Emirates
Contact: Eben Botha
Phone: 00-97-143-365-161; Fax: 00-97-143-364-021
E-Mail: eben.botha@iirme.com

Winter Anesthesiology Conference
Feb 15 - 17, 2010
Cochin, India
Contact: Eva Rudz
Phone: 914-472-2382; Fax: 914-725-2780
E-Mail: winterconf2010@gmail.com

The 5th International Conference on Ocular Infections
Feb 18 - 21, 2010
Palm Beach, FL, United States
Contact: Hila Dayan
Phone: 41-225-330-948
E-Mail: hdayan@paragon-conventions.com

9th Genoa Meeting on Hypertension, Diabetes and Renal Diseases
Feb 25 - 27, 2010
Genoa, Italy
Contact: Ms. Barbara Rossi
Phone: 00-39-0-10-583-224; Fax: 00-39-0-105-531-544
E-Mail: genoameeting@aristea.com

Multidisciplinary Head and Neck Cancer Symposium
Feb 25 - 27, 2010
Chandler, AZ, United States
Contact: Meeting Organiser
Phone: 703-502-1550; Fax: 703-502-7852
E-Mail: cardiology@cuhk.edu.hk

International Congress of Cardiology (ICC)
Feb 26 - 28, 2010
City: Hong Kong, Hong Kong
Contact: Wingman Wong
Phone: 852-2632-3194; Fax: 852-2144-5343
E-Mail: cardiology@cuhk.edu.hk

68th Annual Meeting of the American Academy of Dermatology
Feb 26 - Mar 02, 2010
Miami, FL, United States
Contact: American Academy of Dermatology
Phone: 202-842-3555; Fax: 202-842-4355
E-Mail: cme@aaaai.org

American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting
Feb 26 - Mar 02, 2010
New Orleans, LA, United States
Contact: AAAAI Education Manager
Phone: 414-272-6071
E-Mail: cme@aaaai.org

7th Gastroenterology Hepatology & Endoscopy Symposium
Feb 27- Mar 01, 2010
Cairo, Egypt
Contact: Ms. Fifi Erian
Phone: 20-2-2453-2916 or 20-2-2453-2917; Fax: 20-2-2453-3515
E-Mail: alfa@alfamedical.org

International Congress XXIII on Endovascular Interventions
Feb 28 - 04, 2010
City: Scottsdale, AZ, United States
Contact: Erika Scott
Phone: 602-604-5030; Fax: 602-604-5020
E-Mail: escott@azheart.com
4th Duke Winter Anesthesia and Critical Care Review  
Feb 28- Mar 05, 2010  
Park City, UT, United States  
Contact: Dr Scott Brudney; Phone: 919-681-6437  
E-Mail: Scott.Brudney@Duke.edu

The 19th Annual International Congress of The Egyptian Society of Gynecology and Obstetrics (ESGO): Advances and Debates in Clinical Obstetrics and Gynecology  
Mar 03 - 05, 2010  
Hurghada, Egypt  
Contact: Mr. Alaa Abdalla or Mrs. Wala  
Phone: 2-010-666-1172; Fax: 202-2402-2796  
E-Mail: egycce@link.net

NYSORA World Anesthesia Congress  
Mar 07 - 12, 2010  
Dubai, United Arab Emirates  
Contact: Jo Watling  
Phone: 00-441-462-441-166; Fax: 00-441-462-452-562  
E-Mail: jo.watling@choicealive.com

Interventional Cardiology 2010: 25th Annual International Symposium  
Mar 07- 12, 2010  
Snowmass Village, CO, United States  
Contact: Laurel Steigerwald  
Phone: 760-720-2263; Fax: 760-720-6263  
E-Mail: IC2010@promedicacme.com

29th Annual Dialysis Conference  
Mar 08- 10, 2010  
Houston, TX, United States  
Contact: Office of Continuing Medical Education, University of Missouri  
Phone: 573-882-4105; Fax: 573-882-5666  
E-Mail: beckmannli@health.missouri.edu OR Carrk@health.missouri.edu

Mar 11- 13, 2010  
Abu Dhabi, United Arab Emirates  
Contact: Prof. Mohamed Al-Hajjaj Phone: 00-966-505-419-532; Fax: 0096-14-679-496  
E-Mail: msalhajjaj@yahoo.com

