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Diabetes, Antidiabetic Drugs, and Cancer:
Separating Background Risk from Iatrogenesis

Intekhab Ahmed¹, Samuel Dagogo-Jack²

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²Division of Endocrinology, Diabetes and Metabolism, University of Tennessee Health Science Center, Memphis, Tennessee, USA


Editorial

Diabetes is a well-recognized risk factor for long-term microvascular and macrovascular complications, via mechanisms that include glycemic and nonglycemic mediators. However, an association between diabetes and increased risk of cancer, though first reported in 1932, is less well recognized and often controversial. In 2009, a metaanalysis linking increased risk of cancer with use of insulin in patients with diabetes generated tremendous attention on the subject in the medical literature. Given the high prevalence of cancer and diabetes, both conditions can be expected to occur in certain individuals as a matter of chance. Of critical importance to biomedicine is the question as to whether there is a causal or biologically plausible association between diabetes and cancer and if so, what could be the underlying mechanisms?

The discussion in the literature has tended to separate type 1 diabetes from type 2 diabetes in the consideration of cancer association. Specific data for patients with type 1 diabetes and cancer risk is conflicting. A survey of 28,900 British patients with insulin-treated diabetes, followed for 520,517 person-years, showed a significant increased risk of ovarian cancer in patients with diabetes diagnosed under age 30 years (mostly thought to be type 1). Risks of cancer at other major sites were not substantially raised for people with type 1 diabetes. Similarly, a Swedish cohort study that examined cancer incidence among 29,187 patients, who were hospitalized for type 1 diabetes from 1965 to 1999, reported a 20% increase in overall cancer incidence among type 1 diabetes patients compared to the background age matched population. Specifically, elevated risks of cancers of the stomach, cervix, and endometrium were noted. A fairly consistent finding of increased risk of pancreatic cancer in patients with type 1 diabetes has also been noted.

Most reports and studies on the subject of diabetes and cancer have focused on type 2 diabetes. Support for a link between diabetes and increased cancer risk comes from many globally conducted meta-analyses. Several reports have indicated that diabetic patients are twice as likely to have cancers of the liver, pancreas, and endometrium, compared to persons without diabetes. The link between colon, rectum, breast, and bladder cancers and diabetes also has been observed, though reported association is weaker than the aforementioned cancers. Interestingly, a notable exception is prostate cancer, where lower risk has been consistently reported for diabetic patients.

Potential Mechanisms and Mediators

Some common risk factors shared by diabetes and cancer include obesity, insulin resistance, inflammation, dietary factors, and smoking. It is plausible that the aggregation of these risk factors in a genetically susceptible individual could create favorable grounds for the coexistence of diabetes and cancer. Obesity, a major risk factor for type 2 diabetes has been linked to increased prevalence of several cancers, including adenocarcinoma of the gastric cardia, gall bladder cancer, liver cancer, pancreatic cancer, hematopoietic malignancies, and advanced prostate cancer. A large epidemiological study in the United Kingdom implicated increased adiposity as a contributory factor to increased cancer risk among postmenopausal women. Although the exact mechanisms remain to be elucidated, the adverse metabolic effects of over-nutrition, excess body fat, and insulin resistance represent putative triggers of abnormal cell proliferation in the obese state. At the molecular level, an attractive candidate mediator is hyperinsulinemia (common in obesity, insulin resistance and type 2 diabetes), which could promote...
cell proliferation through cross-activation of insulin like growth factor (IGF-I) receptors\textsuperscript{[19]}. Clearly, further research is needed to unravel the mechanism(s) linking diabetes and cancer.

**Antidiabetes Medications**

Because reports of increased cancer risk were developed mostly from patients already receiving antidiabetic medications, attention has been given to an examination of the specific roles of these agents. At issue is whether insulin and the other medications used for management of diabetes account for, or contribute to, some of the increased risk of cancers in diabetes patients. In general, the metabolic effects of insulin species correlate with binding affinities to the insulin receptor, whereas the mitogenic effects correlate better with IGF-1 receptor affinities. Thus, the finding that insulin analogs have variable (and often weak) binding affinities for IGF-1 receptors\textsuperscript{[10]} suggests that clinical use of insulin in diabetes therapy should have minimal potential for stimulating mitogenesis. Indeed, the findings of the ORIGIN trial, a prospective randomized controlled long-term study, provide reassurance that the use of insulin glargine was not associated with increased risk of cancer in any anatomical region\textsuperscript{[17]}.

With regard to noninsulin agents, a recent metaanalysis using primary data of published studies reported that metformin use was associated with decreased cancer risk, whereas sulfonylureas use was associated with increased risk\textsuperscript{[18]}. The mechanism(s) for any “anticancer” effect of metformin are yet to be clarified from randomized prospective studies. However, such a metformin effect could introduce artificial elevation of cancer risk by non-metformin drugs in clinical, epidemiologic, or database studies of crude cancer rates among diabetic patients taking different medications. Adjustment for multivariables ought to minimize such confounding. Data from the existing randomized controlled trials that included thousands of patients treated with metformin, sulfonylurea or rosiglitazone for many years did not support a cancer-lowering effect of metformin versus rosiglitazone\textsuperscript{[19]}. However, they do not refute the possibility of a difference in cancer incidence among metformin-treated subjects compared with those treated with sulfonylureas\textsuperscript{[19]}. In 2011, the Food and Drug Administration added a warning to pioglitazone label after a weak link between increased risk of bladder cancer and long-term use of pioglitazone was detected in an interim report of a longitudinal cohort study\textsuperscript{[20]}. Further update from that cohort should demonstrate whether the observed weak association strengthens or disappears with accrual of additional patient-years of follow-up. Glucagon-like peptide-1 (GLP-1) agonists also have a warning regarding the risk of medullary thyroid cancer (so far detected only in rodents). Recently, GLP-1 agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors have been associated with histological changes in animal and postmortem human pancreatic tissue\textsuperscript{[21]}, but the significance of those findings has been questioned\textsuperscript{[22]}.

In conclusion, type 2 diabetes and cancer are two prevalent conditions that can be expected to co-exist by chance in many individuals. Several common risk factors shared by both conditions also increase the risk for their coexistence in susceptible persons. Some medications used for treatment of diabetes have been reported to be associated with either increased or decreased risk of certain cancers, but the level of evidence often falls short of the randomized, controlled standard. The few reports from randomized, controlled studies or longitudinal follow-up data provide reassurance that the antidiabetes medications in common use are unlikely to be associated with a significant systematic increase in cancer risk\textsuperscript{[17,19]}. However, continued surveillance and further studies are needed, particularly among patients treated with agents that have been implicated in cancer risk. In this regard, numerous prospective, randomized trials of incretin agents are in progress to answer this question. Drug manufacturers also have been requested to provide all available patient-level data that can help clarify whether any of the anti-diabetes agents in current use poses a significant risk for cancer. In the meantime, physicians should discuss the pros and cons of every medication with their patients, and follow established prescription guidelines.

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Metabolic Acidosis in the Critically Ill and Continuous Renal Replacement Therapy – A Review

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ABSTRACT

Metabolic acidosis is common in critically ill patients in intensive care units with or without acute kidney injury. Metabolic acidosis is usually of multifactorial etiology. Often these patients have lactic acidosis. The routine use of intravenous sodium bicarbonate to manage acidemia is debatable. Continuous renal replacement therapy (CRRT) is often indicated in the management of these oliguric, catabolic sick patients with metabolic acidosis. The extent of acid base changes in CRRT is governed by the intensity of plasma water exchange / dialysis and by the buffer content of the replacement fluid / dialysate used. Bicarbonate containing replacement fluid is the preferred choice over lactate containing fluid as buffering agent in many centers. However, lactate containing replacement fluid can be used in most patients for managing acidemia in CRRT, as it is easily available and less costly.

KEYWORDS: critically ill, CRRT, metabolic acidosis

INTRODUCTION

Acute Kidney Injury (AKI), occurs in critically ill patients often as a part of multiorgan failure. The clinical spectrum of AKI has changed over the past few years from that of a single organ disease managed only by nephrologists in the ward to a disease that occur in intensive care units (ICU), managed both by intensivists and nephrologists[1]. This subset of patients is often septic, fluid-logged, acidaemic and hemodynamically unstable. Continuous renal replacement therapy (CRRT) is one of the common modalities of renal replacement therapy (RRT) used in these patients and is hemodynamically well-tolerated and efficient in achieving good control of uremic milieu, fluid status and acid base balance. During CRRT, alkali administration either by the replacement fluid and / or by diffusive uptake from the dialysate replaces the bicarbonate lost in the buffering of endogenous acid and also that lost across the hemodiafilter. CRRT also removes many endogenous acids accumulated, by convective or diffusive transport across the hemodiafilter. Correction of metabolic acidosis is one of the primary aims in CRRT. Depending on the type of CRRT prescribed the buffer balance is influenced by several factors which in turn not only affects acid base correction but possibly clinical outcomes. The review here briefly deals with metabolic acidosis in critically ill patients and the useful role of CRRT in these scenarios, as to how it rectifies metabolic acidosis and also the importance of buffering agents in the replacement / dialysate fluids.

LITERATURE REVIEW

Metabolic acidosis in critically ill patients is usually of multifactorial etiology. Sepsis with hemodynamic compromise with or without AKI, often with lactic acidosis contributing to a decrease in blood pH, is a common scenario.

Metabolic acidosis with AKI in the critically ill is due to complex interaction between the acidifying effect of unmeasured anions, hyperphosphatemia, hyperlactatemia, hypocalcemia and the minimum alkalinising effect of hypoalbuminemia. In the early stages of AKI, hyperchloremia causes a decrease in strong ion difference (SID) leading to acidosis. In the later stages, unmeasured anions like ketoacids, diverse acids of intermediary metabolism (Kreb’s cycle) like citrate, acetate, fumarate and others like sulphate, urate, oxalate, and propionates are major contributors to acidosis in AKI[2,3]. These unmeasured
anions contribute to nearly 50% of the acidosis. Lactic acidosis in these hemodynamically compromised patients with multiorgan dysfunction also contributes to metabolic acidosis.

The aim and extent of correction of acidosis in the critically ill patients is a matter of debate. Severe metabolic acidosis arbitrarily defined as pH less than 7.1 has a number of adverse effects on the patient including myocardial depression and refractory shock. However, the overall effect of increased extracellular [H+] on the myocardium is related to the underlying disease state producing acidosis, catecholamine response, intracellular energy stores and other variables like tissue oxygen tension, concentration of various electrolytes and lactate. Sepsis and lactic acidosis have a profound negative inotrop effect on the heart than other forms of metabolic acidosis. Also, there are different effects of acidosis seen in animal experimental setting and actual clinical settings. Intravenous bicarbonate therapy for correction of severe acidosis has a basket of adverse effects like hypervolemia, hypernatremia, increase in lactate production, increased pCO2, and also may cause overshoot alkalosis.

Severe metabolic acidosis caused or aggravated by AKI is an indication for RRT when intravenous bicarbonate buffering becomes insufficient or complicates therapy due to fluid logging in the presence of compromised renal function. Additional indications for initiating RRT are often present like hyperkalemia, hypercatabolic states, fluid overload and to replenish sufficient nutrition. Rarely, an acid-base disorder is an exclusive indication for RRT. Metabolic acidosis which is refractory to RRT may define a subset of population with very high mortality and acidosis may reflect underlying severity of illness with poor prognosis. Metabolic acidosis itself, may not be a causative factor in morbidity and mortality in the critically ill.

RRT is a symptomatic therapy of acid base disorder and treatment of underlying disease is essential. Specific physiological end points for acid base intervention via RRT in the critically ill patient are undefined. CRRT especially continuous venovenous hemofiltration (CVVHF) and continuous venovenous hemodiafiltration (CVVHDF) are often used in critically ill hemodynamically unstable patients as these therapies are hemodynamically well-tolerated, correct metabolic abnormalities as they evolve (steady state chemistry) and are highly effective is removing excess fluid even in patients requiring high inotropic support.

CVVHF and CVVHDF remove acids from the body by way of diffusive and convective transport across the hemofilter membrane. The buffer type and concentration can be chosen and replaced by ‘replacement fluids’ without major volume restrictions because fluid balance can be maintained and regulated by adjustments in ultrafiltration rate. In adults about 8-10 times the total amount of body plasma water can be filtered in 24 hrs and replaced by replacement solutions. Generally, higher the ultrafiltration rate, higher the ‘convective’ removal of acidifying substances from the blood and faster replacement of ‘buffering’ agent by replacement fluid and faster control of acidemic status. However, this theoretical advantage of hemofiltration techniques being able to achieve better uremic toxin clearances with high ultrafiltration can be technically demanding to realize whenever ultrafiltration is > 25 l/day. Fluid balancing with replacement fluids and filter clotting due to extracorporeal hemoconcentration poses a problem in practicality. Evidence shows that in CRRT, ultrafiltration rate of between 20 ml/kg body weight/hr to 35 ml/kg/hr achieves optimal uremic toxin clearances and metabolic control in critically ill AKI patients.

It is important to discuss the following to clearly depict how CRRT is helpful to correct acidosis in the critically ill:

- What are the acids which are dialyzable?
- Are ‘bases’ (bicarbonate) also dialysed during CRRT?
- During CRRT, which replacement fluid is preferred for correcting acid-base disorder, ‘bicarbonate based’ replacement fluid or ‘lactate based’?
- Is there any difference in the ‘outcomes’ when bicarbonate based fluid Vs lactate based fluid is used?

CRRT corrects acidosis by way of acid removal and adding buffer to the plasma. CRRT can correct acidemia in most circumstances by 24 / 48 hours and balanced acid base milieu can be maintained for 24 hours a day by virtue of being a continuous technique. The acidifying substances removed by RRT are phosphates and unmeasured anions. Mineral acids have low molecular weight and high diffusibility and hence are dialyzable. Depending on the molecular weight, organic acids can be removed by RRT as well but to variable extent.

Inborn errors of metabolism in the neonates and pediatric age group may present as severe acidosis often along with hyperammonemias. Both ammonia which may cause neurological sequale and the offending organic acids are effectively removed in CRRT, making this a useful adjuvant treatment in the acute management of these patients.

Only small amounts of lactate (< 3 - 5%) are removed by CRRT. The nature and extent of acid base changes brought about by CRRT depends not only on the amount of accumulated acid dialyzed but also on the buffer content of the replacement fluid / dialysate and...
the metabolic rate of these anions\cite{19}. Treatment of lactic acidosis must always address tissue perfusion and oxygenation, hemodynamic stability and management of basic etiology of illness. RRT cannot rectify lactic acidosis and is not the treatment for lactic acidosis.

During standard CRRT, up to 800 - 1000 mmol per day of bicarbonate is lost in the ultrafiltration. During CRRT, buffer is administered to make up for the losses in the ultrafiltration and also to combat base deficit which had occurred due to acidemia. The required ‘buffering agent’ is delivered during CRRT by way of dialysate fluid across the hemofilter to the blood stream and also by way of ‘replacement’ fluid infusion.

Nowadays, dialysate solutions and replacement fluids are commercially, easily available packaged in five liter bags. The same dialysate fluid can be used as replacement fluid infused either pre-hemofilter or post-hemofilter. Available fluid comes in a variety of fluid composition, differing in buffer type and content, amount of sodium, calcium, magnesium and potassium (Table 1).

The patient’s clinical profile, biochemical parameters and ability to metabolize lactate influence the choice of ‘buffers’ in correction of acidosis by continuous RRT in critically ill patients. ‘Acetate’ as a buffer was used previously but it is almost abandoned nowadays as it causes severe vasodilatation and worsens hemodynamic instability\cite{20}. Lactate and bicarbonate containing solutions offer better acidosis control and hemodynamic stability than acetate based solutions. The effect on blood pH of different replacement solution depends on the strong ionic difference (SID) of the fluid. Normal value of plasma SID is 39 ± 1 mmol/l. High SID values of replacement fluid have alkalinizing effects and low values have acidifying effects\cite{21,22}. If the replacement fluid has got high chloride concentration the SID value of the fluid will be low, leading to net plasma chloride gain and hyperchloremic acidosis (HCA). However, the net plasma chloride gain and its effect on acid base status cannot be easily predicted due to multiple variable factors in CRRT. The serum chloride level may fall below the concentration level in the replacement fluid especially in high volume CRRT and exert an alkalinizing effect\cite{23}. The site of replacement fluid infusion, i.e., prefilter or postfilter also has an effect on the ultimate serum concentration of various cations and anions which in turn affects the SID and acid base milieu\cite{24}. At present there is limited data regarding HCA in CRRT.

The choice is made mainly between bicarbonate and lactate as buffers. The evidence for or against lactate or bicarbonate as replacement buffer is less clear cut as there are only few prospective, randomized controlled trials with small patient numbers\cite{25-28}. Data mainly comes from small case series and retrospective cohort studies. A number of case series reported better acidosis control in severely ill patients when lactate was replaced by bicarbonate replacement fluids\cite{29}. However, many controlled studies reported equal efficacy for acidemia correction for the two solutions\cite{26,27}. Again, an important caveat is that the clinical subgroup of patients with high initial blood lactic acid levels have not been included in many studies comparing lactate vs bicarbonate replacement fluids.

Lactate is normally converted in the liver on a 1:1 basis to bicarbonate and is capable of providing sufficient alkali load to correct acidemia, when fully metabolized.

Hyperlactatemia becomes a problem in patients with hepatic dysfunction as ‘lactate’ in replacement fluid is not fully converted to bicarbonate. ‘Lactate intolerance’ during CRRT is defined arbitrarily as a > 5 mmol/l rise in serum lactate levels. Iatrogenic hyperlactatemia may cause hyperglycemia\cite{28}. The effect of this iatrogenic hyperlactatemia on patient outcome viz acidosis, hemodynamic instability and metabolic acidosis in the Critically Ill and Continuous Renal Replacement Therapy ... December 2013

Table 1: Showing some of the CRRT solutions commercially available and their composition (Bicarbonate and lactate composition is highlighted)

<table>
<thead>
<tr>
<th>Component (mM/l)</th>
<th>Peritoneal dialysis fluid (Baxter)</th>
<th>Ringer Lactate solution</th>
<th>Prismasate- L (Gambro renal product)</th>
<th>Prismasate (Gambro renal product)</th>
<th>Hemosol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>132</td>
<td>130</td>
<td>140</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0, 2, 4</td>
<td>0</td>
</tr>
<tr>
<td>Chloride</td>
<td>96</td>
<td>109</td>
<td>109</td>
<td>109</td>
<td>109</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Nil</td>
<td>Nil</td>
<td>-</td>
<td>22/32</td>
<td>32</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.75</td>
<td>1.35</td>
<td>1.25</td>
<td>1.25</td>
<td>1.75</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.25</td>
<td>Nil</td>
<td>0.75</td>
<td>0.75</td>
<td>0.5</td>
</tr>
<tr>
<td>Lactate</td>
<td>40</td>
<td>28</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>1360</td>
<td>Nil</td>
<td>110</td>
<td>0 or 110</td>
<td>Nil</td>
</tr>
</tbody>
</table>

- Peritoneal dialysis fluid contains lactate based buffer and are easily available and can be used for CRRT but the problem is the high glucose content of fluid that can cause hyperglycemia.
- Hemosol / prismasate contains two solutions (Sol A and Sol B) in a single bag of 5l separated by a barrier, which needs to be pre-mixed just prior to the usage.
mortality is unclear. In an early study in patients with combined hepatic and renal failure, lactate based CRRT led to lactic acidosis and hemodynamic compromise\textsuperscript{[29]}. In another prospective study involving 132 patients, no difference was found between bicarbonate based and lactate based fluids in terms of acidosis control and hemodynamic variables\textsuperscript{[30]}. There are no studies which show a significant mortality benefit for either bicarbonate or lactate based replacement fluid in CRRT as patient numbers were small in most series.