1st International (ADDC) Abu Dhabi Diabetes Congress  
Mar 12 - 14, 2010  
Abu Dhabi, United Arab Emirates  
Contact: Congress Manager  
Phone: 44-0-1-903-288-288; Fax: 44-0-1-903-520-520  
E-Mail: secretariat@addc.gr

2010 Winter Escape Emergency Medicine Update  
Mar 15 - 19, 2010  
Terrace, BC, Canada  
Contact: Jim Barr  
Phone: 888-308-3007; Fax: 780-483-5995  
E-Mail: jim@tandtadventures.com

Mar 17- 20, 2010  
Abu Dhabi, United Arab Emirates  
Contact: Prof. Mohamed Al-Hajjaj  
Phone: 00-966-505-419-532; Fax: 0096-14-679-496  
E-Mail: msalhajjaj@yahoo.com

7th World Congress of the International Academy of Cosmetic Dermatology (IACD)  
Mar 18 - 23, 2010  
Cairo, Egypt  
Contact: Ms Sandy Silverstein  
E-Mail: IACD@IACDworld.org

2nd African Middle Eastern Congress on Digestive Oncology  
Mar 19- 21, 2010  
Alexandria, Egypt  
Contact: Ms. Fifi Erian  
Phone: 20-224-532-916/20-224-532-917  
Fax: 20-224-533-515  
E-Mail: alfa@alfamedical.org

Innovations in Plastic Surgery  
Mar 19- 21, 2010  
Fort Lauderdale, FL, United States  
Contact: Diana Sheffey  
Phone: 954-659-5490 Fax: 954-659-5491  
E-Mail: dheffed@ccf.org

Keystone Symposia: HIV Vaccines (X5)  
Mar 21- 24, 2010  
Banff, AB, Canada  
Contact: Keystone Symposia Meeting Organiser  
Phone: 1-800-253-0685 / 1-970-262-1230; Fax: 1-970-262-1525  
E-Mail: info@keystonesymposia.org

14th Pan Arab Conference on Diabetes PACD14  
Mar 23 - 26, 2010  
Cairo, Egypt  
Contact: Mahmoud Ibrahim, MD  
Phone: 2012-213-1868; Fax: 202-2472-9793  
E-Mail: mahlmoud@arab-diabetes.com
7th European Breast Cancer Conference
Mar 24 - 27, 2010
Barcelona, Spain
Contact: ECCO - the European CanCer Organisation,
Avenue E. Mounier 83, B-1200 Brussels, Belgium
Phone: 32-27-750-201
Fax: 32-27-750-200
E-Mail: adline.lewuillon@ecco-org.eu / riitta.kettunen@ecco-org.eu

14th Pan Arab Conference on Diabetes PACD14
Mar 23- 26, 2010
Cairo, Egypt
Contact: Mahmoud Ibrahim, MD
Phone: 2012-213-1868; Fax: 202-2472-9793
E-Mail: mahmoud@arab-diabetes.com

41st Annual Meeting of the Society for Paediatric Nephrology
Mar 25 - 27, 2010
Hamburg, Germany
Contact: Jutta Vach
E-Mail: jutta.vach@conventus.de

Hair and Scalp Diseases in Clinical Practice. International Course and Symposium
Mar 26 - 28, 2010
Warsaw, Poland
Contact: Lidia Rudnicka
Phone: 48-225-081-480; Fax: 48-225-081-492
E-Mail: lidiarudnicka@yahoo.com

Saudi Hypertension Conference 2010
Mar 29 - 31, 2010
Jeddah, Saudi Arabia
Contact: Tawfik Albassam
Phone: 96-638-552-733; Fax: 96-638-552-733
E-Mail: info@shc2009.org

The 3rd Congress of the Asia Pacific Initiative on Reproduction (ASPIRE 2010)
Apr 09 - 11, 2010
Bangkok, Thailand
Contact: KENES International
Phone: 41-229-080-488; Fax: 41-229-069-140
E-Mail: aspire2010@kenes.com

20th Annual Meeting of the European Society of Clinical Microbiology and Infectious Diseases
Apr 10 - 13, 2010
Vienna, Austria
Contact: European Society of Clinical Microbiology and Infectious Diseases
Phone: 41-616-867-799; Fax: 41-616-867-798
E-Mail: info@escmid.org

2010 Annual Conference of the American Society for Laser Medicine and Surgery
Apr 14 - 18, 2010
Phoenix, AZ, United States
Contact: American Society for Laser Medicine and Surgery, 2100 Stewart Avenue, Suite 240, Wausau, WI 54401
Phone: 715-845-9283; Fax: 715-848-2493
E-Mail: information@aslms.org