However, the working group of Acute Dialysis Quality Initiative (ADQI) recommend that bicarbonate based replacement fluid be used for patients with liver failure, presence of lactic acidosis at the initiation of RRT and when high volume hemofiltration is considered\textsuperscript{[31]}. High volume hemofiltration (HVHF) involves ultrafiltration volume filtration more than 50 l/day (varying between 35 – 80 ml/kg/hr)\textsuperscript{[32]}. A bicarbonate based solution seems to be more physiological and has become the buffer of choice in many centers. But bicarbonate solutions are more expensive and unstable as they breakdown to CO\textsubscript{2} and H\textsubscript{2}O. CO\textsubscript{2} may be lost by diffusion from plastic containers and decrease bicarbonate concentration. Also, HCO\textsubscript{3}\textsuperscript{-} form insoluble precipitates with Ca\textsuperscript{2+} and Mg\textsuperscript{2+} when in solution and hence they cannot be mixed until shortly before use. The bicarbonate concentration in the replacement fluid is much higher than the normal serum bicarbonate levels (supraphysiological) as this is necessary to replenish the patient’s base deficit. Lactate based solutions are less costly, more stable and easily available. The use of lactate based solutions in CRRT is well tolerated in most patients. Commercially available solutions are buffered with approximately 40 mmol/l of lactate. Monitoring of arterial lactate levels along with blood gases is advisable when lactate based fluids are used\textsuperscript{[30]}. 

**CONCLUSION**

CRRT is a useful tool in the management of metabolic acidosis in the critically ill patients with hemodynamic instability and multiorgan failure. Being a continuous technique it is helpful in maintaining a balanced acid base milieu 24 hours a day. The extent of acid base changes in CRRT depends on multiple factors like the intensity of dialysis /dialfiltration, the choice of buffering agent, the patients’ ability to metabolize lactate and the site of replacement fluid infusion (pre-filter or post-filter). CRRT is not useful in the primary management of lactic acidosis per se and the underlying etiology for lactic acidosis should be addressed.

Bicarbonate based dialysis fluid and replacement fluids are preferred choice for CRRT, especially in patients with liver failure and pre-existing lactic acidosis. However where cost and availability poses a constraint, most critically ill patients can still be safely managed with lactate containing replacement solutions.

**REFERENCES**

Association between Patients’ Sociodemographic Characteristics and their Satisfaction with Primary Health Care Services in Turkey

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⁴Nolu Aile Sagligi Merkezi (ASM), Kayapinar, Diyarbakir, Turkey
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ABSTRACT

Objective: To investigate the influence of patient’s socio-demographic features on patient’s satisfaction with primary health care (PHC) services in the Turkish population

Design: Cross-sectional and population-based study

Settings: Forty-five family health centers from 15 cities throughout Turkey

Subjects: One thousand two hundred and ten patients were randomly selected. The self-administered study survey was applied.

Main Outcome Measures: Association between patients’ sociodemographic features and patient satisfaction with primary care settings

Results: The mean age of subjects was 37.4 ± 14.7 years. When mean total score for incisions of sociodemographic features was evaluated, it was observed that the patient satisfaction level was high in female than male patients, married than unmarried patients, patients with high income than low income, in employed and unemployed than officers (p = 0.028, p = 0.043, p = 0.001, and p = 0.006, respectively). The patients with high income level had significantly higher level of satisfaction than those with low income in all domains of patient satisfaction. Female patients were more satisfied with communication, medical care, and support and information domains. Married patients were more satisfied with communication and medical care. The officers were less satisfied than other status of occupation. The patients with university level of education were more satisfied than those with middle and high school level of education.

Conclusion: Income level, marital and occupational status of patient’s sociodemographic features had significant influence on satisfaction levels in the Turkish population

INTRODUCTION

As the health care system in Turkey has evolved over the last few years, quality in health care appears more difficult to achieve. In Turkey, transition health care system has been provided, particularly, in primary health care (PHC) settings. Family medicine implementation was initiated in and established since 2005[1, 2].

Health care is an integrated multidisciplinary service. Primary care is the most important and basic step. Therefore, family physicians have a great responsibility to provide PHC services. They are gatekeeper physicians[3,4]. Most of the patients, coming to see their primary care physician (PCP), have explicit expectations and priorities for their medical consultation. Recognition of these expectations is an important step in organizing patient-oriented health care services. Patient expectations depend on a number of factors: health problem and its severity, as well as social and demographic characteristics of patient and physician[5].

Patient satisfaction is a multidimensional healthcare construct influenced by many factors. Health care quality affects patient satisfaction, in turn influencing positive patient behavior, such as loyalty[6]. The measurement of patient satisfaction with family
physician practice is an important determinant and meets the patient’s need and expectations in terms of care and quality of health care\[7\]. Measurement of patient satisfaction can be influenced by several factors, such as patient expectations, questionnaires used and patient’s sociodemographic features\[8,9\]. It is important to evaluate actual measurement reflecting patient satisfaction, although there are some difficulties. Among them, sociodemographic features have great value and constitute an important factor influencing patient satisfaction\[10-12\].

In Turkey, there are two comprehensive studies on patient satisfaction in the PHC setting. The first, conducted by Aktürk et al\[13\] studied patient satisfaction levels before the implementation of the family medicine model. The second, conducted by Baltaci et al\[14\] after the implementation reported that the overall level of patient satisfaction with the family medicine practice in Turkey was higher. The Ministry of Health in Turkey has tried to establish a standardized quality control system in health care services since the last decade. It is clear that it was achieved in hospital care, but scarcely in the PHC setting.

To the best of our knowledge, the present study was the first study which investigated the influence of sociodemographic features on patient satisfaction in PHC setting. Hence, in this study, our objective was to investigate which of the patient’s sociodemographic features have a significant effect on patient satisfaction in family medicine practice in terms of health care throughout Turkey.

**SUBJECTS AND METHODS**

**Study Conduct and Patient Enrollment**

The study was conducted in 45 family medicine centers from 15 cities throughout Turkey between January 2011 and September 2011 by the Department of Family Medicine, School of Medicine, and Duzce University (Fig. 1). The cities were chosen because they were metropolitan areas, representing the overall Turkish population in terms of cultural and sociodemographic similarities. A call for participation in the study was delivered to all family health centers through local directors of the Health Ministry, but only 45 centers responded. Patients between 18 and 80 years of age, admitted to their family medicine centers, were enrolled into the study. Willingness to participate in the study and ability to read and understand the study survey were the inclusion criteria. The study was approved by the ethics committee of our institute (Ethics number: 2011/148). An informed consent was obtained from all participants.

**Study Survey and Data Collection**

A study survey including sociodemographic features “EUROPEP” instrument was structured. The questionnaire was tested in a pilot study in Duzce Province, using a Turkish validated version of EUROPEP instrument\[14,15\]. The self-administered study surveys were distributed to participants, in the waiting room via handout by researchers rather than family physicians. They were collected in the boxes placed in family medicine centers. All survey sheets were sent to the center conducting the study. The study survey consisted of sociodemographic features of participants (age groups, gender, marital status, education level, smoking status, occupation, income level and existence of chronic diseases) and patient satisfaction with primary care (patient-physician communication, accessibility of physicians, medical care provided by health professionals, health care organization and providing information and support
to patients by their family physicians). Age groups were stratified as 18-24, 25-34, 35-60 and over 60 years-old. Questions related to patients’ sociodemographic features and patient satisfaction level were asked to be filled. Patient-physician communication domain was evaluated with six questions: 1) Making you feel you had time during consultations; 2) Taking an interest in your personal situation; 3) Making it easy for you to tell him or her about your problems; 4) Involving you in decisions about your medical care; 5) Listening to you; 6) Keeping your records and data confidential.

Satisfaction with medical care domain was evaluated with five questions: 1) Quick relief of symptoms; 2) Helping you to feel well so that you can perform your normal daily activities; 3) Thoroughness; 4) Physical examination; 5) Offering you advice for preventing diseases. Satisfaction with domain of information and support for medical situation was evaluated with four questions: 1) Explaining the purpose of tests and treatments; 2) Telling you what you wanted to know about your symptoms and / or illness; 3) Helping you deal with emotional problems related to your health status; 4) Helping you understand the importance of following his or her advice. Satisfaction with health organization was measured with two questions: 1) Knowing what he or she had done or told you during contacts; 2) Preparing you for what to expect from specialist or hospital care. Satisfaction with accessibility to the physician was evaluated with six questions: 1) The helpfulness of the staff (other than doctor); 2) Getting an appointment to suit you; 3) Getting through to the practice on the phone; 4) Being able to speak to the general practitioner on the telephone; 5) Waiting time in the waiting room; 6) Providing quick services for urgent health problems. Likert scale (from 1 to 5 points, meaning 1 point: poorest, 2: poor, 3: medium, 4: good and 5: excellent) was used. Mean score for domains of patient satisfaction according to incisions of sociodemographic features was calculated by adding points from all related questions. Meanwhile, mean total score of overall patient satisfaction level according to incisions of patient’s sociodemographic features was computed.

Statistics and data analysis

Descriptive statistics were calculated as frequencies (count and percent) and mean ± standard error of mean (SEM) for mean score for overall and domains of patient satisfaction level. Normality of distribution for data was analyzed by Kolmogorov-Smirnov test. The relationships between sociodemographic variables and subtotal and total scale scores were analyzed by using covariance analysis. A p-value of < 0.05 was considered statistically significant. All data were analyzed using statistical package for social sciences (SPSS version 18.0, Chicago IL). Patient population was decided as target sample size for the study.

RESULTS

Socio-demographic features of participants

One thousand two hundred and ten patients (male: 582, 48.1% and female: 628, 51.9 %) participated in the study. Mean age of all subjects was 37.4 ± 14.7 (range 18 - 80 years old). Majority of them had a middle school level education (n = 497, 41.0%). Among them, frequency of current smokers was found to be 27.3 % (n = 330) (not shown in the table). 67.3% of subjects were married and 32.7% were unmarried. Frequency of participants who had worked as an officer, a self-employed or employee was 53.4%. Remaining 46.6% were not working (e.g., retired persons, students, or housewife). Majority of the participants (n = 714, 59.0 %) had an income level above subsistence wage. Frequency of chronic diseases (diabetes mellitus, hypertension, cardiovascular disease and chronic pulmonary disease) was detected in 22.9% patients (n = 212, Table 1). When mean total score of every incision of income, morbidity, residency, occupation, gender, marital status, education level and age groups were
Influence of patient's socio-demographic features on incisions of sociodemographic features

Table 2: Comparison of mean total score of patient’s satisfaction level for incisions of sociodemographic features

<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>Total score of patient satisfaction (Mean ± SEM**)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84.5 ± 2.2 (80.3 - 88.8)</td>
<td>0.028</td>
</tr>
<tr>
<td>Female</td>
<td>88.5 ± 2.4 (83.8 - 93.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>83.0 ± 2.5 (78.2 - 87.6)</td>
<td>0.043</td>
</tr>
<tr>
<td>High</td>
<td>90.1 ± 2.3 (85.7 - 94.4)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>88.8 ± 2.2 (84.4 - 93.1)</td>
<td>0.197</td>
</tr>
<tr>
<td>Unmarried</td>
<td>84.3 ± 2.5 (79.3 - 89.3)</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>84.3 ± 1.2 (86.3 - 91.4)</td>
<td>0.137</td>
</tr>
<tr>
<td>Rural</td>
<td>84.0 ± 3.8 (76.4 - 91.4)</td>
<td>0.022</td>
</tr>
<tr>
<td>Chronic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88.1 ± 2.5 (83.2 - 93.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>84.9 ± 2.2 (80.6 - 89.2)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Middle school</td>
<td>86.3 ± 2.3 (81.7 - 90.9)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>84.6 ± 2.5 (79.6 - 89.5)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>88.7 ± 2.7 (83.5 - 93.8)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>90.0 ± 2.8 (84.5 - 95.5)</td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>81.1 ± 2.9 (75.4 - 86.9)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>85.3 ± 3.0 (79.5 - 94.1)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>90.1 ± 2.3 (85.1 - 94.1)</td>
<td></td>
</tr>
<tr>
<td>Age groups (years-old)</td>
<td></td>
<td>0.979</td>
</tr>
<tr>
<td>18 - 24</td>
<td>86.2 ± 2.8 (80.8 - 91.6)</td>
<td></td>
</tr>
<tr>
<td>25 - 34</td>
<td>85.9 ± 2.5 (81.9 - 90.6)</td>
<td></td>
</tr>
<tr>
<td>35 - 60</td>
<td>86.7 ± 2.3 (81.8 - 91.6)</td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td>87.2 ± 3.6 (80.3 - 94.2)</td>
<td></td>
</tr>
</tbody>
</table>

*S: Significant, if p < 0.05, **SEM: Standard Error of Mean, ***CI: Confidence interval

compared, it was observed that patient satisfaction level was higher in female patients than male, married patients than unmarried, patients of higher income level than low income, and the officers than the employed and unemployed (p = 0.028, p = 0.043, p = 0.001, and p = 0.006, respectively). Mean total score of every incision of education level, morbidity, residency and age group was not found to be significant (p = 0.224, p = 0.137, p = 0.197, and p = 0.979, respectively).

Satisfaction with patient-physician communication

The effects of patients’ sociodemographic features on patient satisfaction with patient-physicians communication are shown in Table 3. For satisfaction with patient-physician communication, statistically significant differences were observed in patients’ sociodemographic features such as marital status, education level, income level, and occupation but not existence of chronic diseases and age groups. Compared to male patients, satisfaction with patient-physician communication was significantly higher in females (23.3 ± 0.5 versus 24.3 ± 0.6, p = 0.037). It was observed that the married patients were more satisfied than the unmarried ones (24.5 ± 0.6 versus 23.0 ± 0.6, p = 0.006). The patients with university level education had higher satisfaction level, compared to middle and high school (24.6 ± 0.7, 23.3 ± 0.6, 23.4 ± 0.6, respectively; p = 0.048). The patient’s satisfaction level in subjects who had high income level was significantly higher than those with low income level (24.0 ± 0.6 versus 23.2 ± 0.6, p = 0.017). Status of occupation significantly influenced patient satisfaction level, and the officers were significantly different from the unemployed, employed and self-employed subjects (25.3 ± 0.7, 24.5 ± 0.6, 24.7 ± 0.7 and 23.4 ± 0.7, respectively; p = 0.010). Between patients with and without chronic disease, there was no significant difference for satisfaction level (p = 0.334).

Satisfaction with medical care provided by physicians

The influence of patients’ sociodemographic features on patient satisfaction level with medical care is shown in Table 4. While the status of patients’ gender, income level, marital status, residency and occupation significantly influenced patient satisfaction level, the

Table 3: Influence of patient’s socio-demographic features on patient-physician communication domain of patient satisfaction level

<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>Patient-physician communication (Mean ± SEM**)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23.3 ± 0.5 (22.2 - 24.4)</td>
<td>0.037</td>
</tr>
<tr>
<td>Female</td>
<td>24.3 ± 0.6 (23.1 - 25.4)</td>
<td></td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>23.2 ± 0.6 (21.9 - 24.4)</td>
<td>0.017</td>
</tr>
<tr>
<td>High</td>
<td>24.4 ± 0.6 (23.0 - 25.5)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>24.5 ± 0.6 (23.5 - 25.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Unmarried</td>
<td>23.0 ± 0.6 (21.8 - 24.3)</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>24.7 ± 0.3 (24.1 - 25.3)</td>
<td>0.050</td>
</tr>
<tr>
<td>Rural</td>
<td>22.8 ± 0.9 (20.9 - 24.7)</td>
<td></td>
</tr>
<tr>
<td>Chronic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24.0 ± 0.6 (22.8 - 27.2)</td>
<td>0.334</td>
</tr>
<tr>
<td>No</td>
<td>23.5 ± 0.6 (22.4 - 24.6)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>23.4 ± 0.6 (22.2 - 24.5)</td>
<td>0.048</td>
</tr>
<tr>
<td>High school</td>
<td>23.3 ± 0.6 (22.1 - 24.6)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>24.6 ± 0.7 (23.4 - 26.0)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>24.7 ± 0.7 (23.3 - 26.0)</td>
<td>0.010</td>
</tr>
<tr>
<td>Officer</td>
<td>25.3 ± 0.7 (21.1 - 24.0)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>23.4 ± 0.7 (22.0 - 24.8)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>24.5 ± 0.6 (23.4 - 25.7)</td>
<td></td>
</tr>
</tbody>
</table>

*S: Significant, if p < 0.05, **SEM: Standard Error of Mean, ***CI: Confidence interval

α The patients with university education level were more satisfied than from high middle education level; β Officers were less satisfied than the employed and unemployed.
level of education and existence of chronic diseases did not. Compared to male patients, female patients were more satisfied with medical care (20.1 ± 0.5 versus 19.0 ± 0.5, p = 0.020). The patients with low income level were dissatisfied, while those with high income level were more satisfied with medical care provided by their physicians (19.1 ± 0.6 versus 20.0 ± 0.5, p = 0.021). The married patients were more satisfied with medical care, compared to the unmarried ones (20.1 ± 0.5 versus 19.0 ± 0.6, p = 0.036). The patients living in a rural area seemed to be more dissatisfied than in those from an urban area, but not significantly (18.6 ± 0.9 versus 20.2 ± 0.3, p = 0.050). The lowest patient satisfaction level among different occupation (the employed, self-employed, unemployed patients and officers) was observed in the officers (20.2 ± 0.6, 19.2 ± 0.7, 20.0 ± 0.5, and 18.4 ± 0.7, p = 0.034). Residency, education level and existence of morbid disease did not significantly influence patient satisfaction level with medical care (p = 0.050, p = 0.271, p= 0.764, and p= 0.259, respectively).

**Satisfaction with support and information by physicians about their medical situation**

Among sociodemographic characteristics of patients, only income level, gender and status of occupation had a significant effect on patient satisfaction level with items of information and support about their medical situation provided by physicians. Higher satisfaction level was observed in female patients than male (16.1 ± 0.0 versus 15.3 ± 0.4, p = 0.022). The patients with high income level were more satisfied, compared to those with low income level (24.4 ± 0.6 versus 23.2 ± 0.6, p = 0.002). The officers among patients were dissatisfied with information and support provided by their physicians about their medical situation than all of the employed, unemployed and self-employed patients (14.3 ± 0.7, 16.4 ± 0.5, 16.3 ± 0.4, and 15.6 ± 0.6, respectively; p = 0.000) (Table 5).

**Satisfaction with health care organization**

Influence of sociodemographic features on patient satisfaction with health care organization is shown in Table 6. Here, mean patient satisfaction level was observed as significantly different between low and high income level. The patients with high income level were more satisfied with health care organization (8.2 ± 0.3 versus 7.5 ± 0.3, p = 0.004). Education level and occupation status of patients had no significant influence on patient satisfaction level.

### Table 4: Influence of patient’s sociodemographic features on medical care domain of patient satisfaction level

<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>Medical care provided by physicians (Mean ± SEM**)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19.0 ± 0.5 (18.0 - 20.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Female</td>
<td>20.1 ± 0.5 (19.1 - 21.1)</td>
<td></td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>19.1 ± 0.6 (17.8 - 19.9)</td>
<td>0.021</td>
</tr>
<tr>
<td>High</td>
<td>20.0 ± 0.5 (19.1 - 21.0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>20.1 ± 0.5 (19.1 - 21.0)</td>
<td>0.036</td>
</tr>
<tr>
<td>Unmarried</td>
<td>19.0 ± 0.6 (17.8 - 20.0)</td>
<td>0.050</td>
</tr>
<tr>
<td>Residency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>20.2 ± 0.3 (19.7 - 20.8)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>18.6 ± 0.9 (18.1 - 20.3)</td>
<td></td>
</tr>
<tr>
<td>Chronic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19.7 ± 0.6 (18.6 - 20.8)</td>
<td>0.259</td>
</tr>
<tr>
<td>No</td>
<td>19.1 ± 0.5 (18.2 - 20.1)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>19.3 ± 0.5 (18.3 - 20.3)</td>
<td>0.271</td>
</tr>
<tr>
<td>High school</td>
<td>19.1 ± 0.6 (18.6 - 20.2)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>20.1 ± 0.6 (19.1 - 21.1)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td>0.034**</td>
</tr>
<tr>
<td>Employed</td>
<td>20.2 ± 0.6 (19.0 - 21.4)</td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>18.4 ± 0.7 (17.1 - 19.7)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>19.2 ± 0.7 (17.9 - 20.5)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>20.0 ± 0.5 (19.1 - 21.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant, if p < 0.05, **SEM: Standard Error of Mean, ***CI: Confidence interval, α Officers were less satisfied than the employed and unemployed patients

### Table 5: Influence of patient’s sociodemographic features on support and information domain of patient satisfaction level

<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>Support and information (Mean ± SEM**)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15.3 ± 0.4 (14.4 - 16.1)</td>
<td>0.022</td>
</tr>
<tr>
<td>Female</td>
<td>16.1 ± 0.5 (15.1 - 17.0)</td>
<td></td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>15.0 ± 0.5 (14.1 - 16.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>High</td>
<td>16.3 ± 0.4 (15.4 - 17.1)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>16.0 ± 0.4 (15.2 - 16.8)</td>
<td>0.083</td>
</tr>
<tr>
<td>Unmarried</td>
<td>15.3 ± 0.5 (14.3 - 16.2)</td>
<td></td>
</tr>
<tr>
<td>Residency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>15.8 ± 0.2 (15.4 - 16.3)</td>
<td>0.537</td>
</tr>
<tr>
<td>Rural</td>
<td>15.4 ± 0.7 (14.0 - 17.1)</td>
<td></td>
</tr>
<tr>
<td>Chronic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16.0 ± 0.5 (15.1 - 17.0)</td>
<td>0.079</td>
</tr>
<tr>
<td>No</td>
<td>15.3 ± 0.4 (14.5 - 16.1)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>19.3 ± 0.5 (18.3 - 20.3)</td>
<td>0.304</td>
</tr>
<tr>
<td>High school</td>
<td>19.1 ± 0.6 (18.6 - 20.2)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>20.1 ± 0.6 (19.1 - 21.1)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td>0.000α</td>
</tr>
<tr>
<td>Employed</td>
<td>16.4 ± 0.5 (15.4 - 17.5)</td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>14.3 ± 0.7 (13.2 - 15.4)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>15.6 ± 0.6 (14.4 - 16.7)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>16.3 ± 0.4 (15.4 - 17.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant, if p < 0.05, **SEM: Standard Error of Mean, ***CI: Confidence interval, α Officers were less satisfied than the employed and self-employed patients.
Satisfaction with accessibility to physician’s practice

Compared to patients with low income level, those with high income level were more satisfied with accessibility domain of patient satisfaction (21.2 ± 0.8 versus 18.4 ± 0.9, p = 0.000). However, there were no significant differences for satisfaction level with accessibility domain among other sociodemographic features of patients, including gender, marital status, education level, occupation and existence of chronic diseases. On the other hand, the officers had significantly lower satisfaction level, compared to the unemployed and employed patients (18.4 ± 1.1 versus 20.7 ± 0.9 and 20.7 ± 1.0, p = 0.041 and p = 0.015, respectively) (Table 7).

DISCUSSION

The present study investigated the influence of patient’s sociodemographic features on satisfaction level with primary care for the overall level and its five domains (communication, medical care, information and support about the medical condition, health organization and accessibility to family physician’s practice). The study demonstrated that patient’s sociodemographic features had a considerable influence on patient satisfaction level with health care and its providers. Particularly, income level, marital and occupational status among sociodemographic features had a significant influence on satisfaction level with almost all domains of health care. It was detected that income level had the most significant influence on all domains of patient satisfaction level. In the study, total score for patient satisfaction level was found to be significantly different in gender, residency, occupation, income level and marital status. These factors had a significant influence on patient satisfaction.

We expected that sociodemographic features of our patients have an effect on patient satisfaction level in primary care settings. In recent decades, Turkey has tried to establish new goods and gain European standards in health systems, especially in primary care settings. Therefore, the present study is the first study conducted in Turkey that investigated the influence of sociodemographic features on patient satisfaction after family medicine program was implemented.\[16\]

There are some theories describing patient satisfaction: fulfillment theory, discrepancy theory, equity theory and social comparison theory, all defining satisfaction as measurement between what is given to the patient and what patient received.\[17\] There are many methods to measure quality in health care systems. Patient satisfaction is important and a good indicator for measuring quality in health care. Many

### Table 6: Influence of patient’s sociodemographic features on health organization domain of patient satisfaction level

<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>Health organization (Mean ± SEM**) (95% CI***)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7.7 ± 0.2 (7.2 - 8.2)</td>
<td>0.167</td>
</tr>
<tr>
<td>Female</td>
<td>8.1 ± 0.3 (7.5 - 8.5)</td>
<td></td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Low</td>
<td>7.5 ± 0.3 (7.1 - 8.1)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8.2 ± 0.3 (7.6 - 8.7)</td>
<td>0.291</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>7.9 ± 0.3 (7.5 - 8.4)</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>7.7 ± 0.3 (7.2 - 8.3)</td>
<td>0.752</td>
</tr>
<tr>
<td>Residency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>7.8 ± 0.1 (7.5 - 8.0)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>8.0 ± 0.4 (7.1 - 8.8)</td>
<td></td>
</tr>
<tr>
<td>Chronic disease</td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td>Yes</td>
<td>8.1 ± 0.3 (7.5 - 8.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7.7 ± 0.3 (7.2 - 8.1)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td>0.093</td>
</tr>
<tr>
<td>Middle school</td>
<td>8.1 ± 0.3 (7.6 - 8.6)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>7.6 ± 0.3 (7.1 - 8.1)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>8.0 ± 0.3 (7.4 - 8.5)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>Employed</td>
<td>8.1 ± 0.3 (7.5 - 8.7)</td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>7.4 ± 0.3 (7.1 - 8.1)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>7.7 ± 0.3 (7.1 - 8.4)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>8.1 ± 0.3 (7.6 - 8.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant, if p < 0.05, **SEM: Standard Error of Mean, ***CI: Confidence interval

### Table 7: Influence of patient’s sociodemographic features on accessibility domain of patient satisfaction level

<table>
<thead>
<tr>
<th>Sociodemographic features</th>
<th>Accessibility to physicians (Mean ± SEM**) (95% CI***)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>renovations</td>
<td>0.117</td>
</tr>
<tr>
<td>Male</td>
<td>19.3 ± 0.8 (17.8 - 20.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20.3 ± 0.9 (18.6 - 22.1)</td>
<td></td>
</tr>
<tr>
<td>Income level</td>
<td>renovations</td>
<td>0.000</td>
</tr>
<tr>
<td>Low</td>
<td>18.4 ± 0.9 (16.7 - 20.2)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>21.2 ± 0.8 (19.6 - 22.8)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>renovations</td>
<td>0.243</td>
</tr>
<tr>
<td>Married</td>
<td>20.3 ± 0.8 (18.7 - 21.9)</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>19.4 ± 0.9 (17.5 - 21.2)</td>
<td></td>
</tr>
<tr>
<td>Residency</td>
<td>renovations</td>
<td>0.412</td>
</tr>
<tr>
<td>Urban</td>
<td>20.4 ± 0.4 (19.5 - 21.3)</td>
<td></td>
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<tr>
<td>Rural</td>
<td>19.3 ± 1.4 (16.5 - 22.0)</td>
<td></td>
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<tr>
<td>Chronic disease</td>
<td>renovations</td>
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</tr>
<tr>
<td>Yes</td>
<td>20.3 ± 0.9 (18.5 - 22.1)</td>
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</tr>
<tr>
<td>No</td>
<td>19.3 ± 0.8 (17.8 - 20.9)</td>
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<tr>
<td>Education level</td>
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</tr>
<tr>
<td>Middle school</td>
<td>20.2 ± 1.0 (18.2 - 22.1)</td>
<td></td>
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<tr>
<td>High school</td>
<td>19.2 ± 0.9 (17.4 - 21.0)</td>
<td></td>
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<tr>
<td>University</td>
<td>20.1 ± 0.9 (18.2 - 22.0)</td>
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<tr>
<td>Occupation</td>
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</tr>
<tr>
<td>Employed</td>
<td>20.7 ± 1.0 (18.7 - 22.6)</td>
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<tr>
<td>Officer</td>
<td>18.4 ± 1.1 (16.3 - 20.5)</td>
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<td>Self-employed</td>
<td>19.5 ± 1.1 (17.4 - 21.6)</td>
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</tr>
<tr>
<td>Unemployed</td>
<td>20.7 ± 0.9 (19.1 - 22.4)</td>
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</tbody>
</table>

*Significant, if p < 0.05, **SEM: Standard Error of Mean, ***CI: Confidence interval
validated instruments were used to measure patient satisfaction level. The EUROPEP instrument was widely used in many European countries, including Turkey. \[18, 19\]

Female and male patients also have different communication styles, with women tending to present more personal history and symptom information during a visit than their male counterparts. Female patients also value more time and explanations from their physicians than male patients and in some settings; receive more total time and communication from their physicians. Woods et al\[20\] studied the effect of gender on patient satisfaction in hospital care and reported that women expressed significantly less satisfaction compared to men for some items related health care provided by physicians, nurses and all health staff members. Campbell et al\[21\] found that gender had no effect on overall patient satisfaction level in primary care. In our study, we found that female patients were more satisfied overall, and with three domains of the health care, compared to their male counterparts. The result might be due to cultural and national diversity. Schmittiel et al\[22\] reported that female patients place a higher value than male patients on physicians’ communication skills and personal manner. Female patients also appeared to value technical skills more highly than male patients. We also found that female patients were more satisfied with patient-physician communication domain of patient satisfaction.

In some studies, it was shown that education level of the patient could influence communication skills and styles. Patients with higher education level can easily communicate with physicians. Bu-Alayyan et al\[23\] reported that patients with high education level were more satisfied with primary care. In our study, patient who graduated from the university had higher patient satisfaction level with the domain of patient-physician communication, compared to those with a lower education level. We also found that education level did not influence overall score of patient satisfaction level. On the other hand, Al-Sakkak et al\[24\] reported that the patient with low education level was more satisfied.

We found that there is no influence of marital status on total score of overall patient satisfaction level. However, married patients were more satisfied with patient-physician communication (p = 0.006) and medical care (p = 0.036) domains of patient satisfaction, compared to unmarried patients. In contrast, Tucker et al\[25\] reported that being married was negatively correlated with patient satisfaction level (single and married, correlation coefficient = -0.01). In this study, we classified marital status of our patients into two categories: married and unmarried. We assigned single and divorced patients into unmarried category, because the number of divorced people in Turkish population is quite low.

In our study, income level was a major feature affecting the patient satisfaction level with primary care. Mean score for overall and all separate domains of patient satisfaction measurement were observed in the patients with high income level than those with low income. Similarly, Fong et al\[26\] reported that patients with high income level were more satisfied than those with low income. It was consistent with our results. In contrast, Yan et al\[27\] reported that patients with high income level were more dissatisfied.

In our study, living in rural area or urban area was found not having any significant influence on overall and the five domains of patient satisfaction level. In contrast, patients living in rural areas were found to be more satisfied than in urban area in China\[27\]. Geitona et al\[28\] studied on medication use and patient satisfaction, and reported that living in rural area was related with higher satisfaction. We found that officer patients were less satisfied with primary care. Bu-Alayyan et al\[23\] reported that working patients were more satisfied, but they did not classify occupation status into subclasses such as employed, self-employed and officer.

Many studies have found that younger patients were less satisfied than older almost regardless of other sociodemographic features; for example, in Norway\[29\] and Sweden\[30\]. In the present study, we found no significant relationship between patient satisfaction level and age groups. We also found that patient satisfaction level was not significantly related with increased age, based on covariant analysis (not shown in text). Jaipaul et al\[31\] reported that patient satisfaction level was positively correlated with increased age, but over 80 years old.

The existence of a chronic disease increases frequency of patient’s visit to primary care settings. Among patients seeking primary care, those with a chronic disease use health care facilities more than others. Therefore, it is very important to measure and compare their patient satisfaction level in comorbid situations. Jatrana et al\[32\] found that having no morbid condition had a lower mean continuity care in primary care (2.99, 95% CI: 2.97 - 3.01) than those reporting two or more comorbid conditions (3.35, 95% CI: 3.32 - 3.38). In our study, there was no influence of a chronic disease on five domains of patient satisfaction level. Heje et al\[33\] reported that patients with chronic disease were more satisfied than patients without a chronic condition. In this study, we did not report the number and type of morbid conditions.

One of the strengths of this study was its sample characteristics. The participants were randomly selected. Another strength of the study resulted from its methods. The study survey was selfadministered and applied by researchers rather than family physicians. Thus, possible bias was avoided. There were some limitations for the study. Measurement of
patient’s satisfaction level in illiterate patients was not taken into consideration as they were excluded from the study. Secondly, the patients in the waiting room of family health center were enrolled. Out of these, the patients who had to wait for a long time might have given a low score.

CONCLUSION
Patient satisfaction level was significantly influenced by their sociodemographic features, particularly income level, marital and occupational status and gender. Therefore, it is essential to take into consideration potential factors that can influence patient satisfaction level. The study results can influence health ministry bureaucrats in Turkey to develop new strategies and prioritized programs for improving health care systems, and aid health providers to objectively measure patient satisfaction and evaluate feedback.

ACKNOWLEDGMENT
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REFERENCES
Original Article

Antenatal Ultrasound Diagnosis of Fetal Anomalies at a University Hospital

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ABSTRACT

Background: Antenatal ultrasound is an essential tool for detection of fetal anomalies. Early detection of congenital anomalies can reduce the expected morbidity and mortality.

Objectives: To highlight the role of antenatal ultrasound in detection and characterization of fetal anomalies, and to study the incidence and distribution of congenital anomalies at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia (KSA)

Design: Cross-sectional observation study

Setting: Department of Diagnostic Radiology and Fetal Medicine Unit at KAUH, Jeddah, KSA during the period 2008 - 2011

Intervention: Antenatal ultrasound

Subjects: Five thousand and thirty pregnant females were subjected to antenatal ultrasound (US) at KAUH diagnostic radiology department and fetal medicine unit from January 2008 to September 2011. The age of participating females ranged from 16 to 49 years. Data were collected and statistically analyzed using SPSS 10.0 program. Statistical significance was accepted if p-value < 0.05.

Main Outcome Measures: The incidence of congenital anomalies

Results: Cardiac and umbilical cord anomalies have statistically significant relation with maternal age (p-value < 0.05). The most frequent abnormalities detected are of the brain (40.6%), the urinary system (39.4%) and the cardiovascular system (37.5%).

Conclusions: The high prenatal detection rates for common congenital anomalies of the CNS, cardiovascular and urinary systems are similar to those found in previous reports. Unexpectedly, abdominal anomalies were the fourth largest anomalies detected. By using more sophisticated, highly sensitive machines in addition to greater expertise, well-trained radiologists and sonographers specialized in obstetrics, more specific and early detection of different anomalies can be possible in the future.

INTRODUCTION

Routine ultrasound (US) fetal screening for congenital abnormalities has become an established practice for many years. US examination gives a great amount of information about the anatomical structure and to some extent the physiological state of fetus especially in the second trimester. US have a role in analyzing in detail the fetal anatomy to detect or exclude structural abnormalities. There is no doubt that US examination is able to increase the identification of malformations. US performance is based on technical and organizational variables including the number of exams performed, operator experience, type of equipment used, and the health policy, and also on variables that are related to the structural abnormalities such as the gestational period in which the examination should be performed and severity and type of malformation[1].

A congenital anomaly is an abnormality of structure, function or body metabolism that is present at birth and results in physical or mental disability, or is fatal. Each year, eight million children are born worldwide with congenital anomalies, out of which 3.3 million die before the age of five; 3.2 million of the survivors may be mentally and / or physically disabled[2]. Depending on their severity and the need for medical or surgical intervention, fetal malformations are subdivided into major and minor malformations following guidelines set out by the European Registers of Congenital Anomalies and Twins (EUROCAT)[3]. The morbidity
and mortality of fetal anomalies increases with advancing gestation. Therefore, early detection of such abnormalities will result in the reduction of such complications.

The diagnostic ability of US is well established by a number of studies[4,5]. US scan provides the next best alternative to primary prevention of congenital anomalies[6]. Early pregnancy US scanning at 11-14 weeks can detect certain fetal abnormalities. Detection rates are better after 13 weeks of gestation and is further improved with the use of transvaginal probe. Some women who are at risk of delivering a baby with congenital anomalies are offered a detailed scan at around 24 to 28 weeks[7].

The prevalence of birth defects depends upon the population being scanned. However, it is comparable all over the world; about 3% in the United States[6], 2.5% in India[7] and 2 - 3% in the United Kingdom[8]. In industrialized countries, structural abnormalities represent the first cause of prenatal death (20 - 25%) and are the most common cause of infant morbidity after prematurity[11,9]. EUROCAR (European surveillance of congenital anomalies) recorded a total prevalence of major congenital anomalies of 23.9 per 1000 births for 2003 - 2007[10]. With more recent equipment and application of 3D & 4D techniques, conditions such as cleft lip / palate and congenital cardiac abnormalities are more readily diagnosed and at an earlier gestational age[11]. Antenatal Doppler application has been proven to be a valuable adjunct to fetal assessment because often Doppler flow abnormalities will precede detectable fetal abnormalities of growth, amniotic fluid, and placental insufficiency and can help assess the severity of fetal compromise when these abnormalities are suspected. 3D US technology has helped in redefining traditional methods of CT and MRI images. The next and the most advanced technique is the 4D US that adds the element of time to the 3D process redefining traditional methods of CT and MRI images. Some cases using high frequency endovaginal probe (5 -7.5 MHz) 2D – 3D – 4D. A Voluson 730 expert general electric (GE) US machine was used for all cases. The types of birth defect and age of mother along with the detailed anatomical survey at the time of scan were entered in a database file and statistically analyzed using Statistical Package for Social Sciences Version 10.0 (SPSS Inc, Chicago, IL, USA) for data entry. Analyses included percentages. No incidence or prevalence was included. The chi-square test was used to compare differences between groups. Statistical significance was accepted at a p-value < 0.05.

RESULTS

The incidence of congenital anomalies in our study population was 3.18% where out of the 5030 pregnant females subjected to antenatal US, 160 showed congenital anomalies of their fetuses. Ten percent of patients had previous offspring with similar or different congenital malformation. All females were classified according to their age into five groups: (< 20 years) five patients, (20 - 35 years) 109 patients, (35 - 40 years) 27 patients, (40 - 45 years) 14 patients, and (45 - 49 years) five patients. The largest percentage of females was in the fertility age group of 20 - 35 years, which represented 68% of all cases. The prevalence of congenital anomalies detected in relation to different age groups is shown in Table 1. The distribution of the total abnormalities detected among the study population is shown in Fig. 1. They were classified according to the body system affected. It is to be mentioned that many cases had multiple anomalies of different organs. The most frequent anomaly detected were brain anomalies (40.6%). Fig. 2 shows the distribution of different brain anomalies wherein, hydrocephalus is the most common abnormality (68.4%). The least common brain abnormalities were encephalocoele and Dandy-Walker malformation (2.5%
Anomalies of the urinary system were the second most frequently detected finding (39.4%). It included hydronephrosis (58%), multicystic dysplastic kidney (25.4%), and infantile polycystic kidneys (16.6%). The third most frequently detected anomaly was found in the cardiovascular system (37.5%). Abdominal anomalies represented 35% of all cases. This included; non-specific ascites (43%), omphalocele (23%), intestinal obstruction (21%) and diaphragmatic hernia which represented only 13% of cases. Chest anomalies represent 14.4% of our cases. It included hypoplastic lung (66.4%), pleural effusion (26.6%)
and cystic lung malformation (7%). Spinal anomalies represented 13.1% of cases, where meningocele was the commonest. Anomalies of the musculoskeletal system represented 12.5% of the total anomalies. It included; skeletal hypoplasia (50%), rocker bottom foot (18%), clenched hand (16%), club foot (10%), and otocephalus imperfect (6%). Three D and 4D US is of great help to detect these anomalies. Only 9.4% had facial anomalies in the form of cleft lip and palate (53.2%), micrognathia (38%) and deficiency in the orbital region (8.8%). The least frequently detected anomaly was of the soft tissue where 3.75% of fetuses had cystic hygroma within the neck. Other different abnormalities detected in our study are fetal growth retardation (15%) and generalized edema (7.5%). The placental position localization is an essential part of the examination. Half the cases had anterior placenta, 40% had posterior placenta, 7.5% had fundal placenta while placenta previa was found in only 2.5% of cases. Single umbilical artery was diagnosed by finding only two vessels on a cross section of the cord, or a vessel seen on only one side of the fetal bladder. It represented 4.4% of our cases in association with other anomalies. Most cases showed normal amniotic fluid volume (52%) while in 25% cases polyhydramnios was diagnosed. 16.5% of cases had anhydramnios, and only 6.5% had oligohydramnios.