The 45th Annual Meeting of the European Association for the Study of the Liver (EASL 2010)
Apr 14 - 18, 2010
Vienna, Austria
Contact: Secretariat: KENES International
Phone: 41-22-807-0360
Fax: 41-22-328-0724
E-Mail: easloffice@easloffice.eu

Valves in the Heart of the Big Apple VI: Evaluation & Management of Valvular Heart Diseases 2010
Apr 15 - 17, 2010
New York State, NY, United States
Contact: Leslie J. Yerman
Phone: 212-561-9879; Fax: 212-452-2027
E-Mail: info@heartvalveconference.com

2010 Annual Meeting of the American Society for Aesthetic Plastic Surgery (ASAPS)
Apr 22 - 28, 2010
Washington, DC, United States
Contact: American Society for Aesthetic Plastic Surgery (ASAPS)
Phone: 800-364-2147; Fax: 562-799-1098
E-Mail: asaps@surgery.org

British Renal Society: BRS Conference 2010
Apr 26 - 29, 2010
Manchester, England, United States
Contact: Conference Secretariat
Phone: 44-1-483-764-114; Fax: 44-1-483-727-816
E-Mail: brs@britishrenal.org

The 1st International Congress on Controversies in Allergology and Immunology
Apr 29 - 01, 2010
Sorrento, Italy
Contact: Conference Secretariat: KENES International
Phone: 41-229-080-488; Fax: 41-229-069-140
E-Mail: immuno@kenes.com

The 4th International Conference of Biomarkers in Chronic Diseases
May 04 - 06, 2010
Riyadh, Saudi Arabia
Contact: Conference Secretariat
Phone: 00-96-614-675-939; Fax: 00-96-614-675-931
E-Mail: biomarkers@ksu.edu.sa
The European Congress on Obstetrics and Gynaecology (EBCOG)
May 05 - 08, 2010
Antwerp, Belgium
Contact: Congress Secretariat
Phone: 32-9-233-8660; Fax: 32-9-233-8597
E-Mail: EBCOG2010@semico.be

7th Metabolic Syndrome, Type II Diabetes and Atherosclerosis Congress (MSDA)
May 12 - 16, 2010
Marrakesh, Morocco
Contact: Lily-Claude LEVASSEUR
Phone: 33-139-042-424; Fax: 33-139-040-741
E-Mail: msda2010@agence-plb.com

FIP World Congress of Podiatry
May 13 - 15, 2010
Amsterdam, Netherlands
Contact: Wendy van Buren
Phone: 31-0-348-443-251; Fax: 31-0-348-446-920
E-Mail: fip2010@mccm.nl

26th Iranian Congress of Radiology
May 13 - 16, 2010
Tehran, Islamic Republic of Iran
Contact: Conference Secretariat - ISR
Phone: 0098-21-4446-2078; Fax: 0098-21-4441-1224
E-Mail: info@icr2010.ir

World Congress of Immunodiseases and Therapy
May 15 - 17, 2010
Beijing, China
Contact: Kayla Liu
Phone: 0086-411-8479-9479; Fax: 0086-411-8479-9629
E-Mail: kayla@webbitmail.cn

14th Annual International Congress on Hematologic Malignancies
May 17- 20, 2010
Whistler, BC, Canada
Contact: Physicians’ Education Resource, 3500 Maple Ave, Suite 700 Dallas, TX 75219
Phone: 888-949-0045; Fax: 214-367-3304
E-Mail: info@pergrouplp.com

10th International Congress of Immunology and Allergy of Iran
May 18 - 20, 2010
Tehran, Islamic Republic of Iran
Contact: Dr. Mandana Sattari
Phone: 982-123-872-573; Fax: 982-122-439-952
E-Mail: info@icia2010.com

6th World Congress of the International Society of Physical and Rehabilitation Medicine
Jun 04 - 09, 2011
San Juan, Puerto Rico
Contact: Werner Van Cleemputte, Managing Director
Medicongress Waalpoel 28/34, B-9960 Assenede, Belgium
Phone: 32-0-93-443-959; Fax: 32-0-93-444-010
E-Mail: werner@medicongress.com

29th European Academy of Allergy and Clinical Immunology Congress (EAACI)
Jun 05 - 09, 2010
London, England, United Kingdom
Contact: Congress Secretariat
E-Mail: eaaci2010@congrex.com

International College of Neuropsychopharmacology 2010 Congress
Jun 06 - 10, 2010
Hong Kong, China
Contact: Organiser
Phone: 0-1-355-244-966; Fax: 0-1-355-249-959
E-Mail: cinp2010@congrex.com

13th International Conference on Emergency Medicine
Jun 09 - 12, 2010
Singapore, Singapore
Contact: Stella Chee
Phone: 65-63-795-261; Fax: 65-64-752-077
E-Mail: admin@icem2010.org

Euroanaesthesia 2010: The European Anaesthesiology Congress
Jun 12 - 15, 2010
Helsinki, Finland
Contact: Secretariat
Phone: 32-0-27-433-290; Fax: 32-0-27-433-298
E-Mail: registration@euroanesthesia.org

World Congress of Cardiology
Jun 16- 19, 2010
Beijing, China
Contact: Conference Secretariat: KIE
Phone: 551-150-521-215; Fax: 551-150-520-286
E-Mail: tjioekie@uol.com.br

CARS 2010 - Computer Assisted Radiology and Surgery - 24th International Congress and Exhibition
Jun 23 - 26, 2010
Geneva, Switzerland
Contact: CARS Conference Office - Mrs. Franziska Schweikert
Phone: 49-7742-922-434; Fax: 49-7742-922-438
E-Mail: office@cars-int.org
Psoriasis International Network Congress 2010  
Jul 01-04, 2010  
Paris, France  
Contact: Congress Secretariat  
Phone: 33-0-153-858-259  
Fax: 33-0-153-858-283  
E-Mail: pso2010@mci-group.com

World Congress of the World Federation of Hemophilia  
Jul 10-14, 2010  
Buenos Aires, Argentina  
Contact: Maria Milagros Salas - Congress & M Manager  
Phone: 1-514-394-2837  
E-Mail: hemophilia2010@wfh.org

7th International Congress on Neuroendocrinology  
Jul 10 - 15, 2010  
Rouen, France  
Contact: Secretary General: William Rostene, INSERM U.732 Hôpital Saint-Antoine, 184, rue du Fauborg Saint Antoine 75012 Paris, France  
Phone: 33-149-284-676  
E-Mail: william.rostene@st-antoine.inserm.fr

16th World Congress of Basic & Clinical Pharmacology  
Jul 13 - 23, 2010  
Copenhagen, Denmark  
Contact: Prof. Kim Brøsen / Tina Ludvig  
E-Mail: kbrøsen@health.sdu.dk / tludvig@health.sdu.dk

XVIII International AIDS Conference (AIDS 2010)  
Jul 18 - 23, 2010  
City: Vienna, Austria  
Contact: International AIDS Society HQ, PO Box 20, CH - 1216 Cointrin, GENEVA, Switzerland  
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15th World Congress on Heart Disease, Annual Scientific Sessions 2010  
Jul 24 - 27, 2010  
Vancouver, BC, Canada  
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The 26th International Pediatric Association Congress of Pediatrics (IPA 2010)  
Aug 05 - 09, 2010  
Johannesburg, South Africa  
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World Congress on Refractive Error  
Sep 20 - 22, 2010  
Durban, South Africa  
Contact: Conference Secretariat  
Phone: 27-31-201-1470; Fax: 27-31-201-1510  
E-Mail: events@confcall.co.za

American College of Surgeons 96th Annual Meeting  
Oct 03-07, 2010  
Washington, DC, United States  
Contact: American College of Surgeons  
Phone: 312-202-5000; Fax: 312-202-5001  
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The 26th International Pediatric Association Congress of Pediatrics (IPA 2010)  
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14th International Congress of Immunology  
Aug 22 - 27, 2010  
Kobe, Japan  
Contact: Prof. Masayuki MIYASAKA  
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28th World Congress of Endourology  
Sep 01 - 04, 2010  
Chicago, IL, United States  
Contact: Bailey-Turner Chernise  
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European Society of Urogenital Radiology: 2010 Symposium of the ESUR  
Sep 09 - 12, 2010  
City: Bruges, Belgium  
Contact: ESUR Head Office  
Phone: 43-15-334-064  
Fax: 43-15-334-064 - 448  
E-Mail: ESURSecretary@ecr.org