**DISCUSSION**

Second trimester US has proved to be an essential tool for detection of various fetal anomalies. In our study, the percentage of detected anomalies was 3.18%. Although 50 - 60% of all structural abnormalities can be detected as early as 11 - 14 weeks of gestation, the optimum timing for a full fetal structure survey appears to be around 20 weeks[13]. Congenital anomalies are the leading cause for neonatal morbidity and mortality as mentioned by Copel *et al* who stated that “prenatal recognition of birth defects is generally regarded as being advantageous and desirable. For several disorders, including some cases of cardiac defects, prenatal detection has been shown to improve management and overall outcomes of the affected newborns”[14]. Differences in reported birth prevalence rates of congenital malformations over time and among countries, or even within the same country among regions, may be attributed to one or more factors such as design of the study (hospitalbased or populationbased, prospective or retrospective), definitions, classifications and inclusion criteria used, type of surveillance system, etiological differences of malformations, accuracy of diagnosis and gestational age at which the ultrasound was performed[15]. These make comparison of rates among studies difficult and probably not very informative. The actual prevalence of these anomalies is difficult to determine since various classifications exist which are based on the timing of diagnosis (natal or perinatal), the type of abnormality (major or minor), and on the kind of registration that is used by the various centers. In literature, the prevalence of structural abnormalities in the perinatal period varies from 2 to 5%[16]. The incidence of congenital anomalies vary from low - as reported by El-Shafei *et al*, (1·86%)[17], Naderi (1·66%)[18] and Harrison, from Nigeria (1·4%)[19] to high as found in Copenhagen (Villumsen AL, 1970 – 3.8%) and Canada (Baird *et al*, 1991 – 4.7%), respectively[20,21]. As compared to some neighboring Arab countries, there is still a difference in the prevalence of congenital anomalies. Fetal anomalies represents 24.6 / 1000 births in Oman[22], 10.5 / 1000 births in Al-Ain, United Arab Emirate (UAE)[23] and 16.6 / 1000 births in Abu-Dhabi[24]. Even within Saudi Arabia, some regional variations are present. The incidence of anomalies detected in Al-Khobar, Eastern Saudi Arabia was 17 / 1000[25], in Al-Qassim was 0.89 / 1000 births[26], in Al-Hafuf was 17.4 / 1000 births[27] and in Jeddah was 16 / 1000 births[28].

In the current study, we included only antenatal cases. No postnatally detected anomaly cases, abortion cases or chromosomal based anomalies were included. This had an effect on our results. In a study done in Spain in 1999 over 22 years, a total of 1006 malformed fetuses or neonates were identified at abortion or delivery. The prevalence of fetal abnormalities was 3.03%. Fetal anomalies were diagnosed antenatally in 788 (78.33%) cases which means that a considerable number of cases could not be diagnosed in the antenatal scan[29]. We preferred to collect cases coming in the second trimester for anomaly scan owing to their large number compared to those coming in the first trimester. This had an effect on the incidence of
anomalies detected. In a study by Carrera et al., in 2003, 59.44% of the total cases were diagnosed before 22 weeks of gestation meaning that second trimester detected cases could not be representative of the actual percentage of fetal anomalies[29]. It is important to take the percentages of recent studies only into consideration, because the rapid advancement of US techniques by time with implementation of 3D, 4D techniques and advancement of the transducer strength and resolution of images has had a great effect on the diagnostic accuracy and hence reported percentages. In the study by Carrera et al., in 2003 the detection of malformed fetuses increased from 19.75% in the first phase of the study (1970 - 1974) to 96.33% in the last phase (1990 -1991)[29].

Ultrasound detection of congenital anomalies when correlated to the maternal age may add to the knowledge of physicians and parents to avoid getting pregnancy in the extremes of ages. It has come to the attention of researchers that the extremes of maternal age, meaning women over the age of 40 years and women who are 20 years or less, may be related to chromosomal and nonchromosomal structural abnormalities in the fetus[30]. For mothers aged 35 – 39 years, the prevalence of birth defects ranges from 32 - 44 per 1000 births. In mothers 40 years and older, 24 - 50 per 1000 births are affected by nonchromosomal abnormalities. Some specific abnormalities found to be associated with advanced maternal age include congenital heart defects, hypospadias, craniosynostosis, club foot, and diaphragmatic hernia. Women aged 35 – 39 years will deliver one to four additional cases of congenital heart defects per 1000 births. In mothers aged 40 years and above, that number jumps to 30. There is also a significant association with increased odds of birth defects and maternal age less than 20 years. In mothers younger than 15 years of age, the prevalence of these abnormalities is from 37 to 46.9 per 1000 births[30]. In our study, cardiovascular system anomalies shows a statistically significant correlation to the maternal age where the p-value was < 0.05. These anomalies are found to be about 40% in females less than 20 years of age, and jumps to 100% in those more than 45 years old. Brain, urinary tract and cardiac anomalies are the most frequently detected respectively. This is to some extent similar to the results of Nasrat et al in Jeddah[31], where the major congenital anomalies observed were of the central nervous system (CNS), followed by cardiovascular system (CVS) and then by chromosomal anomalies. We noticed the preponderance of CNS and CVS anomalies in many studies such as those by Lin et al[32] who found that congenital heart disorders were the most common, and Wen et al, where neural tube defects were the commonest[33]. In the current study, brain anomalies represented 40.7% of the total anomalies. Among these anomalies, hydrocephalus was the most prominent 68.4%, while Dandy-Walker anomaly was the lowest (2.5%). This matches with the result of Alia et al, where hydrocephalus was the most commonly encountered brain anomaly (36.1%)[34]. Also in a study by Al-Jama, CNS anomalies were the most common conditions encountered (48.8%). Out of those CNS defects, hydrocephalus was the most common (54 babies), followed by anencephaly (33) and meningocele (26)[29]. The most common renal anomaly detected was hydrenephrosis (58% of all renal anomalies). This result is more or less similar to the result of Crane et al, where detection rate for hydrenephrosis cases was the commonest (38.5%) but is different from the study of Alia et al, where polycystic kidney was the commonest anomaly (37.5%)[31]. In our study, polycystic kidneys represent only 16.6% of all anomalies.

Cardiac anomalies represent 37.5% in our series. Cardiomegaly represents 33.2% of cases while in only 16%, atrial or ventricular septal defects could be definitely diagnosed. Unfortunately, chromosomal study results are not routinely done to confirm the known relationship of some cardiac anomalies to genetic disorders (e.g., atrial septal defect to Down’s syndrome). The overall prenatal detection rate for congenital heart diseases was 25% in the studies of Copel et al,[14] and of Bonnet et al,[30]. In another study by Balakumar, cardiomegaly was the commonest anomaly detected (21%)[36].

Unexpectedly, many abdominal anomalies were highly diagnosed in our study (35%) while in previous reports these anomalies were not ranked among the commonest fetal anomalies. In a study of Csabay et al, CNS abnormalities rank almost equally with cardiovascular abnormalities, musculoskeletal, and renal abnormalities as among the most important group of fetal structural defects encountered[35]. In another study by Dastigiri et al, the most frequent abnormalities detected by US were of the kidney (19 / 20) followed by CNS (30 / 36)[35]. In our series, omphalocele represents 23% of cases, while the more serious diaphragmatic hernia represents 13% which is a relatively high incidence. Birth prevalence of diaphragmatic hernia has been estimated at 1.7 - 5.7 per 10,000 in a study by Skari et al[38]. Congenital diaphragmatic hernia is associated with a high mortality rate with a high percentage of survivors having longterm morbidity. Currently, the exciting possibility of in utero repair of fetal CDH is being investigated[38].

Chest, spinal and musculoskeletal anomalies are less frequently detected in our study. They represent about 14.4%, 13% and 12.5% respectively. The commonest skeletal anomaly detected is skeletal hypoplasia (50%), and the least is osteogenesis imperfecta (8%). Bone hypoplasia is a highly diagnosed anomaly in our study, while in other studies (e.g., Stoll et al)[39], the percentages of limb reduction defects diagnosed on
prenatal scan were (24.6%). Fetal growth monitoring is an important item in antenatal US. Fetal growth retardation represents 15% of the anomalies in our study which warrants close followup and Doppler study of the umbilical cord to detect possible anomalies. In addition to screening for fetal anomalies, US has an important role in detection of placental and amniotic fluid abnormalities. Abnormal placental position was found in 9.4% of cases. As far as we searched in the literature, no definite correlation was found between abnormal placental position and fetal anomalies.

Based on our study we can conclude that antenatal US anomaly scan especially in the second trimester has been found to be a very essential tool in detection of possible fetal anomalies. Early detection of fetal anomalies may guide the physician to take special precautions and do careful followup of the mother and fetus during the rest of pregnancy. In addition, some minor anomalies can be corrected in utero, while major anomalies need extensive postnatal care. Routine antenatal US screening as compared to selective (high risk) screening has been found economically justifiable[40]. It helps for careful antenatal surveillance and judicious timing of delivery[41,42]. All this has increased the responsibilities of doctors from just delivering the baby to a state where he or she has to cater from diagnosis to timing of delivery to future planning of pregnancies[43].

CONCLUSION

In summary, this study shows that the percentage of congenital anomalies detected (3.18%) is comparable with the internationally reported anomaly percentages. High prenatal detection rates for common congenital anomalies such as CNS, cardiac and renal anomalies were noticed as found in most studies. Unexpectedly, abdominal anomalies are the fourth most commonly detected anomalies. Less detection rates for other less common but important anomalies such as musculoskeletal, chest, spinal and facial anomalies is noticed. By using more sophisticated, highly sensitive machines in addition to high expertise, well-trained sonographers specialized in obstetric US, more specific and early detection of various anomalies will be possible in the future.

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REFERENCES


Electrophysiologic Effects of Statins in Patients with Ischemic Cardiomyopathy and Ventricular Tachyarrhythmia

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ABSTRACT

Objectives: Statin therapy may be beneficial not only to reduce the risk of vascular events but also to reduce the risk of ventricular arrhythmias and sudden cardiac death. We evaluated the effects of statins on electrophysiologic parameters in patients with ischemic cardiomyopathy and established ventricular tachyarrhythmia.

Design: Prospective study

Subjects and Methods: Eleven patients (all male, mean age 57.9 ± 6.64 years), with ischemic cardiomyopathy and ventricular tachyarrhythmia on admission were included in the study.

Setting: Two academic tertiary care centers

Interventions: A baseline electrophysiologic study was performed before implantable-cardioverter defibrillator (ICD) implantation. Forty milligram of atorvastatin was started and electrophysiologic study was repeated one month later and results were compared.

Main Outcome Measures: Basic intervals, corrected sinus node recovery time (cSNRT), sino-atrial conduction time (SACT), atrio-ventricular node refractory period (AVNRP), atrio-ventricular Wenckebach period (AVWP), ventricular refractory period (VRP), ventriculo-atrial dissociation measurement, corrected QT (QTc) interval and QT dispersion were measured. Also, ventricular arrhythmia inducibility was evaluated with various techniques.

Results: Although, QTc interval and QT dispersion decreased significantly with statin treatment (p < 0.05), there were no statistically significant differences in the measurements of basic intervals, cSNRT, SACT, AVNRP, AVWP, VRP and ventriculo-atrial dissociation compared to pretreatment measurements (p > 0.05). Additionally, while induction of ventricular tachyarrhythmia occurred in 72.7% of patients before statin therapy, this rate decreased to 36.4% with treatment (p = 0.13).

Conclusion: Statin treatment led to significant decreases in QTc interval and QT dispersion, but it did not change other electrophysiologic parameters significantly.

INTRODUCTION

Ventricular tachyarrhythmia is one of the most common cause of the sudden cardiac death (SCD)[1] and accounts for more than 50% of the deaths in patients with heart disease. Many studies revealed that statins have been associated with a reduction in mortality in patients with coronary artery disease[2,3]. Two large secondary prevention trials have provided evidence that statins also reduced SCD[2,3] and some recent studies suggest that statins may have anti-arrhythmic effects[4-8]. However, whether their effect of reducing arrhythmias is due to anti-ischemic effects[9-11] or direct anti-arrhythmic properties are unknown. In addition to their well-known anti-atherogenic and plaque stabilization effects[12], some electrophysiologic effects of statins have also been demonstrated (i.e., increasing heart rate variability, decreasing the ventricular late potentials and variability of QT dispersion and decreasing corrected QT (QTc) interval)[13-17]. Although these findings support the possible direct anti-arrhythmic action of statins, their effects on other electrophysiologic parameters have not been evaluated. The aim of this study was to investigate the effects of statins on electrophysiologic parameters in patients with ischemic cardiomyopathy and ventricular arrhythmia.

SUBJECTS AND METHODS

Eleven patients (all male; mean age 57.91± 6.64 years, range: 45 – 66 years) diagnosed with ischemic...
cardiomyopathy with New York Heart Association (NYHA) functional class I or II, left ventricular ejection fraction (LVEF) < 35%, and admitted to the hospital with hemodynamically stable monomorphic ventricular tachyarrhythmia were prospectively enrolled in the study. None of these patients were taking a statin or antiarrhythmic drug except a beta-blocker for at least six months. Patients with baseline rhythm other than sinus, acute coronary syndrome on presentation, severe valvular heart disease, electrolyte abnormality and other systemic disease were excluded. All patients were on standard heart failure medications including a beta-blocker. The medications of the patients were not altered during the study period. The investigational protocol described herein was approved by local ethics committee and informed consent was obtained from all patients.

Electrophysiologic study (EPS) was performed in all patients before implantable-cardioverter defibrillator (ICD) implantation and baseline measurements were obtained. In patients who needed antiarrhythmic medication for terminating ventricular arrhythmia on admission, intravenous lidocaine was used and electrophysiologic study was performed at least one week later in these patients. Amiodarone was never used. Forty milligram atorvastatin was added to the routine treatment after the EPS because of ischemic heart disease. One month later, EPS was repeated with same measurement and results were compared.

Electrophysiologic study: Three diagnostic catheters were placed at the superior portion of the right atrium, bundle of His, and right ventricular apex via the right femoral vein. The basic conduction intervals (PA: measured between earliest recorded atrial activity and the rapid deflection of the atrial electrogram on the bundle of His catheter; AH: measured between the atrial electrogram recorded by the bundle of His catheter and the beginning of the His electrogram itself; HV: measured between the His electrogram and the earliest recorded ventricular activation; PR: duration between the onset of atrial depolarization to the onset of ventricular depolarization; QRS: duration of ventricular activation; QT: combination of ventricular activation and repolarization; BCL: sinus cycle length) and the other electrophysiologic measurements were recorded.

1. Corrected sinus node recovery time (cSNRT): Overdriving atrial pacing was performed for 30 seconds and first spontaneous beat after terminating the pacing was recorded. The time between the last pacing and the first spontaneous beat was measured. Because sinus node recovery time (SNRT) depends on sinus rate, cSNRT was derived by calculating the difference between SNRT and sinus cycle length. To accurately determine the cSNRT, measurements were repeated with various cycle length pacing (800 ms, 700 ms, 600 ms, 500 ms, 450 ms, 400 ms, 350 ms) and the longest time was accepted as cSNRT.

2. Sinoatrial conduction time (SACT), derived by Narula method: Eight atrial extra stimuli, which are faster than intrinsic heart rate, were given after rest sinus cycle length was measured. First spontaneous beat after terminating the pacing was recorded and the time between the last pacing and the first spontaneous beat was measured. This measurement equals the sum of the 2 x SACT and sinus cycle length. SACT was derived from this equation.

3. Atrial effective refractory period (AERP): Eight atrial stimuli (S1) with 600 ms cycle length followed by one extra stimulus (S2) were given. Coupling interval (S1 - S2) was gradually decreased. The longest S1 - S2 interval, which S2 did not depolarize the atrium, was accepted as AERP.

4. Atrioventricular node effective refractory period (AVNERP): Eight atrial stimuli (S1) with 600 ms cycle length followed by one extra stimulus (S2) were given. Coupling interval (S1 - S2) was gradually decreased. The longest S1 - S2 interval, which S2 was not conducted to the ventricle via AV node, was accepted as AVNERP.

5. Atrio-ventricular Wenckebach cycle length (AVWCL): Incremental atrial pacing (maximum 200 beats/min that equals 300 ms cycle length) was performed gradually until block occurred at the level of the AV node or infra-node and ceased 1:1 conduction. The cycle length that caused ceasing of 1:1 AV conduction was recorded as AVWCL.

6. Ventricular effective refractory period (VERP): Eight ventricular stimuli (S1) with 600 ms cycle length following by one extra stimulus (S2) were given. Coupling interval (S1 - S2) was gradually decreased. The longest S1 - S2 interval, which S2 did not depolarize the ventricle, was accepted as VERP.

7. Ventriculoatrial dissociation cycle length (VDCL): Incremental ventricular pacing was performed gradually until ventriculoatrial dissociation occurred. The cycle length that caused ventriculo-atrial dissociation was recorded as VDCL.

8. Corrected QT interval (QTc) interval was calculated from continuous 12 lead electrocardiography (ECG) tracings that was recorded at a speed 100 mm/sec and QTc interval was derived according to formula.

9. QT dispersion: It was recorded as time difference between leads that have longest and shortest QT interval, derived from continuous 12 lead ECG tracings that was recorded at a speed 100 mm/sec\cite{18}. 

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Finally, whether ventricular arrhythmia could be induced was evaluated by using various techniques (programmed extra stimulation, multiple extra stimulation, short-long-short sequence).

**Statistical Analysis:** Results are expressed as mean ± standard deviation (SD). The paired sample t test was used for the comparison of quantitative data. The Mc Nemar test was used for the comparisons of qualitative data. A p-value of < 0.05 was considered statistically significant.

### RESULTS

All patients had a history of significant coronary stenosis (> 50%) at least in one coronary artery. The number of patients, who had one, two and three vessel coronary disease, was 4, 3, and 4, respectively and five patients had a history of coronary artery bypass graft surgery. All patients had reduced LVEF (< 35%) with segmental wall motion abnormality on echocardiography.

There was no significant difference in the basic conduction intervals (PA, AH, HV, PR, QRS, QT, BCL) of the patients at baseline and after statin therapy (Table 1). Except the QTc interval and QT dispersion, there were no significant differences in other electrophysiologic parameters between pre and post- treatment measurements. QTc interval and QT dispersion decreased statistically significantly with statin treatment (444.1 ms Vs 431.2 ms, p = 0.018; and 36.0 ms Vs 29.1 ms, p = 0.028, respectively) (Table 2). While induction of ventricular tachyarrhythmia occurred in 72.7% of patients before taking the statin, this rate decreased to 36.4% with treatment. Morphologies and hemodynamic consequences of ventricular tachyarrhythmias, which were induced during electrophysiologic study, were similar with admission tachyarrhythmias. Even though there was a trend for a reduced rate of tachyarrhythmia induction after statin therapy, this was not statistically significant (p = 0.125) (Table 3).