38th Annual Meeting of the International Society for Pediatric Neurosurgery  
Sept 13 - 16, 2010  
Jeju, Korea  
Contact: Gordon Mccomb  
E-Mail: gmcomb@chla.usc.edu

World Congress on Palliative Care  
Oct 05-08, 2010  
City: Montreal, QC, Canada  
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WHO-Facts Sheet

1. A Strategy to Prevent and Treat Diarrhoea – the Second Biggest Killer of Children
2. Antiviral Use and the Risk of Drug Resistance Pandemic (H1N1) 2009
3. International Day for Disaster Reduction
4. Cardiovascular Diseases (CVDs)
5. Visual Impairment and Blindness

Compiled and edited by
Babichan K Chandy


1. A STRATEGY TO PREVENT AND TREAT DIARRHOEA – THE SECOND BIGGEST KILLER OF CHILDREN

Global campaigns to fight diarrhoea - the second deadliest illness for children - must be re-energized to prevent the deaths of millions in the developing world, UNICEF and the World Health Organization (WHO) said today as they released a new report on the disease.

“It is a tragedy that diarrhoea, which is little more than an inconvenience in the developed world, kills an estimated 1.5 million children each year,” said UNICEF Executive Director, Ann M. Veneman. “Inexpensive and effective treatments for diarrhoea exist, but in developing countries only 39 per cent of children with diarrhoea receive the recommended treatment.”

The report, “Diarrhoea: Why Children Are Still Dying and What Can Be Done,” lays out a seven-point plan that includes a treatment package to reduce childhood diarrhoea deaths and a prevention strategy to ensure long-term results:
1. Fluid replacement to prevent dehydration;
2. Zinc treatment;
3. Rotavirus and measles vaccinations;
4. Promotion of early and exclusive breastfeeding and vitamin A supplementation;
5. Promotion of hand washing with soap;
6. Improved water supply quantity and quality, including treatment and safe storage of household water; and
7. Community-wide sanitation promotion.

Campaigns targeting childhood diarrhoea in the 1970s and 1980s achieved success by scaling up the use of oral rehydration solution (ORS) to prevent dehydration and by educating caregivers. In spite of the promising results of these campaigns, in recent years the international community has shifted its focus to other global emergencies. There is now an urgent need to focus once more on preventing and treating diarrhoea.

WHO and UNICEF recommend treating diarrhoea with low-osmolarity ORS and zinc tablets, which decrease the severity and duration of the attack. These treatments are simple, inexpensive and life-saving.

Access to clean water and good hygiene practices are extremely effective in preventing childhood diarrhoea. Hand washing with soap has been shown to reduce the incidence of diarrhoeal disease by over 40 per cent, making it one of the most cost-effective interventions for reducing child deaths from this neglected killer.

Yet despite the known benefits of improving water supply and sanitation, some 88 per cent of diarrhoeal diseases worldwide are attributable to unsafe water, inadequate sanitation and poor hygiene. As of 2006, an estimated 2.5 billion people were not using improved sanitation facilities, and nearly 1 in every 4 people in developing countries was practicing open defecation.

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2. ANTIVIRAL USE AND THE RISK OF DRUG RESISTANCE PANDEMIC (H1N1) 2009

As of 4 October 2009, worldwide, there have been more than 375,000 laboratory confirmed cases of pandemic influenza H1N1 2009 and over 4500 deaths reported to WHO.
As many countries have stopped counting individual cases, particularly of milder illness, the case count is significantly lower than the actually number of cases that have occurred. WHO is actively monitoring the progress of the pandemic through frequent consultations with the WHO Regional Offices and member states and through monitoring of multiple sources of data.

In the temperate regions of the Northern Hemisphere, transmission of influenza virus and rates of influenza-like-illness (ILI) continue to increase marking an unusually early start to fall and winter influenza season in many countries. Geographically widespread influenza is being reported throughout North America, with the United States reporting ILI levels elevated above the seasonal baseline for the past month and Mexico reporting a high intensity of respiratory diseases for the past three weeks. In Canada, although overall ILI activity remains low, focal increases have been reported in the western part of Canada. In Europe and Central and Western Asia, early transmission of influenza virus continues to increase in many countries, with more intense focal activity being reported in a few. National or regional ILI levels remained elevated above the baseline in parts of the United Kingdom (Northern Ireland and Scotland), Ireland, and Israel. In Ireland, a high intensity of respiratory diseases has been reported for the past two weeks, with the highest rates of ILI reported among children aged 5-14 years old. In addition to Ireland and Israel, widespread geographic spread of influenza virus is also now being reported in Belgium, the Netherlands, and Cyprus. At least 10 countries in the region are also reporting an increasing trend in respiratory diseases activity. In Japan, influenza activity continues to be elevated above the seasonal epidemic threshold since week 33, most recently in the large population centers.