### DISCUSSION

The principal results of this prospective study are (1) QTc interval shortens and QT dispersion decreases with statin treatment. (2) Statin treatment is associated with a trend toward decreased ventricular tachyarrhythmia induction.

Many studies demonstrated that statins decrease the incidence of ventricular arrhythmias (VA)\(^{[4-8]}\) and this result may, at least in part, account for the statin-induced decrease in cardiovascular mortality. Statins significantly reduce the incidence of appropriate ICD shocks for life-threatening ventricular arrhythmias in patients with coronary artery disease (CAD) and ICD

### Table 1: Basic intervals

<table>
<thead>
<tr>
<th>Interval</th>
<th>Before treatment Mean ± SD</th>
<th>On treatment Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH</td>
<td>88.00 ± 21.43</td>
<td>88.00 ± 18.04</td>
<td>0.99</td>
</tr>
<tr>
<td>HV</td>
<td>60.91 ± 9.25</td>
<td>61.36 ± 12.03</td>
<td>0.833</td>
</tr>
<tr>
<td>PA</td>
<td>20.09 ± 7.15</td>
<td>21.45 ± 7.20</td>
<td>0.454</td>
</tr>
<tr>
<td>PR</td>
<td>158.73 ± 34.94</td>
<td>166.45 ± 32.47</td>
<td>0.078</td>
</tr>
<tr>
<td>QRS</td>
<td>111.82 ± 28.85</td>
<td>109.63 ± 28.32</td>
<td>0.540</td>
</tr>
<tr>
<td>QT</td>
<td>362.00 ± 34.52</td>
<td>354.63 ± 35.56</td>
<td>0.379</td>
</tr>
<tr>
<td>BCL</td>
<td>747.45 ± 153.86</td>
<td>751.63 ± 158.31</td>
<td>0.907</td>
</tr>
</tbody>
</table>

AH: measured between the atrial electrogram recorded by the His bundle catheter and the beginning of the His electrogram itself; HV: measured between the His electrogram and the earliest recorded ventricular activation; PA: measured between earliest recorded atrial activity and the rapid deflection of the atrial electrogram on the His bundle catheter; PR: duration between the onset of atrial depolarization to the onset of ventricular depolarization; QRS: duration of ventricular activation; QT: combination of ventricular depolarization to the onset of ventricular repolarization; BCL: sinus cycle length; SD: standard deviation

**Table 2: Electrophysiologic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment Mean ± SD</th>
<th>On treatment Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSNRTSJ</td>
<td>216.09 ± 67.12</td>
<td>200.00 ± 59.29</td>
<td>0.450</td>
</tr>
<tr>
<td>Narula SACT[^{st}]cor</td>
<td>103.59 ± 47.96</td>
<td>110.45 ± 61.59</td>
<td>0.690</td>
</tr>
<tr>
<td>AVNERP[^{plt}]</td>
<td>269.09 ± 66.40</td>
<td>270.91 ± 59.57</td>
<td>0.921</td>
</tr>
<tr>
<td>AVWP[^{t}]</td>
<td>363.64 ± 59.88</td>
<td>344.54 ± 50.47</td>
<td>0.309</td>
</tr>
<tr>
<td>VERP[^{f}]</td>
<td>223.64 ± 16.89</td>
<td>230.91 ± 13.75</td>
<td>0.181</td>
</tr>
<tr>
<td>VA + Dissociation</td>
<td>448.18 ± 108.32</td>
<td>450.00 ± 86.83</td>
<td>0.951</td>
</tr>
<tr>
<td>QTc[^{c}]</td>
<td>444.18 ± 33.97</td>
<td>431.27 ± 34.92</td>
<td>0.018*</td>
</tr>
<tr>
<td>QT Dispersion</td>
<td>36.00 ± 9.21</td>
<td>29.18 ± 8.11</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

\[^{§}\] = corrected sinus node recovery time; \[^{\par}\] = sinoatrial conduction time; \[^{\ast}\] = atrio-ventricular node effective refractory period; \[^{\|}\] = atrio-ventricular Wenckebach period; \[^{\#}\] = ventricular effective refractory period; \[^{\&}\] = ventriculo-atrial; \[^{\p}\] = p < 0.05; SD = standard deviation, \[^{\dagger}\] = corrected QT

**Table 3: Induction of ventricular tachyarrhythmia**

<table>
<thead>
<tr>
<th>Induction of ventricular tachyarrhythmia</th>
<th>Before treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes n (%)</td>
<td>No n (%)</td>
</tr>
<tr>
<td>On treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (36.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No</td>
<td>4 (36.4)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (72.7)</td>
<td>3 (27.3)</td>
</tr>
</tbody>
</table>
implants. It was also suggested that statin treatment may have a beneficial effect on the incidence of VA in the setting of acute myocardial infarction. Two large randomized studies suggest that statins might exert a beneficial effect on the incidence of lethal VA and reduce the relative risk of SCD. In this regard, the recent guidelines of the American College of Cardiology (ACC) / American Heart Association (AHA) / European Society of Cardiology (ESC) for the management of VA recommend that statin therapy could be beneficial in patients with CAD to reduce the risk of vascular events, possibly VA and SCD. Although the definite mechanism of this effect is unknown, there are several proposed mechanisms including direct antiarrhythmic effect by affecting different electrophysiologic components and anti-ischemic effect by reducing ischemia-related ventricular tachyarrhythmias. Statins can prevent progression and promote regression of atherosclerotic plaques and may contribute to the plaque stabilization in high-risk atherosclerotic lesions. These effects lead to a reduced risk of plaque rupture, thereby preventing ischemia-induced electrophysiologic effects that predispose to VA.

It is known that some electrophysiologic changes can predispose to VA and statins are suggested to have beneficial effects on these electrophysiologic parameters. Decreased heart rate variability is associated with decreased parasympathetic tone and has been shown to be a predictor of arrhythmic events and some clinical studies demonstrated that statins are associated with increased heart rate variability. Although exact mechanism of this effect is unknown, it may be associated with decreasing caveolin-1 expression and facilitating nitric oxide synthase function with concurrent improvement of heart rate variability. Ventricular late potentials are considered to originate from areas of slow and non-homogenous conduction within the diseased myocardium and are also thought to represent delayed activation of damaged myocardium that serves as an anatomical substrate for repeated VA. It has been shown that early statin administration leads to a significant decrease in the incidence of ventricular late potentials and VA in patients with acute myocardial infarction. Increased QT variability and QTc interval prolongation have been associated with heterogeneity in ventricular repolarization and changes in autonomic nervous tone that predispose to the development of VA and sudden cardiac death. It has been demonstrated that atorvastatin therapy decreases QT variability and shortens QTc intervals in patients with advanced heart failure. Treatment with fluvastatin for 12 months led to a decreased variability of QT dispersion in another small study. These statin-induced changes may reflect multiple beneficial pleiotropic effects of statins, including modulation of autonomic nervous tone and stabilization of ventricular repolarization. Additionally, statin therapy may also result in alterations in transmembrane ion channel properties by affecting ventricular conduction and excitability. Vyas et al suggests an immediate effect of these drugs rather than a delayed effect related to a slowing of the rate of progression of atherosclerosis. All of these studies supported that statins may have direct antiarrhythmic effects independent of antiischemic properties but the exact mechanism is unknown. However, a recent review concluded that an antiischemic rather than a primary antiarrhythmic effect emerges as the likely mechanism of sudden cardiac death reduction with statins and some studies did not show a beneficial effect of statins on life-threatening arrhythmias.

The heterogeneity of the conduction and refractoriness are important features for reentrant tachyarrhythmias and increased QT dispersion is associated with heterogeneity of the ventricular refractoriness. Also it is well known that, increased QTc interval can promote ventricular tachyarrhythmia. Both QTc prolongation and increased QT dispersion are associated with higher mortality rate in patients with moderate and severe left ventricular dysfunction. Our study demonstrated that statin therapy might have beneficial effect on QT dispersion and QTc interval and these findings are consistent with the findings of prior smaller studies. However, there was no significant effect of statins on the other electrophysiologic parameters (e.g., refractoriness, conduction time), which were not evaluated before.

**Study limitations**

This is a small study where each patient served as his own control, without a separate control group not receiving statin therapy. The small number of patients does not allow reliable conclusions regarding the effect of statins on the inducibility ventricular arrhythmias. Additionally, the dose and duration of the statin treatment was chosen arbitrarily. In electrophysiologic studies, errors may occur due to differences in catheter placement sites. Presence of an ICD lead in the right ventricle may have also affected measurements in the follow-up EPS, performed after the ICD implantation. All patients were on beta-blocker treatment and this may have affected measurements.

**CONCLUSION**

Statins seem to have beneficial effect against arrhythmias but definite mechanism of this antiarrhythmic effect is unknown. In this study, we found favorable effects on QT dispersion and QTc interval with statin treatment, but we observed that
the other electrophysiologic parameters did not change significantly.

ACKNOWLEDGEMENTS

This study was executed and reported independently; no company or institution supported it financially.

Conflict of interest: None declared.

REFERENCES

Variant Analysis of the Sirtuin (SIRT1) Gene in Multiple Sclerosis

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⁴Department of Neurology, Namik Kemal University Medical Faculty, Edirne, Turkey

ABSTRACT

Objective: Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting the central nervous system. Although the exact pathogenesis of MS is unknown, it is generally considered to be an autoimmune disease, with numerous genetic and environmental factors determining disease susceptibility and severity. Sirtuin 1 (SIRT1) is a neuroprotective enzyme in MS patients. The aim of our study was to investigate the relationship between a genetic variant of SIRT1 and MS.

Design: Controlled prospective study

Setting: Department of Neurology, Bülent Ecevit University Medical Faculty, Zonguldak, Turkey

Subjects and Methods: We determined SIRT1 genotypes by polymerase chain reaction (PCR) and confronting two-pair primers (CTPP) methods in 93 MS patients and 100 healthy controls

Intervention: For genetic analysis, 5 ml of venous blood was drawn from each patient into tubes containing EDTA

Main Outcome Measures: SIRT1 gene polymorphisms and recorded expanded disability status scale (EDSS) for MS patients

Results: We found a significant difference between the rs2273773 polymorphism of the SIRT1 gene of MS and the control group (p = 0.011). We also found an association between MS disease and the haplotypes of rs7895833, rs7069102 and rs2273773 polymorphisms.

Conclusion: We have shown that rs2273773 polymorphism of the SIRT1 gene might be a risk factor for MS disease in the Turkish population. Also, additional studies are needed to clarify the role of the SIRT1 gene in the pathogenesis of MS disease.

INTRODUCTION

Multiple sclerosis (MS) is known as an autoimmune disease, with numerous genetic and environmental factors determining disease susceptibility and severity. Although the pathogenesis of MS is not clear, multiple sclerosis has also been considered a neurodegenerative disease because of the coexistence of permanent axonal damage, neuronal loss and neurological disability¹-³. Susceptibility to MS is thought to be conferred by a combination of genetic and environmental factors⁴-⁵. The four clinical phenotypes of MS have been determined: relapsing-remitting MS (RR-MS), primary progressive MS (PP-MS), progressive relapsing MS (PR-MS) and secondary progressive MS (SP-MS).

Virus infections of the CNS, vascular factors and/or disturbed immune mechanisms are implicated in the pathogenesis of MS. In recent studies, altered redox balance and increased oxidative stress in the pathogenesis of MS have been suggested as influencing factors⁶-⁷. Sirtuin 1 (SIRT1) is a member of the sirtuin family of NAD +/- dependent deacetylases. Also, in mammals, yeast and higher organisms it deacetylates histones, which increase DNA stability and longterm survival⁸-¹⁰. SIRT1 controls numerous physiologic processes and protects cells against oxidative stress. Its activity is dependent on NAD, which affects electronic transmission of mitochondria and cellular oxygen supply. A decrease in NAD and SIRT1 activity is responsible for high p53 acetylation and c-Jun N-terminal kinase activation, which are related to cell activation, inflammation and atherosclerosis. These pathways can be prevented by the antioxidant resveratrol¹¹-¹⁴. SIRT1 is located in the cytoplasm and the nucleus. Its targets are known as...
FOXO1, FOXO3, PGC-1a, p53, NF-kB, Notch, HIF1a, LXR, FXR and SREBP1c[15]. SIRT1 is associated with longevity, oncogenesis, metabolic regulation and neurodegenerative diseases[16,17]. It has been suggested that SIRT1 could play a protective role in MS patients[23]. For this purpose, this study investigated the potential role that SIRT1 gene polymorphisms play in MS. The SNP of rs7895833 in the promoter region, rs7069102 in intron 4, and rs2273773 in exon 5 were selected for this study. These polymorphisms may affect the promoter activity and change the activity of the SIRT1 gene[18]. We have genotyped the polymorphisms (rs7895833, rs7069102 and rs2273773) of the SIRT1 gene to determine their association with MS disease in the Turkish population.

SUBJECTS AND METHODS

Population of the Study

The protocol was approved by the regional ethical committee, and procedures were performed according to the principles of The Helsinki Declaration. We analyzed 93 Turkish patients with MS diagnosed according to the revised McDonald criteria[19]. Once enrolled, a neurologist administered questionnaires, and blood samplings were drawn at the same visit. In the questionnaire, the patients were asked to report the onset time, character, and location, duration of the pain, associated symptoms, history and medications. We evaluated 93 MS patients (61 RR-MS, 29 SP-MS and 3 PP-MS) (mean age 30.42 ± 10.33 years) from the database of the Department of Neurology, Bulent Ecevit University Faculty of Medicine. We recorded expanded disability status scale (EDSS) for those patients. A total of 100 (32.61 ± 10.21 years) unrelated, age and sex-matched controls were selected from the same geographic area as the control sample. Table 1 shows the demographic characteristics of MS patients and healthy controls.

Genotyping

After written, informed consent was obtained, venous blood samples were collected into vacutainer plastic tubes containing sodium/potassium EDTA. Polymerase chain reaction (PCR) and confronting two-pair primers (CTPP) methods for rs7895833, rs7069102 and rs2273773 polymorphisms have been shown previously[18]. The SIRT1 gene polymorphism (rs7895833, rs7069102 and rs2273773) genotypes were determined by PCR and CTPP methods. DNA was extracted with a Genejet Genomic DNA purification kit (Thermo K0772). Primers, annealing temperatures and fragments of these polymorphisms are shown in Table 2. PCR was performed in a 25 μl volume with 50 ng DNA, 100 μM dNTPs, 20 pmol of each primer, 1.5 mM MgCl2, 1 x PCR buffer with (NH4)2SO4 (Fermentas, Vilnius, Lithuania) and 1U Taq DNA polymerase (Fermentas, Vilnius, Lithuania). Amplification was performed on an automated thermal cycler (Techne Flexigene, Cambridge, UK). PCR conditions for SIRT1 gene polymorphisms were 3 min for initial denaturation at 95 ºC, 35 cycles, 45 s at 94 ºC for denaturation, 1 min at 64 ºC for annealing and 2 min at 72 ºC for extension, followed by 7 min at 72 ºC for final extension. PCR products were directly analyzed by electrophoresis on 3% agarose gels, and each allele was identified according to its size.

Statistical Analysis

The Hardy–Weinberg equilibrium was verified using the chi-square test and by estimating the expected genotypic frequencies on the basis of the development of the square of the binomial for these polymorphisms. Allelic and genotypic distributions among the different groups were compared using the likelihood-ratio chi-square test or Fisher’s exact test. Haplotype analysis was used to evaluate the effect of the genes. Platform (http://analysis.bio-x.cn/myAnalysis.php) and SPSS 11.5 for Windows program were used to implement statistical analysis.

RESULTS

According to the data we obtained, 93 MS patients (mean age 45 ± 2.0 years) and 100 (49.8 ± 0.8 years) unrelated, age and sex-matched controls were compared. There were no significant differences in the distribution of age and gender between MS and control patients (p > 0.05) (Table 1).

Table 1: Clinical parameters of subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (Yrs) (Mean ± SE)</th>
<th>EDSS ”median (IQR)”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>100</td>
<td>45 ± 2.0</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>93</td>
<td>49.8 ± 0.8</td>
<td>5.12 (2.03 – 7.56)</td>
</tr>
<tr>
<td>RR-MS</td>
<td>61</td>
<td>41.6 ± 2.0</td>
<td>1.22 (0.35 – 3.38)</td>
</tr>
<tr>
<td>SP-MS</td>
<td>29</td>
<td>50.2 ± 0.4</td>
<td>5.58 (3.18 – 7.80)</td>
</tr>
<tr>
<td>PP-MS</td>
<td>3</td>
<td>55.4 ± 0.4</td>
<td>5.80 (4.70 – 8.02)</td>
</tr>
</tbody>
</table>

EDSS = Expanded disability status scale; MS = Multiple sclerosis; RR-MS = relapsing-remitting MS; SP-MS = secondary progressive MS; PP-MS = primary progressive MS

According to our results, a meaningful difference was found between the rs2273773 polymorphism of the SIRT1 gene in the MS and the control groups. Also, logistic regression analysis showed that the C allele for the rs2273773 polymorphism might be a risk factor for MS disease (p = 0.011; OR = 1.686; 95% CI = 1.127-2.523). The RR-MS group C alleles of the SIRT1 gene rs2273773 polymorphism were found to have a higher frequency
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Table 2: Primers and PCR conditions for rs7895833, rs7069102 and rs2273773 polymorphisms of SIRT1 gene.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Primers Sequence</th>
<th>An. Temp (°C)</th>
<th>Fragment Size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7895833</td>
<td>Forward primer 1: CCCAGGGTTCAACAAATCTATGTG</td>
<td>64</td>
<td>AA; 320, 241 bp</td>
<td></td>
</tr>
<tr>
<td>SIRT1</td>
<td>Forward primer 2: GGGTGTAAGAGGTACCCCAAG</td>
<td></td>
<td>AG; 320, 241, 163 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reverse primer 1: GCTTCCATATCATTAGGTCAC</td>
<td></td>
<td>GG; 320, 136 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reverse primer 2: CTTCCCAATCACGCTTTATC</td>
<td></td>
<td>GG; 320, 136 bp</td>
<td></td>
</tr>
<tr>
<td>rs7069102</td>
<td>Forward primer 1: GTACGACGAACTACAGGCCGT</td>
<td>64</td>
<td>CC; 391, 167 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forward primer 2: GAGAACAGAAGTTTCATCTGC</td>
<td></td>
<td>CC; 391, 167 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reverse primer 1: CATATCTGCAGAATAATGGCTTTTC</td>
<td></td>
<td>CC; 391, 167 bp</td>
<td></td>
</tr>
<tr>
<td>rs2273773</td>
<td>Forward primer 1: GTTGTGGCAGATCATCTACGCC</td>
<td>63</td>
<td>CC; 314, 135 bp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forward primer 2: CTCTCTGTCACAAATCTCATGCT</td>
<td></td>
<td>CT; 314, 135 bp</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Genotypes and alleles of rs7895833, rs7069102 and rs2273773 polymorphisms of SIRT1 gene and risk of developing in MS

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Healthy controls n (%)</th>
<th>Multiple sclerosis n (%)</th>
<th>χ²</th>
<th>All MS OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7895833</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>93 (46.5)</td>
<td>96 (51.6)</td>
<td>0.011 (all MS)</td>
<td>1.327 (0.69 - 2.58)</td>
</tr>
<tr>
<td>A</td>
<td>107 (53.5)</td>
<td>100 (48.4)</td>
<td>0.004 (RR-MS)</td>
<td>1.041 (0.53 - 2.06)</td>
</tr>
<tr>
<td>GC</td>
<td>31 (33.3)</td>
<td>31 (33.3)</td>
<td>NS</td>
<td>0.986 (0.49 - 1.99)</td>
</tr>
<tr>
<td>AG</td>
<td>35 (35.0)</td>
<td>35 (35.0)</td>
<td>NS</td>
<td>0.951 (0.48 - 1.89)</td>
</tr>
<tr>
<td>AA</td>
<td>36 (36.0)</td>
<td>36 (36.0)</td>
<td>NS</td>
<td>0.951 (0.48 - 1.89)</td>
</tr>
<tr>
<td>rs7069102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>123 (61.5)</td>
<td>115 (62.5)</td>
<td>NS</td>
<td>0.718 (0.39 - 1.36)</td>
</tr>
<tr>
<td>G</td>
<td>77 (38.5)</td>
<td>74 (38.5)</td>
<td>NS</td>
<td>0.718 (0.39 - 1.36)</td>
</tr>
<tr>
<td>CC</td>
<td>44 (44.0)</td>
<td>44 (44.0)</td>
<td>NS</td>
<td>0.718 (0.39 - 1.36)</td>
</tr>
<tr>
<td>CG</td>
<td>35 (35.0)</td>
<td>35 (35.0)</td>
<td>NS</td>
<td>0.718 (0.39 - 1.36)</td>
</tr>
<tr>
<td>GG</td>
<td>21 (21.0)</td>
<td>21 (21.0)</td>
<td>NS</td>
<td>0.718 (0.39 - 1.36)</td>
</tr>
<tr>
<td>rs2273773</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>112 (56.0)</td>
<td>100 (56.0)</td>
<td>NS</td>
<td>0.86 (0.39 - 1.87)</td>
</tr>
<tr>
<td>C</td>
<td>88 (44.0)</td>
<td>88 (44.0)</td>
<td>NS</td>
<td>0.86 (0.39 - 1.87)</td>
</tr>
<tr>
<td>TT</td>
<td>32 (32.0)</td>
<td>32 (32.0)</td>
<td>NS</td>
<td>0.86 (0.39 - 1.87)</td>
</tr>
<tr>
<td>TC</td>
<td>48 (48.0)</td>
<td>48 (48.0)</td>
<td>NS</td>
<td>0.86 (0.39 - 1.87)</td>
</tr>
<tr>
<td>CC</td>
<td>20 (20.0)</td>
<td>20 (20.0)</td>
<td>NS</td>
<td>0.86 (0.39 - 1.87)</td>
</tr>
</tbody>
</table>

NS = not significant; MS = Multiple sclerosis; RR-MS = relapsing-remitting MS; SP - MS = secondary progressive MS; PP - Ms = primary progressive MS

Table 4: Haplotype analysis for rs7895833, rs7069102 and rs2273773 polymorphisms of SIRT1 gene and the risk of developing MS

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>All MS (N = 93) n (%)</th>
<th>Controls (n = 100) n (%)</th>
<th>OR †</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCT</td>
<td>25 (13.4)</td>
<td>49 (49.5)</td>
<td>1.04</td>
<td>0.096 (0.49 - 1.99)</td>
</tr>
<tr>
<td>ACT</td>
<td>21 (11.3)</td>
<td>29 (29.0)</td>
<td>1.09</td>
<td>0.727 (0.43 - 1.35)</td>
</tr>
<tr>
<td>GCC</td>
<td>42 (22.6)</td>
<td>75 (75.0)</td>
<td>1.07</td>
<td>0.320 (0.17 - 0.59)</td>
</tr>
<tr>
<td>ACC</td>
<td>28 (15.1)</td>
<td>30 (30.0)</td>
<td>1.00</td>
<td>0.940 (0.49 - 1.82)</td>
</tr>
<tr>
<td>GGT</td>
<td>10 (5.4)</td>
<td>19 (19.0)</td>
<td>1.06</td>
<td>0.654 (0.35 - 1.21)</td>
</tr>
<tr>
<td>AGT</td>
<td>24 (12.9)</td>
<td>16 (16.0)</td>
<td>1.57</td>
<td>0.859 (0.45 - 1.65)</td>
</tr>
<tr>
<td>GCC</td>
<td>19 (10.2)</td>
<td>11 (11.0)</td>
<td>0.90</td>
<td>0.830 (0.39 - 1.76)</td>
</tr>
<tr>
<td>AGC</td>
<td>17 (9.1)</td>
<td>32 (32.0)</td>
<td>1.04</td>
<td>0.931 (0.48 - 1.81)</td>
</tr>
</tbody>
</table>

MS = Multiple sclerosis; OR = odds ratio, CI = confidence interval
† These haplotypes might be a risk factor for all MS types
of rs7895833, rs7069102 and rs2273773 polymorphisms of the SIRT1 gene. The result of this analysis shows that there is no association with EDSS score and rs7895833, rs7069102 and rs2273773 polymorphisms of the SIRT1 gene (p > 0.05).

**DISCUSSION**

In the present study, we identified that SNPs within the SIRT1 gene were nominally associated with susceptibility to MS disease. We also identified a haplotype consisting of the three SNPs in the SIRT1 gene.
gene. Also, we have found three haplotypes that had a stronger association with MS disease. We analyzed for RR-MS, SP-MS, PP-MS and all MS with SIRT1 gene rs7895833, rs7069102 and rs2273773 polymorphisms. We have shown that the rs2273773 polymorphism of the SIRT1 gene might be important for MS disease. SIRT1 plays an important role not only in the regulation of aging and longevity but also in the development and/or progression of age-associated metabolic diseases, such as obesity, gastric cancers, diabetes, Parkinsonism and MS[3,18,22-25].

It has been determined not only that axonal damage and neuronal loss are significant pathologic components of MS and experimental autoimmune encephalomyelitis (EAE) but that this neuronal damage is thought to cause the permanent neurologic disability often seen in MS patients. Current treatments for MS involve immunomodulation, which can reduce the incidence of inflammatory relapses[26-29]. Recently, it has been shown that the SIRT1 gene might be associated with MS pathogenesis. SIRT1 is emerging as a promising target candidate for therapeutic interventions in metabolic and neurodegenerative disorders[3].

Pennisi et al demonstrated an increase of Sirtuin-1 (SIRT1) levels in plasma from MS patients. Therefore, they speculated on the protective role of this soluble protein in MS[3]. Also, it was shown that SIRT1 activation has great potential for preventing neuronal loss throughout the central nervous system in MS disease[30]. However, to the best of our knowledge, SIRT1 gene polymorphisms have not been investigated in MS patients. The results of our study support the conclusions of Pennisi et al. In this situation, SIRT1 might be an effective component in battling MS disease.

CONCLUSION

In this study, we found a relationship between the rs2273773 polymorphism of the SIRT1 gene and MS disease. In addition to this result, GCC, AGT and GGC haplotypes for rs7895833, rs7069102 and rs2273773 polymorphisms of the SIRT1 gene could be risk factors for all types of MS disease in the Turkish population (Table 4). An association between SIRT1 gene polymorphisms and MS had not been shown before this study. In further studies, SIRT1 gene expression may be analyzed in a larger group of MS patients. Also, additional studies are needed to clarify the role of the SIRT1 gene in the pathogenesis of MS disease.

REFERENCES


Acquired Multiple Clotting Factor Inhibitors in Children

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4Faculty of Medicine, Kuwait University, Kuwait

ABSTRACT

Background: Acquired childhood multiple clotting factor inhibitors are rare especially in the absence of lupus anticoagulants. They may represent multiple specific inhibitors or may be non-specific, resulting from molecular mimicry or cross-reacting antibodies. Their exact nature and natural history are not well known.

Objective: To report our experience with seven children presenting with prolonged activated partial thromboplastin time (APTT), with or without bleeding, not corrected by mixing, and showing deficiency of > one clotting factor.

Design: Prospective review
Setting: Mubarak Hospital, Kuwait
Subjects: Patients referred to the pediatric hematology unit between 2010 and 2012 with deranged coagulation profiles with or without bleeding, without a previous or family history of a bleeding disorder. They all had multiple clotting factor deficiencies.

Main Outcome Measures: Control of bleeding and normalization of coagulation factors and APTT

Results: The patients were aged 6 months to 8 years; three presented with mild to moderate bleeding and five had preceding viral infections. Factor IX was decreased in all cases in addition to deficiencies of factors VIII, X and/or XI in various combinations. There was spontaneous recovery in five patients in whom the factors and APTT normalized within two to five months. One patient died from massive pulmonary hemorrhage and another with nephropathy remains the same after two years.

Conclusion: Multiple acquired inhibitors are not uncommon in children, tend to follow viral infections, and are usually transient and not associated with severe bleeding.

KEY WORDS: acquired clotting factor inhibitors

INTRODUCTION

The interpretation of screening tests for coagulation disorders is not always straightforward in the pediatric age group. This is because prothrombin time (PT) and activated partial thromboplastin time (APTT) are usually prolonged, even in normal children and reference values are not always available[1,2]. Children may also develop clotting factor inhibitors following viral infections, immunizations, autoimmune diseases or malignancies[3-5]. These inhibitors may be specific (i.e., directed against a single factor) occurring either spontaneously as in acquired hemophilia or secondary to previous replacement therapy (as alloantibodies). However, they may be non-specific, in which case they are associated with multiple factor inactivation. Quite often, this is caused by lupus anticoagulants that are anti-phospholipid antibodies which, although they cause prolonged APTT, are not associated with bleeding, but may, in fact, cause thrombosis[6-8]. Acquired inhibitors are differentiated from inherited factor deficiencies by the mixing study in which normal plasma normalizes the screening test when a true deficiency exists, but fails to do so if an inhibitor is present[3,5,10]. Appropriate factor assays are then carried out to identify which factor is deficient.

In the unusual situation of multiple factor deficiencies, in the absence of lupus anticoagulant, unraveling the pathogenesis is not easy and there are different possibilities. Some specific factor inhibitors can cause artifactual decreases in the in-vitro levels of other clotting factors[11], but on the other hand, there may, indeed, be multiple specific inhibitors. Cross-
Coagulation factors VIII, IX, XI and XII activity were determined by performing a modified APTT assay. Correction of the clotting time of the deficient plasma is proportional to the concentration of that factor in the patient plasma. This was determined on an automated coagulometer ACL 9000 (Instrumentation Laboratory SpA - V.le Monza 338 - 20128 Milano, Italy)\textsuperscript{[12]}. Normal values of factors VIII and XII are 50 - 150%, IX and XI are 65 - 150%.

Lupus anticoagulant (LA) was detected using two methods - the Russell’s Viper Venom Time (American Diagnostica Inc, CT, USA) followed by automated confirmatory test on the ACL 9000 (International Laboratory Company, Italy, IL Test LA Screen and IL Test LA Confirm tests). LA Screen and LA Confirm are therefore unaffected by contact factor abnormalities, factor VII, VIII and IX deficiencies or inhibitors\textsuperscript{[13]}.

All the patients had complete blood count. Bacteriological tests including blood cultures and virology were done in those who presented with febrile illness. Other appropriate routine investigations were done depending on the presentation. The patients have been followed as out-patients for varying lengths of time with regular monitoring of the PT and APTT.

RESULTS

Tables 1 and 2 summarize the presentation and findings in the patients.

Table 1: Demographics and presentation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Bleeding at presentation</th>
<th>Preceding illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.5</td>
<td>F</td>
<td>None</td>
<td>Viremia</td>
</tr>
<tr>
<td>II</td>
<td>6.0</td>
<td>F</td>
<td>None</td>
<td>Chest infection</td>
</tr>
<tr>
<td>III</td>
<td>2.5</td>
<td>F</td>
<td>None</td>
<td>URTI</td>
</tr>
<tr>
<td>IV</td>
<td>0.5</td>
<td>M</td>
<td>None*</td>
<td>Viral infection</td>
</tr>
<tr>
<td>V</td>
<td>0.75</td>
<td>F</td>
<td>Hematoma</td>
<td>URTI</td>
</tr>
<tr>
<td>VI</td>
<td>6.0</td>
<td>F</td>
<td>Ecchymoses</td>
<td>URTI</td>
</tr>
<tr>
<td>VII</td>
<td>8.0</td>
<td>F</td>
<td>Epistaxis</td>
<td>None</td>
</tr>
</tbody>
</table>

* Patient developed massive pulmonary hemorrhage as a terminal event

CASE HISTORIES

Patient 1: A 5-month-old Egyptian female infant was born at 26 weeks’ gestation with a birth weight of

Table 2: PT, APTT and clotting factor assay

<table>
<thead>
<tr>
<th>Patient</th>
<th>PT (sec)</th>
<th>APTT (sec)</th>
<th>APTT after mixing</th>
<th>F VIII (%)</th>
<th>F IX (%)</th>
<th>F XI (%)</th>
<th>F XII (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>14.3</td>
<td>91.9</td>
<td>67.4</td>
<td>Normal</td>
<td>18.4</td>
<td>30.6</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>14</td>
<td>59</td>
<td>53</td>
<td>Normal</td>
<td>13.9</td>
<td>21.3</td>
<td>Normal</td>
</tr>
<tr>
<td>III</td>
<td>13.6</td>
<td>&gt;180</td>
<td>95</td>
<td>10</td>
<td>2.2</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>62</td>
<td>62</td>
<td>Normal</td>
<td>33</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>V</td>
<td>12.9</td>
<td>56</td>
<td>52</td>
<td>Normal</td>
<td>45</td>
<td>51</td>
<td>29</td>
</tr>
<tr>
<td>VI</td>
<td>14.7</td>
<td>81.9</td>
<td>69</td>
<td>1</td>
<td>0.79</td>
<td>23.5</td>
<td>Normal</td>
</tr>
<tr>
<td>VII</td>
<td>15.7</td>
<td>96.6</td>
<td>90</td>
<td>14</td>
<td>9</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

PT = prothrombin time; APTT = activated partial thromboplastin time; F = factor
A 6-month-old Filipino girl admitted to elective caesarian section (CS) because of previous CS. She had an uneventful neonatal period and there was no previous history of prolonged bleeding. However, one week before presentation she developed cough and fever. There was no family history of a bleeding disorder.

On physical examination she looked well with no petechiae or ecchymoses or localized swelling. She had unilateral subconjunctival hemorrhage. The liver and spleen were not palpable. Her blood counts were normal with platelets of 496 x 10^{10}/l and blood film was normal. Serum immunoglobulins and complements were normal and normal. Virology screening was negative. PT was 13 sec, but APTT was > 3 min and on mixing was 95 sec. Factor VIII was 10% and factor IX 2.2%. No specific treatment was given and by the 3rd month of follow-up, the coagulation profile and factors were back to normal.

Patient IV: A 5-month-old Kuwaiti boy, a product of preterm CS at the 35th week of gestation because of maternal eclampsia, had a birth weight of 1.750 kg. He was discharged from the special care baby unit (SCBU) after one month. At the age of four months, he was noticed to be jaundiced and severely pale. There were no dysmorphic features, no skin rash or peripheral lymphadenopathy; the liver and spleen were not palpable. His Hb was 2.8 g/dl, reticulocytes of 0.4%, WBC 10.7 x 10^{9}/l and platelets 284 x 10^{10}/l. The RBC morphology was normal and the blood film showed activated lymphocytes. Direct Coomb's test was negative and G6PD was not deficient. Apart from elevated alkaline phosphatase and conjugated moderate hyperbilirubinemia, the liver transaminases were not elevated. Abdominal ultrasonography was essentially normal; skeletal survey did not show any bone abnormalities. Urine organic acids and lysosomal enzyme study were negative. A diagnosis of probable viral infection with reticulocytopenia was made. TORCH screening was negative. The PT was 12.2 sec, while APTT was 62.1 without correction on mixing. Factor assay showed factor VIII of 152%, IX 33%, XI 39%, and XII of 18%. He was transfused with packed RBCs on several occasions. There were no petechiae, ecchymoses or mucosal bleeding. He was stabilized and discharged from the hospital. However, after two weeks, his APTT was found to be >180 sec. He was readmitted and given fresh frozen plasma. However, he developed massive acute pulmonary hemorrhage, which he did not survive.

Patient V: A 6-month-old Filipino girl admitted with a 10-day history of coryzal symptoms and cough with respiratory distress and was diagnosed as acute bronchiolitis. While in the hospital, she had one episode of hematemesis. There was no previous
likely due to non-specific inhibitors in association with an otherwise previously-healthy individual, it is more predominant in combination with factor V or IX. Some have been reported, usually involving factor VIII coagulation factor deficiencies are extremely rare, but are encountered as part of extensive acquired coagulopathy. When seen in plasma, all the patients had plasma activity of more than one coagulation factor. When seen in plasma, they may be specific inhibitors resulting in the reduced plasma activity of more than one coagulation factor.

The seven patients in the present report did not have a family or previous significant history of bleeding. They did not have LA and most had a preceding acute illness, especially upper respiratory tract infection. They were all young children with four below the age of one year and interestingly all except one were female. None presented with severe bleeding although four had mild to moderate episodes including epistaxis, subconjunctival hemorrhage, ecchymoses and hematemesis. None required any special measures to achieve hemostasis. However, patient no. 4 had massive pulmonary hemorrhage as a terminal event. He was the only mortality in the series. Unfortunately an autopsy was not obtained and the nature of the underlying problem was undetermined.

Although the number is quite small, the female preponderance in this report may be significant. Gender differences have long been recognized in human innate and adaptive immunity with females having a more heightened response. For this reason, females are more prone to autoimmune diseases and this is thought to be due to genetic, hormonal and environmental factors. Since the patients in this report are mostly infants and young children, it would appear that genes located on the X chromosome and not sex hormones might be contributing to this phenomenon.

Four patients had some form of infection preceding the presentation; in two patients this was a possible viral upper respiratory tract infection, while one had viremia (EBV and herpes) and one had recurrent chest infection. One patient had a nephropathy of undetermined etiology. It was only two patients who had no history of preceding infection and no underlying chronic medical issues. This is consistent with previous reports that acquired clotting factor inhibitors, while rare, are more likely to be associated with infections. Common viral infections are often associated with low-titer, polyspecific autoantibodies. These tend to be transient as in our patients, but while progression to an established autoimmune disease is possible, it is rare. The underlying mechanism appears to be molecular mimicry between viral nuclear antigens and target autoantigens especially when they share homologous amino acid sequences.

The APTT ranged from 56 sec to > 3 min while the PT was essentially normal in all the patients. The APTT did not show any significant correction on mixing with normal plasma. Compared to the normal values for the clotting factors in our laboratory, all the patients had > 1 factor deficiency (see Table 1). The most commonly

**DISCUSSION**

Multiple clotting factor deficiencies are usually encountered as part of extensive acquired coagulopathy as in liver disease, disseminated intravascular coagulopathy (DIC), vitamin K deficiency or during treatment with oral anticoagulants. Familial multiple coagulation factor deficiencies are extremely rare, but some have been reported, usually involving factor VIII in combination with factor V or IX. When seen in an otherwise previously-healthy individual, it is more likely due to non-specific inhibitors in association with LA which are antiphospholipid antibodies acting as non-specific clotting factor inhibitors causing prolonged APTT, but more likely to be associated with thrombosis rather than bleeding. However, they may be specific inhibitors resulting in the reduced plasma activity of more than one coagulation factor.

Patient VI: A 6-year-old previously-healthy Kuwaiti girl presented with large ecchymotic patches on both lower limbs of three days’ duration with no associated mucous membrane bleeding or hemarthroses. There was no previous history of bleeding and the family history was not contributory. On examination she was not ill-looking or toxic. Apart from the ecchymotic patches, there were no other pertinent findings. CBC was normal with platelet count of 352 x 10^9/1. Her PT was 14.7 sec and APTT 81.9 sec and 68.2 sec after mixing. Clotting factors were: VIII 1%, IX 0.79%, XI 23.5%. By the 9th week of presentation the coagulation profile normalized by the fifth month of follow up.