In the tropical regions of the Americas and Asia, influenza virus transmission persists, however influenza activity remained variable. Geographically widespread to regional influenza activity continues to be reported throughout the tropical region of the Americas without a consistent overall trend (and increasing trend in parts of the Caribbean, and decreasing in much of tropical Central and South America). High intensity respiratory diseases activity was reported in Columbia, Cuba, and El Salvador, and moderate healthcare impact was experienced in many countries; two countries, Barbados and St. Lucia, reported severe healthcare impact. As influenza transmission slowly declines in many parts of South and Southeast Asia, several countries are reporting geographically regional spread (India, Bangladesh, and Thailand) or localized spread (Sri Lanka and Myanmar) of influenza activity; and most countries in the region have reported experiencing a low health care impact since late September.

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3. INTERNATIONAL DAY FOR DISASTER REDUCTION

Urgent action needed to protect hospitals from natural hazards

The tragedies that struck the Asia and Pacific region in early October 2009 underscore the urgent action that must be taken to better protect hospitals from natural disasters. Large-scale human suffering is exacerbated when the very services that are most needed to save lives - hospitals, clinics and other health facilities - are counted among the casualties.

The UN International Strategy for Disaster Reduction (UNISDR) dedicated its annual International Day for Disaster Reduction of 14 October 2009, to the urgent need to make “Hospitals Safe from Disasters.” Dozens of hospitals and health facilities each year are themselves impacted by floods, hurricanes, cyclones, earthquakes and other natural hazards because safety measures were not integrated in their design, location or construction.

The “Hospitals Safe from Disasters” theme was also used for the 2008-09 World Disaster Reduction campaign held on 14th of October, 2009. This two-year campaign has been a joint initiative of UNISDR, the World Health Organization and the World Bank aimed at ensuring people’s access to functioning health facilities during and after natural hazards. The ISDR system is using today’s event to highlight the gains made during the campaign and the work that still needs to be done in making hospitals safer from disasters.

“Since the beginning of the campaign, much has been achieved to make hospitals safer but more investments are still needed to improve the functionality of hospital when disasters occur,” says Margareta Wahlström, Special Representative of the UN Secretary-General for Disaster Risk Reduction.

According to a recent WHO survey, only 50% of all country’s health sectors have a budget allocation for risk reduction and emergency preparedness.

Hospitals and health facilities are in the frontline when floods, hurricanes, cyclones, and earthquakes strike and many are adversely impacted because safety measures were not integrated in their design, construction and functionality. There are at least 90,000 hospitals and other health facilities in the
world’s 49 least-developed countries, many of which are vulnerable to disasters, including those related to the harmful effects of climate change.

“No new hospital should be built unless it can withstand the impact of natural hazards,” Ms Wahlström adds. “Existing health facilities should also be assessed for their safety and action take to improve their safety and the level of their preparedness.”

Several countries in Latin America and the Caribbean have already assessed the safety of their health facilities and set priorities for making improvements. Mexico has demonstrated that it is possible to make hospitals safer by applying a Hospital Safety Index to more than 1000 of its high-risk facilities. The Hospital Safety Index measures 145 crucial spots in hospitals that will allow their safety classification according to three main levels.

The Hospital Safety Index has now been applied to many facilities in Bolivia, Ecuador and Peru and in countries elsewhere in the world, such as Oman, Sudan and Tajikistan. Dubai, within the United Arab Emirates has also committed to assessing half of its hospitals by 2010 and the remainder by the end of 2011. Hundreds of health professionals worldwide have been trained in emergency preparedness.

WHO will continue working with governments to achieve the objectives of the campaign and assure that they remain a priority for governments together with financial institutions, private and non-government organizations, professional bodies, health institutions and workforce, and international agencies. Preparedness and risk reduction is the way ahead in health and humanitarian action.

The last Global Platform for Disaster Risk Reduction held in Geneva proposed that by 2011 national assessments of the safety of existing health facilities should be undertaken, and that by 2015 concrete action plans for safer hospitals should be developed and implemented in all disaster prone countries. Hospital safety will remain one of the main elements of the new UNISDR campaign on cities at risk that will be launched next year.

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4. CARDIOVASCULAR DISEASES (CVDs)

What are cardiovascular diseases?

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels and include:

- coronary heart disease – disease of the blood vessels supplying the heart muscle
- cerebrovascular disease - disease of the blood vessels supplying the brain
- peripheral arterial disease – disease of blood vessels supplying the arms and legs
- rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria
- congenital heart disease - malformations of heart structure existing at birth
- deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs.

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots.

KEY FACTS

- CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.1 million people died from CVDs in 2004, representing 29% of all global deaths. Of these deaths, an estimated 7.2 million were due to coronary heart disease and 5.7 million were due to stroke.
- Low- and middle-income countries are disproportionally affected: 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women.
- By 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death. The largest percentage increase will occur in the Eastern Mediterranean Region. The largest increase in number of deaths will occur in the South-East Asia Region.

The risk factors for cardiovascular disease

The most important behavioural risk factors of heart disease and stroke are unhealthy diet, physical inactivity and tobacco use. Behavioural risk factors are responsible for about 80% of coronary heart disease and cerebrovascular disease.

The effects of unhealthy diet and physical inactivity may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, and overweight and obesity; these are called ‘intermediate risk factors’.

There are also a number of underlying determinants of CVDs, or, if you like, “the causes of the causes”.

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These are a reflection of the major forces driving social, economic and cultural change – globalization, urbanization, and population ageing. Other determinants of CVDs are poverty and stress.

Common Symptoms of heart attacks and strokes

Often, there are no symptoms of the underlying disease of the blood vessels. A heart attack or stroke may be the first warning of underlying disease. Symptoms of a heart attack include:

- pain or discomfort in the centre of the chest;
- pain or discomfort in the arms, the left shoulder, elbows, jaw, or back.

In addition the person may experience difficulty in breathing or shortness of breath; feeling sick or vomiting; feeling light-headed or faint; breaking into a cold sweat; and becoming pale. Women are more likely to have shortness of breath, nausea, vomiting, and back or jaw pain.

The most common symptom of a stroke is sudden weakness of the face, arm, or leg, most often on one side of the body. Other symptoms include sudden onset of: numbness of the face, arm, or leg, especially on one side of the body; confusion, difficulty speaking or understanding speech; difficulty seeing with one or both eyes; difficulty walking, dizziness, loss of balance or coordination; severe headache with no known cause; and fainting or unconsciousness.

People experiencing these symptoms should seek medical care immediately.

What is rheumatic heart disease?

Rheumatic heart disease is caused by damage to the heart valves and heart muscle from the inflammation and scarring caused by rheumatic fever. Rheumatic fever is caused by streptococcal bacteria, which usually begins as a sore throat or tonsillitis in children.

Rheumatic fever mostly affects children in developing countries, especially where poverty is widespread. Globally, almost 2% of deaths from cardiovascular diseases is related to rheumatic heart disease, while 42% of deaths from cardiovascular diseases is related to ischaemic heart disease, and 34% to cerebrovascular disease.

Symptoms of rheumatic heart disease

Symptoms of rheumatic heart disease include: shortness of breath, fatigue, irregular heart beats, chest pain and fainting.

- Symptoms of rheumatic fever include: fever, pain and swelling of the joints, nausea, stomach cramps and vomiting.
- Treatment
- Early treatment of streptococcal sore throat can stop the development of rheumatic fever.

Reducing the burden of cardiovascular diseases

Heart disease and stroke can be prevented through healthy diet, regular physical activity and avoiding tobacco smoke. Individuals can reduce their risk of CVDs by engaging in regular physical activity, avoiding tobacco use and second-hand tobacco smoke, choosing a diet rich in fruit and vegetables and avoiding foods that are high in fat, sugar and salt, and maintaining a healthy body weight.

Comprehensive and integrated action is the means to prevent and control CVDs.

- Comprehensive action requires combining approaches that seek to reduce the risks
throughout the entire population with strategies that target individuals at high risk or with established disease.

- Examples of population-wide interventions that can be implemented to reduce CVDs include: comprehensive tobacco control policies, taxation to reduce the intake of foods that are high in fat, sugar and salt, building walking and cycle ways to increase physical activity, providing healthy school meals to children.

- Integrated approaches focus on the main common risk factors for a range of chronic diseases such as CVD, diabetes and cancer: unhealthy diet, physically inactivity and tobacco use.