Patient VII: A 71⁄2-year-old Kuwaiti girl presented with one episode of epistaxis lasting for three hours that stopped spontaneously. She developed flu-like symptoms with fever four days before presentation. She had such previous episodes but those were short lasting. Otherwise there was no other significant past medical or family history. On examination, she was not ill-looking or toxic. There were no petechiae or ecchymoses. The liver and spleen were not palpable. CBC was normal, with platelet count of 353 x 10^9/1. PT was 13.6 sec and APTT 95.6 sec. There was no correction on mixing and factor VIII was 14% and IX 9%. By the fourth week of presentation, the clotting factors were back to normal although the APTT was only marginally prolonged (44 sec). She has not required any treatment and is still being followed as an outpatient.

Patient III: A 8-year-old previously-healthy Kuwaiti girl presented with lower gums bleeding for two days. She had such previous episodes but those were short lasting. She had a nephropathy of undetermined etiology. It was only two patients who had no history of preceding infection and no underlying chronic medical issues. This is consistent with previous reports that acquired clotting factor inhibitors, while rare, are more likely to be associated with infections. Common viral infections are often associated with low-titer, polyspecific autoantibodies. These tend to be transient as in our patients, but while progression to an established autoimmune disease is possible, it is rare. The underlying mechanism appears to be molecular mimicry between viral nuclear antigens and target autoantigens especially when they share homologous amino acid sequences.

The APTT ranged from 56 sec to > 3 min while the PT was essentially normal in all the patients. The APTT did not show any significant correction on mixing with normal plasma. Compared to the normal values for the clotting factors in our laboratory, all the patients had > 1 factor deficiency (see Table 1). The most commonly
affected was factor IX in seven patients, XI in five, VIII in three and XII in two patients. There was only one patient in whom factor activity was ≤ 1% (0.79% for factor IX and 1.0% for factor VIII). In five patients, there was at least one factor with < 20% activity. The presentation was usually mild without any significant prolonged bleeding requiring active intervention. Unfortunately one patient had massive pulmonary hemorrhage and died. The contribution of his underlying illness to this process was undetermined. The degree of deficiency in the affected factors would, indeed, suggest that we are probably dealing with multiple specific inhibitors.

The coagulation profile normalized in five out of seven patients within a few weeks to months. Two patients still have prolonged APTT more than six months after presentation, although there have been no bleeding episodes. They continue to be followed and their antinuclear antibody status is being monitored because they may, indeed, be candidates for an established autoimmune disease.

CONCLUSION
Acquired multiple clotting factor inhibitors are not uncommon in children. It affects girls more than boys, tends to follow viral infections, is not usually associated with severe bleeding and is usually transient. More studies are required to understand the nature and concentration of the inhibitors and their pathogenesis.

REFERENCES
Predictors of Quality of Life in Renal Transplant Recipients

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Kuwait Medical Journal 2013; 45 (4): 324 - 328

ABSTRACT

INTRODUCTION

The presence of end stage renal disease (ESRD) has a negative impact on patients’ quality of life (QOL). Renal transplantation is well-recognized to provide a better QOL than other modalities of renal replacement therapy.

OBJECTIVES: To evaluate the QOL in our renal transplant recipients and to determine the factors that influences it at our institution

DESIGN: Cross-sectional observational study

SETTING: Universiti Kebangsaan Hospital, Malaysia

SUBJECTS: Renal transplant recipients between 18 and 75 years who have been transplanted more than one year

MAIN OUTCOME MEASURE(S): QOL was assessed using the Short Form-36 questionnaire that has been validated in the Malay language

RESULTS: Thirty nine patients (29 male, 10 female) were enrolled. The SF-36 scores were physical functioning (47.85 ± 6.93), role physical functioning (49.51 ± 11.08), general health (51.43 ± 6.22), vitality (60.53 ± 6.61), social functioning (50.85 ± 9.26), mental health (55.74 ± 7.16), bodily pain (58.55 ± 7.51), role emotional functioning (49.09 ± 12.01), physical component summary (49.37 ± 6.87) and mental component summary (55.23 ± 6.66). Predictors of QOL were education (p < 0.001), serum albumin (p = 0.017) and hemoglobin (p = 0.02). Increasing age negatively impacted physical functioning (p = 0.029). We also found those who received a commercial transplant had a lower mental health compared to those done locally (p = 0.031).

CONCLUSION: Predictors of QOL in our renal transplant cohort were age, education, serum albumin and hemoglobin.

INTRODUCTION

The presence of end stage renal disease (ESRD) has a negative impact on patients’ quality of life (QOL). It also affects their general well-being and personal relationships and reduces a patients’ lifespan. One of the key features in treating patients with ESRD is optimising general health and well-being. It is well-recognized that kidney transplantation not only offers the best long term outcome but is also associated with a better QOL compared to dialysis[13]. However, kidney transplantation is not suitable for everyone and is limited by the lack of available donors.

QOL is assessed using health-related QOL questionnaires. These health-related questionnaires measure a patients functioning and general health perception in three major domains: physical, psychological and social domains. Factors affecting QOL in renal transplant patients include age, gender, socio-economic and educational status, co-morbidities, type of renal transplant, serum hemoglobin and kidney function[45]. Studies have shown that Asian patients have a lower QOL than their European counterparts[67].

There are no studies that have assessed the QOL in transplant patients in our local setting. QOL has been shown to improve after kidney transplantation but kidney disease continues to impact QOL because of co-morbidities and side-effects of immunosuppressive medications. The purpose of this study was to determine the QOL in our renal transplant (RTx) patients and the factors affecting QOL like education level, age, type of transplant, serum hemoglobin and albumin.

SUBJECTS AND METHODS

All RTx patients followed up at our institution were screened when they attended their routine outpatient clinic visit. Patients were enrolled if they met the inclusion and exclusion criteria during the three month screening period.

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Patients

All RTx patients under follow-up at our center were screened for eligibility criteria. Patients >18 and <75 years of age and able to understand either English or Malay language were enrolled. Patients with amputations were excluded as we could not assess their physical ability on the questionnaire. Patients with malignancy, prolonged or multiple admissions to hospital were excluded. RTx patients had to be >1 year post-transplantation. The risk of rejection is highest in the first six months, they are on higher doses of steroids and most problems with infections occur early on. All these would negatively impact on QOL.

Demographics and Laboratory Parameters

Demographics collected included age, gender, race, socioeconomic status, co-morbidities, type of renal transplant and laboratory parameters. All transplant patients are reviewed at least on a two monthly basis and routine blood investigations are done on each clinic visit. We took the mean of three results of serum urea and creatinine, albumin and hemoglobin (Hb) in the preceding six months.

Quality of Life

QOL was evaluated using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) questionnaire in either English or Malay language. Patients were given a choice of the language they preferred to fill in the questionnaire which was done when they attended their clinic visit. SF-36 was done once and all questions had to be answered for the questionnaire to be valid. SF-36 contains 36 questions that are subdivided into eight dimensions: physical functioning, role limitations because of physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems and general health. These eight dimensions are summarized into two scales: Physical Component Summary (PCS) score derived from physical functioning, role functioning physical, vitality, bodily pain and general health perceptions and Mental Component Summary (MCS) score which includes social functioning, role function emotional, mental health, vitality and general health. Scores are added up and range from 0 to 100 with higher scores denoting a better QOL.

Statistical analysis

Statistical analysis was done using SPSS software version 20 (SPSS Inc, Chicago, IL, USA). All numerical data were subjected to normality testing and normally distributed data are expressed as mean ± standard deviation (SD). One way analysis of variance (ANOVA) was used for multiple categories. Pearson’s rank correlation coefficient was used for the association between QOL and clinical / laboratory variables. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 39 patients were enrolled. Their demographics are shown in Table 1. Fifty-nine percent of our transplant patients had a commercial living unrelated renal transplant. We found patients with a living related / spousal transplants to have a shorter transplant duration than the commercial living unrelated transplants (52.99 ± 25.76 Vs 77.01 ± 37.90, p = 0.031). There was no difference in terms of serum creatinine, MDRD GFR, albumin and hemoglobin between the living related / unrelated transplants compared to the commercial transplants.

The SF-36 scores are shown in Table 2. There was no difference in QOL between men and women. However, we did find a significantly higher serum creatinine in men compared to women (109.2 ± 21.8 Vs 88.3 ± 29.3, p = 0.022). We found no differences in QOL in those who

Table 1: Socio-demographics of renal transplant recipients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number (%)</th>
<th>Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (74.4)</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Female</td>
<td>10 (25.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Malay</td>
<td>8 (20.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>25 (64.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>4 (10.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (5.1)</td>
<td></td>
<td></td>
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<tr>
<td>Marital status</td>
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<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Single / Divorced</td>
<td>10 (25.6)</td>
<td></td>
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</tr>
<tr>
<td>Married</td>
<td>29 (74.4)</td>
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<tr>
<td>Education</td>
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<tr>
<td>Primary</td>
<td>5 (12.8)</td>
<td></td>
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</tr>
<tr>
<td>Secondary</td>
<td>12 (30.8)</td>
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<td></td>
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<tr>
<td>Tertiary</td>
<td>22 (56.4)</td>
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<tr>
<td>Employment</td>
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<tr>
<td>Employed</td>
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<td>Unemployed</td>
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<td></td>
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<tr>
<td>Retired</td>
<td>5 (12.8)</td>
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<td>Housewife</td>
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<tr>
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<td>Co-morbidities</td>
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<tr>
<td>Diabetes</td>
<td>5 (12.8)</td>
<td></td>
<td>&lt; 0.001</td>
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<tr>
<td>Hypertension</td>
<td>18 (46.5)</td>
<td></td>
<td>&lt; 0.001</td>
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<tr>
<td>Transplant Type</td>
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<td>0.337</td>
</tr>
<tr>
<td>Living related/unrelated</td>
<td>16 (41.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial (living / cadaveric)</td>
<td>23 (59.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.46 ± 11.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (months)</td>
<td>67.16 ± 35.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>43.85 ± 3.30</td>
<td></td>
<td></td>
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<tr>
<td>Urea (mmol/l)</td>
<td>5.14 ± 1.58</td>
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<td></td>
</tr>
<tr>
<td>Creatinine (umol/l)</td>
<td>103.85 ± 25.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRD GFR (ml/min/1.73 m2)</td>
<td>71.49 ± 15.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.04 ± 1.31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MDRD GFR = Modification of diet in renal disease glomerular filtration rate
Table 2: QOL scores in renal transplant recipients

<table>
<thead>
<tr>
<th>QOL domain</th>
<th>SF 36 scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>47.85 ± 6.93</td>
</tr>
<tr>
<td>Role physical functioning</td>
<td>49.51 ± 11.08</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>58.55 ± 7.51</td>
</tr>
<tr>
<td>General health</td>
<td>51.43 ± 6.22</td>
</tr>
<tr>
<td>Vitality</td>
<td>60.53 ± 6.61</td>
</tr>
<tr>
<td>Social functioning</td>
<td>50.85 ± 9.26</td>
</tr>
<tr>
<td>Role emotional functioning</td>
<td>49.09 ± 12.01</td>
</tr>
<tr>
<td>Mental health</td>
<td>55.74 ± 7.16</td>
</tr>
<tr>
<td>Physical Component Summary (PCS)</td>
<td>49.37 ± 6.87</td>
</tr>
<tr>
<td>Mental Component Summary (MCS)</td>
<td>55.23 ± 6.66</td>
</tr>
</tbody>
</table>

predicted by QOL in renal transplant recipients were single or married. The living related / spousal transplant patients had a higher mental health score compared to the commercial renal transplants (58.68 ± 5.64 Vs 53.69 ± 7.50, p = 0.034).

All the eight dimensions in QOL correlated with each other positively as expected. Age correlated inversely with physical function (p = 0.029) and is shown in Fig. 1. Older patients had a trend towards lower physical component summary (p = 0.058). The level of education positively correlated with physical functioning (p < 0.001), social functioning (p = 0.024), mental health (p = 0.039), general health (p = 0.018), vitality (p = 0.019) and mental component summary (p < 0.001). There was a correlation with type of transplant (commercial or non-commercial) and mental health (p = 0.031).

DISCUSSION

QOL can be measured in several ways and we chose SF-36 as it is comprehensive and has been validated in Malay language. Renal transplantation is associated with a better QOL and our findings concur with others[3,8,9]. The RTx patients had higher scores in most dimensions on the SF-36 score compared to hemodialysis and peritoneal dialysis patients but lower than the healthy Malaysian population[10-12]. RTx improves QOL for several reasons including better physical ability, freedom from dialysis (mentally and time saved not doing dialysis). The higher serum hemoglobin and albumin as a result of transplantation, better kidney function and reduced protein loss from dialysis also affect physical and mental abilities, thereby improving QOL.

There were more male patients in both the cadaveric and live related RTx group (p = 0.004). It is well-recognized that most live kidney donors are female[13,14]. Females are more likely to donate a kidney than men. At least half of the RTx were done overseas due to the low cadaveric rate of transplants in Malaysia and greater availability of commercial donors in certain parts of the world. The male patients had the financial ability to afford a commercial donor as they were working and earning an income.

Our study revealed no differences in QOL between men and women and this may be because of a significantly higher number of male transplant patients (p = 0.004). However, some studies have shown men to have a lower QOL than women[15,16]. This has been attributed to the men not being able to adapt easily to the chronic illness.

Although the predominant ethnic population and dialysis population are Malays in Malaysia, we found that a higher number of Chinese patients were transplanted. This may be because of cultural reasons. Furthermore, there may be financial barriers to transplantation. Indeed when we analyzed the proportion of patients transplanted overseas, this was again predominantly Chinese. This may be because the Chinese patients went to China due to the availability of organs and their ability to communicate in their own dialect. This was prior to the tightening of legislation for commercial transplantation. We found no effect of marital status on QOL. Others have demonstrated married patients had better QOL than single
patients\textsuperscript{[17,18]}. This can be explained by the emotional support received within the family environment and this has been described as an important predictor of mental QOL especially among ESRD patients\textsuperscript{[19]}. Our study demonstrated a bias in demographics as very few diabetics received a RTx. Diabetes is the leading cause for ESRD in Malaysia. Many diabetics have severe end organ damage by the time they seek nephrology services treatment and may not be medically suitable for a transplant especially due to cardiovascular disease. The living related RTx patients had a shorter duration of follow-up than the commercial transplants. This is because our institution started doing RTx nine years ago. The association between socio-economic status and health has been well documented\textsuperscript{[20-22]}. We found those with a higher education have a better QOL. One would expect with a higher level of education, they would be more likely to be employed and have better paid jobs and hence higher income. We did not assess income as many patients were not willing to divulge their accurate income. Our study demonstrated a strong inverse correlation of age with physical function. Several studies have shown that as one gets older, their QOL reduces due to general frailty and reduced physical strength\textsuperscript{[23]}. This holds true for transplant patients although the decrement would be lower in RTx patients than dialysis patients. Age correlated inversely with PCS and Sayin et al found older age and male gender to be negative predictors of QOL\textsuperscript{[15]}. We should therefore pay more attention to older patients and routinely offer them physiotherapy to build up their physical strength. We found albumin to correlate positively with general health and this has been previously demonstrated\textsuperscript{[11]}. Higher albumin levels correlated with higher SF-36 scores\textsuperscript{[24]}. Mingardi et al found that both age and albumin were independently associated with physical function\textsuperscript{[29]}. Albeit being the best marker, albumin has been used as a surrogate marker for nutritional status, morbidity and mortality. Serum hemoglobin has been associated with a better QOL. One would expect that with better hemoglobin, there would be better strength, memory and attention\textsuperscript{[25]}. Our study also demonstrated this fact and is in keeping with other studies\textsuperscript{[23]}. Serum hemoglobin is also a modifiable factor which we can address to improve patients QOL. We found no differences in QOL between transplants done overseas and locally but we noticed that the commercial cadaveric transplants recipients had a lower mental health. We believe this is due to the fact that there was a trend towards them being older (p = 0.065). Our study has consistency, reliability and validity as all the variables correlated with each other. The other strength is the homogeneity of our sample as it was a single center, thereby eliminating bias in terms of immunosuppressive regimen. There are some limitations to our study. It was a cross-sectional study, therefore the QOL score was at a particular moment in time. Ideally, checking over a period of time is more reflective as QOL varies with time and with the development of treatment complications. We did not look at the household income as it was difficult to get a true estimate. Not everyone wants to divulge this information and whatever is revealed is not truly reflective of their total household income. CONCLUSION RTx patients had a good QOL and this was predicted by age, education, serum albumin and hemoglobin. However, RTx is not easily accessible to all due to the shortage of donors and excessive demand. REFERENCES


Case Report

Extraperitoneal Presentation of Pseudomyxoma Peritonei as a Pleural Effusion: A Case Report

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Kuwait Medical Journal 2013; 45 (4): 329 - 331

ABSTRACT

Pseudomyxoma peritonei (PMP) can occur in the pleural cavity presenting as pleural effusion, either as a primary disease of mucin producing adenocarcinomas of the lung or as a metastasis from PMP originating in the peritoneum. We report the case of a 64-year-old male with metastatic poorly differentiated mucinous adenocarcinoma of the lung who progressed and developed a pleural effusion that proved to be hemorrhagic pseudomyxoma in the pleura in the absence of abdominal manifestations.

KEY WORDS: adenocarcinoma, lung neoplasms, peritoneal metastasis

INTRODUCTION

Pseudomyxoma peritonei (PMP) is an unusual condition in which gelatinous fluid collections are associated with mucinous implants on the peritoneal surfaces and omentum. PMP can occur in the pleural cavity presenting as pleural effusion, either as a primary disease or metastasis from PMP[1,2]. PMP is a rare clinical manifestation of mucin producing adenocarcinomas. An extensively metastasized adenocarcinoma developed a PMP that affected not only the peritoneal cavity but also the pleura[3]. Extra-peritoneal presentations of PMP are exceedingly rare[3] although there are rare cases in which the adenocarcinoma of the lung is considered the origin of the PMP[4]. We report a case of primary pseudomyxoma in the pleura in the absence of abdominal manifestation because of its rarity and to highlight the presentation of such cases.

CASE REPORT

A 64-year-old male, ex-smoker, a known case of COPD, and IHD, presented with hemoptysis for which he underwent bronchoscopy with multiple biopsies taken. Histopathology suggested the diagnosis of poorly differentiated mucinous adenocarcinoma of the lung, which was confirmed by immunostains (TTF-1 +, CK7 +, CK20 -, CEA +, CDX2 -, PSA -, PGP9.5 -, p63 -). Work-up staging was done in November 2007 that showed evidence of extensive bony and suprarenal gland metastases. Patient received first line of palliative chemotherapy (cisplatin + gemcitabine), on which he had disease progression. Subsequently, he was started on the second line chemotherapy (single agent, thrice weekly docetaxel) and monthly zoledronic acid injection. The patient achieved good partial response and was referred to palliative care clinic for further follow-up. On 26 March 2009, the patient was reviewed in ER with generalized body pain and shortness of breath. On examination, the patient was alert, well oriented, and apprehensive. He was not in obvious distress. His vital signs were stable with an oxygen saturation > 95% on room air. The only significant finding on examination of the chest was reduced breath sound at the left lung field and mild abdominal distension. Blood results were acceptable. Chest Xray (CXR) revealed complete left lung opacification. He was put on morphine sulphate 2.5 mg/ SC/4 hourly, and prophylactic low molecular weight heparin, and other supportive measures. A couple of days later, the patient showed face puffiness and rapid deterioration in his chest condition manifested by gradual decrease in saturation and increase in shortness of breath.

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Urgent CT-CAP was done which showed massive left sided pleural effusion with underlying collapse, mediastinal shift to the right side, multiple right lung and subpleural metastases and pulmonary artery obstruction (tumoral thrombotic occlusion). Due to significant disease progression and patient’s poor performance status, he was considered a candidate for ‘do not resuscitate’ (DNR) orders. The patient’s status and palliative goals of the management at this stage were explained fully to his family. Trial for thoracocentesis and chest tube insertion were done but no fluid was drained. The surgeon injected normal saline and thrombolytic agents (streptokinase 5000 U) to dissolve any possible clots but failed to get any drainage. The patient’s condition continued to deteriorate with low oxygen saturation (70%) till he passed away. During removal of the chest tube, a huge hemorrhagic gelatinous mass, blocking the tube, was detected. The specimen was sent for histopathology and was reported as PMP.