The treatment options

There are several treatment options available such as:

- Effective and inexpensive medication to treat nearly all CVDs.
- Survivors of a heart attack or stroke are at high risk of recurrences and at high risk of dying from them. The risk of a recurrence or death can be substantially lowered with a combination of drugs – statins to lower cholesterol, drugs to lower blood pressure, and aspirin.
- Operations used to treat CVDs include coronary artery bypass, balloon angioplasty (where a small balloon-like device is threaded through an artery to open the blockage), valve repair and replacement, heart transplantation, and artificial heart operations.
- Medical devices are required to treat some CVDs. Such devices include pacemakers, prosthetic valves, and patches for closing holes in the heart.

There is a need for increased government investment through national programmes aimed at prevention and control of CVDs and other noncommunicable diseases.

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5. VISUAL IMPAIRMENT AND BLINDNESS

Global trends

Global trends since the early 90s show reduced rates of visual impairment worldwide, and a shift in the causes. Visual impairment and blindness caused by infectious diseases have been greatly reduced (an indication of the success of international public health action), but there is a visible increase in the number of people who are blind or visually impaired from conditions related to longer life expectancies.

Globally about 314 million people are visually impaired, 45 million of them are blind.

Presbyopia, the inability to read or perform near work that occurs with ageing, causes visual impairment if it is not corrected. The scope of the problem is not known, but preliminary studies indicate that the problem could be vast, especially in developing countries.

Key facts

- About 314 million people are visually impaired worldwide, 45 million of them are blind.
- Most people with visual impairment are older, and females are more at risk at every age, in every part of the world.
- About 87% of the world’s visually impaired live in developing countries.
- The number of people blinded by infectious diseases has been greatly reduced, but age-related impairment is increasing.
- Cataract remains the leading cause of blindness globally, except in the most developed countries.
- Correction of refractive errors could give normal vision to more than 12 million children (ages five to 15).
- About 85% of all visual impairment is avoidable globally.

There are four levels of visual function:

- normal vision
- moderate visual impairment
- severe visual impairment
- blindness.

Who is at risk?

By age: About 82% of all people who are visually impaired are age 50 and older (although they represent only 19% of the world’s population).

Increasing numbers of people are at risk of age-related visual impairment as the global population grows and demographics shift to a higher proportion of older people, even in developing countries.

Child blindness remains a significant problem globally. An estimated 1.4 million blind children below age 15 will live in blindness for many years. In addition, more than 12 million children ages five to 15 are visually impaired because of uncorrected refractive errors (near-sightedness, far-sightedness or astigmatism): conditions that could be easily diagnosed and corrected with glasses, contact lenses or refractive surgery.

By gender: Studies consistently indicate that females have a significantly higher risk of being visually impaired than males, in every region of the world, and at all ages.
Geographically: Visual impairment is not distributed uniformly throughout the world. Approximately 87% of visually impaired people live in developing countries.

Source: WHO/Prevention of Blindness

Causes of blindness
Globally, the leading causes of blindness, in order of frequency, are:
- cataract (a clouding of the lens of the eye that impedes the passage of light),
- uncorrected refractive errors (near-sightedness, far-sightedness or astigmatism),
- glaucoma (a group of diseases that result in damage of the optic nerve),
- age-related macular degeneration (which involves the loss of a person’s central field of vision).

Other major causes include corneal opacities (eye diseases that scar the cornea), diabetic retinopathy (associated with diabetes), blinding trachoma, and eye conditions in children such as cataract, retinopathy of prematurity (an eye disorder of premature infants), and vitamin A deficiency.

Prevention
Globally, about 85% of all visual impairment and 75% of blindness could be prevented or cured worldwide.

Since the 90s, areas of significant prevention progress on a global scale include:
- further development of eye health care services, which has led to increased availability and affordability;
- increased commitment to prevention and cure from national leaders, medical professionals and private and corporate partners;
- higher awareness and use of eye health care services by patients and the general population; and
- implementation of effective eye health strategies to eliminate infectious causes of vision loss.

WHO response
WHO works with Member States and public and private partners to prevent blindness and restore sight in every part of the world. WHO provides technical assistance, monitoring and coordination among partners to strengthen country-level efforts to eliminate avoidable blindness, treat eye diseases, expand access to eye health services, and increase rehabilitation for people with residual visual impairment (including tools and skills for daily life).

For more information contact: WHO Media centre.
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# Yearly Author Index

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