DISCUSSION

PMP is a unique condition characterized by diffuse collections of gelatinous material in the abdomen and pelvis and mucinous implants on the peritoneal surfaces. The term PMP was originally applied to intraperitoneal mucinous spread originating from a cystadenoma of the appendix[5] but also peritoneal dissemination of mucus producing adenocarcinomas of the appendix, large and small bowel, lung, breast, pancreas, stomach, bile ducts, gallbladder, and fallopian tubes / ovary[6]. It may represent a pathologic diagnostic term to both benign and malignant mucinous neoplasms that produce abundant extracellular mucin[7]. In our case, malignant process represented by extracellular mucin secreting adenocarcinomas, the lung as a primary origin of pseudomyxoma was confirmed clinically and radiologically. The lung as an origin was reported in the literature but it was proved to be rare process[8]. PMP is a rare clinical manifestation of mucin producing adenocarcinomas.
An extensively metastased adenocarcinoma developed a pseudomyxoma that affected not only the peritoneal cavity but also the pleura[1,2,8,9]. It manifests similar to other pleural effusion cases but dyspnea may be the most common symptom[10]. There are no specific laboratory findings to establish diagnosis but it is not uncommon to detect elevation of some tumor markers (CEA, CA 125, CA 19-9)[4,10]. This finding is compatible with the blood result of our patient since there was an elevation of CEA = 16, 6 (0 – 0.5 ng/ml), which reflects the status post-disease progression as well as the development of PMP in the pleura. In CT imaging, the mucinous material has a similar density to fat and has a heterogeneous appearance. Also, there was a big difference in the CT density number (HU) = 23 in our case and the fat density (-50 to –100). This was attributed to the heterogeneity of the pleural fluid, particularly its hemorrhagic nature that is an expected consequence of malignancy and pulmonary thromboembolism. Sometimes, progressive punctuate calcification can be found in the abdomen[11]. In our case, there were no obvious calcifications in the CT findings; this may be explained by the rapid growth and aggressiveness of the tumor. Involvement of the pleural cavity by PMP carries an unfavorable prognosis. The age-adjusted five-year survival for patients with peritoneal mucinous carcinomatosis is seven percent[12]. Whenever possible, the same guidelines for intraabdominal disease should be followed: i.e., extensive cytoreductive procedures with local and/or systemic chemotherapy[2,8,13].

CONCLUSION
Extraperitoneal presentation of PMP as a pleural effusion without any abdominal manifestations is very rare. Treatment is mainly cytoreductive surgery. This cannot be done in many cases due to the advanced stage at presentation and the poor prognosis of intrathoracic malignancies. Overall, the prognosis is poor and the main goal of treatment is palliation.

REFERENCES
Case Report

Colobronchial Fistula as a Complication of Advanced Colorectal Cancer: A Case Report

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North West Armed Forces Hospitals, Tabuk, Kingdom of Saudi Arabia

Kuwait Medical Journal 2013; 45 (4): 332 -334

ABSTRACT

Colo-bronchial fistulae due to colon cancer are extremely rare and associated with significant morbidity and mortality. The treatment is surgical. We describe a case of colo-bronchial fistula and severe pneumonia in a patient with advanced colorectal cancer. The aim is to add conservative therapy as an option in cases with poor prognosis.

KEY WORDS: adenocarcinoma, bronchial fistula, colon cancer, malignancy

INTRODUCTION

Colorectal cancer is a common malignancy throughout the world in both men and women. It was the most common cancer diagnosed in men and the third most common in women in Saudi Arabia in 2006[1]. Several complications may arise from colorectal cancer. Most of these complications arise in advanced disease. The complications are bowel obstruction, perforation, bleeding, intractable pain and rarely fistulae.

Gastrointestinal (GI) fistulae are abnormal duct like communications between the gut and another epithelial lined surface. It can arise from a variety of etiologies including inflammatory bowel disease, surgery, radiation, trauma, and malignancy.

Colobronchial fistulae belong to the aforementioned group. It is a lifethreatening complication of advanced colon cancer. Surgery is the backbone of treatment as soon as the diagnosis is established, but colostomy and antibiotics may be an alternative in advanced and poor prognosis cases.

We report the relevant radiological and clinical findings in a case of colobronchial fistula as a result of advanced colon cancer.

CASE REPORT

A 65-year-old male, ex-smoker, who was not known to have any medical problems presented in October 2010 to the Pulmonology clinic with a five-month history of cough and left chest wall and upper abdominal pain. Clinically, there was decreased air entry in the left lower lung and mild crepitations. Blood work showed mild anemia with a Hb of 9.8 g / dl and elevated tumor markers (CA19–9 > 700 u/ml and CEA > 100 ng/ml). A chest X-ray revealed an elevated left diaphragm, density at the lower third of left lung field obliterating the left costophrenic angle, clear right pulmonary field, and distended bowels. Computed tomography (CT) of the chest, abdomen and pelvis with contrast revealed a large irregular lobulated / multiloculated hypodense mass in the colon (splenic flexure) invading the colon, left hemidiaphragm and the left lung (Fig.1, 2). It continued with thick cystic wall like lesion containing small air fluid level in the periphery of left mid-zone and some surrounding atelectasis and infiltration, left pleural reaction and pleural thickening and small left paratracheal lymph nodes. Also seen were multiple pulmonary nodules of small size bilaterally (metastasis), multiple focal lesion in the liver (metastasis) and lytic lesions in the right side of L5 vertebral body and right iliac crest (metastasis).

The patient underwent colonoscopy which showed large growth at the splenic flexure. Multiple biopsies were taken and histologic examination revealed a well-differentiated adenocarcinoma.

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The patient was reviewed in oncology clinic as an established case of metastatic colonic adenocarcinoma (liver, lung and bone). He received three cycles of palliative chemotherapy XELOX (oxaliplatin and capecitabine) regimen. Two weeks after the third cycle of chemotherapy, the patient was reviewed in emergency department with fever, loss of appetite, constipation, dyspnea and cough with brown, malodorous sputum. On admission, physical examination revealed mild pallor, cachexia, fever (39.4 °C), low breath sounds at the left lung base and occasional rales. The general visceral systems review, other than pulmonary was unremarkable. No pleural rub or wheeze was heard. The cardiac examination was otherwise normal. There were no palpable lymph nodes and no skeletal tenderness. The abdomen appeared unremarkable as did the neurological and extremity examinations. Blood oxygen saturation on room air was 98% and an arterial blood gas analysis revealed a pH of 7.53, paCO$_2$ 39 mmHg, HCO$_3$ 32 mmol/l, and pO$_2$ of 100 mmHg. A chest X-ray revealed left basal lung consolidation and distended bowels. Sputum analysis showed fecal materials along with the identification of mixed colic bacterial flora and abundant presence of Trichomonas. CT chest, abdomen and pelvis revealed the following changes in comparison to the previous CT study: The transverse and descending colon appeared more distended with air and fecal matter. The coronal reconstruction showed lateral defect of the left hemidiaphragm measuring 9.1 mm. The pleuroperitoneal mass in the left lower chest and upper abdomen showed central cavitation with air-fluid levels connected to the bronchial tree. There were no appreciable changes in the lung, bone and liver metastases. The loculated fluid collection was evacuated and filled with air instead (opened into bronchial tree). Patchy consolidation in the left lower lobe, right upper lobe, and the apical segment of right lower lobe (bronchial spread of the cavity contents) was seen.

The patient was treated with metronidazole (500 milligram three times a day), pipracillin and tazobactam (4.5 g three times a day) and moxifloxacin (400 mg once a day). He was scheduled to undergo ileostomy, but unfortunately, the patient’s general condition deteriorated. A chest X-ray showed diffuse air space consolidation in both lungs, mainly in the perihilar area consistent with aspiration pneumonia and ARDS. He became desaturated and comatose and succumbed two days later.

**DISCUSSION**

The development of a fistula between the bronchial tree and abdominal organs is an uncommon event\[2\]. Abdomino-bronchial fistulae include bronchobiliary, gastrobronchial, enterobronchial, colobronchial, and splenobronchial fistulae\[3\]. Colobronchial fistulae are likely the rarest ones within this group\[2\].

Subdiaphragmatic abscesses, Crohn’s disease, large bowel carcinoma, appendicitis and previous colon surgery are the clinical conditions most often associated with colobronchial fistulae\[2\]. Other medical literature reported colobronchial fistulae as a consequence of rare etiology like radiotherapy\[4\], peritoneotomy and hyperthermic intraperitoneal chemotherapy (HIPEC)\[2\], tuberculosis, and after intrahepatic iridium implants for hepatoblastoma pediatric patient\[5\]. In most cases of colobronchial fistula, there is a long history of chronic abdominal sepsis with a proved or suspected subphrenic abscess\[6\].
Like in our case, the splenic flexure is the most frequently involved colon segment due to its cranial location, the direct contact with diaphragm and the absence of the liver that plays a protective role towards the right hemidiaphragm.[2]

The clinical picture is characterized by recurrent pulmonary infections, respiratory failure and cough with dark and feculent sputum. The symptom of fecoptysis may be the presenting feature of colonic carcinoma.[7] This was the case with our patient.

The diagnosis of colobronchial fistula is often insidious. Physical and microbiological analyses of the expectorated sputa may be of help.[2] The diagnosis is usually, but not always, confirmed by barium enema, although this may be dangerous: in two patients rapid deterioration followed reflux of fecal matter into the lungs and this may have contributed to the deaths of two others. Bronchography might be considered as alternative diagnostic procedure.[6]. A double-lumen tube (DLT) and isolated single-lung ventilation causing abdominal distension can assist in the diagnosis and localization of the fistula[5]. None of these procedures were done since the condition of the patient was unstable and the CT findings demonstrated the fistula. Contrast-enhanced CT may be considered a surrogate to barium enema when it reveals a clear communication between the colon and the bronchial space.[8].

Colobronchial fistula often requires surgical treatment with resection of the involved colic segment and sometimes pulmonary lobectomy.[2]. In some cases fecal diversion may be required.[6]. Anesthesia for patients with colobronchial fistulae represents an indication for endobronchial intubation and one-lung anesthesia[9].

In treating this condition, our patient was considered unfit for such procedures and was prepared for ileostomy diversion only along with antibiotic coverage because of the advanced tumor stage and poor prognosis. However, conservative therapy with antibiotic administration and total parenteral nutrition seldom obtains spontaneous resolution of the fistula.[2].

CONCLUSION
Colobronchial fistula with underlying advanced colon cancer markedly increases patient morbidity and mortality. Unlike other fistulae etiologies, majority of cases which do not respond to systemic therapy may not be fit for aggressive interventions.

REFERENCES
Case Report

Gamma Knife Radiosurgery for Recurrent Anaplastic Ependymoma with Intracranial Disseminations: A Case Report

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ABSTRACT

Intracranial ependymomas are relatively rare type of gliomas which have high recurrence rates after multimodal therapy with surgery, fractionated radiation therapy and chemotherapy. We report the case of a 15-year-old girl with recurrent anaplastic ependymoma (WHO grade III) who underwent multiple surgical excisions for a right temporoparietal tumor in 1998, followed by fractionated radiation therapy and chemotherapy. Eleven years after initial treatment, follow-up imaging of the brain demonstrated tumor recurrence with multiple intracranial dissemination. Clinically, the patient was asymptomatic. We managed her with gamma knife radiosurgery at our center. The recurrent ependymoma along with four intracranial disseminations were defined with gamma plan and a prescription dose of 16 Gy was delivered to the mean target volume of 1.56 ml (range 0.159 - 5.7 ml) with a mean isodose line of 54.3% (range 50 - 65%). Images on post-radiosurgery follow-up at 21 months revealed complete remission of the recurrent ependymoma and significant decrease in size of all disseminations.

KEY WORDS: cerebrospinal dissemination, ependymoma, stereotactic radiosurgery

INTRODUCTION

Ependymomas represent 5 - 6% of primary intracranial neoplasms developing in adults and 8 - 13% of all pediatric brain tumors[1,2]. Ependymomas have aggressive behavior, regardless of their histological grade according to World Health Organization (WHO) classification[3]. The standard treatment strategy for ependymomas comprises of complete surgical resection, fractionated radiation therapy (RT) and chemotherapy. Surgery often results in subtotal removal because of their critical locations. Ependymomas are considered to be relatively radio-sensitive and various types of radiation therapy such as fractionated RT, fractionated stereotactic RT and cranio-spinal irradiation have been used and seem to increase the survival period and delay recurrence for several years[4]. Chemotherapy has not yielded a significant role in survival of patients but children with subtotal resected ependymomas have been treated in attempt to avoid deleterious effects of RT and have shown good results[5]. Recurrent disease develops within five years in 40 - 70% of patients. The extent of tumor resection and control of local recurrences are the main factors affecting the treatment outcome[4]. Cerebrospinal dissemination occurs in approximately 13% of patients and high grade anaplastic ependymomas have more propensity to disseminate few years after the initial diagnosis[1,7]. Stereotactic radiosurgery (SRS) is a non-invasive technique that may be helpful for controlling the ependymoma involving the crucial structures and SRS may minimize the number of direct surgical interventions required for controlling the lesion. Our case report appraises the literature on the efficacy of this technique for the treatment of recurrent anaplastic ependymoma with intracranial dissemination.

CASE REPORT

History: A 14-year-old girl presented to pediatric emergency with severe headaches and persistent vomiting 12 years ago in 1998. After initial management, magnetic resonance imaging (MRI) of the brain demonstrated a large enhancing lesion in
the right temporoparietal region with mass effect. The patient underwent total surgical excision of the tumor. Histopathology revealed anaplastic ependymoma (WHO grade III). Cerebrospinal fluid (CSF) cytology was negative on the onset of disease. After surgery, the patient received fractionated RT and chemotherapy. The patient had unremarkable status in the following years. After seven years of initial management, at the age of 11 years, she was brought again to emergency with same complaints. A MRI brain discovered tumor recurrence with marked surrounding edema. She underwent radiosurgery and was advised to repeat fractionated RT which she refused. Serial follow-up images showed no residual lesion except localized focal gliosis and necrosis and diffuse deep white matter chronic radiation sequelae. Positron Emission Tomography (PET) scan demonstrated findings that were highly suspicious for local recurrence in the right posterior parietal lobe at the surgical bed. After four years of repeat-surgical-excision of the tumor, a follow-up MRI brain revealed tumor recurrence with multiple intracranial disseminations. There was no evidence of seedings in the spinal cord. Clinically, the patient was asymptomatic and was advised to undergo fractionated RT and chemotherapy which she refused and was referred to us for management with stereotactic radiosurgery. We advised the patient to repeat biopsy of the tumor for appropriate management of the disease but the patient refused for any invasive intervention. So we decided to treat her with gamma knife radiosurgery on the basis of previous histopathology report. Clinically, she was alert and oriented. Karnofsky Performance Score (KPS) was 100. All intracranial nerves were intact. Motor and sensory systems were normal. There were no cerebellar signs. All other systems were unremarkable.

**Treatment:** After admission in gamma suit, the procedure started with an application of Leksell stereotactic frame under local anesthesia and intravenous conscious sedation. The patient underwent high resolution 3-dimensional MRI brain with gadolinium enhancement and the fiducials were checked. Images were exported to the gamma knife computer for dose planning through Dicom software system. A gamma plan was prepared after defining the target areas on MR images of the brain using the Leksell gamma plan (LGP®) software. The targets were an enhancing recurrent ependymoma with four small disseminations in different locations of the brain (Fig. 1): one in the right frontal horn of the lateral ventricle, one in the left frontal horn; one in the mid
part of the 3rd ventricle and one at the left aspect of the 4th ventricle. The mean target volume was 1.56 ml (range 0.159 - 5.7 ml). The mean prescription dose was 16 Gy with a mean isodose line of 54.3% (range 50 - 65%). The mean number of isocenters was 3.3 (range 1 - 8), used to formulate a conformal radiosurgery dose plan. Stereotactic radiosurgery was performed with 201 sources of cobalt-60, using Leksell Gamma Knife, Model 4-C (Elekta Instruments AB). After completion of the procedure, stereotactic frame was removed and the patient was given intravenous methylprednisolone to avoid any acute adverse radiation effect. The patient was discharged from the hospital on the same day.

Follow-up: The follow-up period of this patient was 20 months. Imaging was achieved at 6 and 18 month intervals after radiosurgery which revealed complete remission of the recurrent tumor and significant reduction in size of all the disseminations (Fig. 2). The patient is in a good clinical condition.

DISCUSSION

Complete surgical excision is still the basis of treatment for intracranial ependymomas as an initial mode of management. Residual or recurrent ependymomas can be managed with adjuvant therapies like cranio-spinal fractionated RT, chemotherapy and stereotactic radiosurgery. In spite of the development of all these techniques, recurrence is still a big issue. Subtotal resection, young age of the patient, location, and high grade anaplastic ependymomas are the factors responsible for recurrence and cerebrospinal disseminations. The extent of the resection is the key prognostic factor and location of the tumor determines the extent to which tumor removal is possible. Local field RT may be more effective than whole brain radiation therapy (WBRT). After failed initial treatment, stereotactic radiosurgery may be the only potentially effective management strategy that remains. Although few reports have been published on the management of recurrent ependymomas with radiosurgery, yet results are encouraging. Stereotactic radiosurgery can also be used as a boost after surgical excision and post-operative fractionated RT and has shown excellent results of progression-free survival as compared to the patients who were treated with radiosurgery as a salvage mode after failure of all other treatment modalities. Kano et al published a series of 39 patients with 56 intracranial ependymomas of different grades treated with gamma knife radiosurgery at the University of Pittsburgh. All patients had undergone surgery and fractionated RT while 14 patients had an additional treatment with chemotherapy. Thirty six percent of the patients had intracranial disseminations and 23% patients had spinal seedings. Follow-up results showed the overall survival rates of 60%, 36% and 32% at 1, 3 and 5 years after gamma knife and the progression-free survival rates of 81.6%, 45.8%, and 45.8% respectively.

Stafford et al reported a series of patients with recurrent ependymomas at Mayo clinic, treated with radiosurgery after primary management with surgery and fractionated RT. The median overall survival rate was 3.4 years (range, 1.4 - 5 years) at the median follow-up of 22.5 months (range, 2.5 - 60 months). In our case, the patient was initially managed with multiple surgical excisions of the tumor, fractionated RT and chemotherapy and after seven years of initial management, she had recurrence and underwent redo surgery but refused for fractionated RT. Four years later, she had a recurrence again with intracranial disseminations. Endo et al reported two cases of intracranial anaplastic ependymomas with nodular disseminations managed by repeated gamma knife radiosurgery that resulted in tumor control over 21 months. We have managed this case with gamma knife radiosurgery as an adjuvant therapy for recurrent ependymoma and primary mode for small disseminations. Post-radiosurgery follow-up images demonstrated very good results for the earlier treated targets with gamma knife but new disseminations appeared beyond the previous radiosurgery fields. It indicates that despite relatively good local control of recurrent ependymoma after radiosurgery, the incidence of disseminations is high and shows the failure in primary management. Radiosurgery as a boost, in combination with surgery, fractionated RT and chemotherapy would prevent local failure and therefore, prevent the need for any salvage or palliative strategies.

CONCLUSIONS

Total surgical excision, followed by postoperative fractionated RT and chemotherapy is the standard therapeutic approach in ependymoma treatment but stereotactic radiosurgery has proved to be an effective and safe treatment in combination with other multimodal therapies. A longer follow-up and additional experience with more number of patients is necessary to evaluate the total survival and progression-free survival rates.

REFERENCES


Case Report

Isolated Pancreatic Tuberculosis: A Medical Disease Causing Surgical Dilemmas: Case Report and Review of Literature

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ABSTRACT

Tuberculosis (TB) affecting the pancreas is rare even in endemic countries for tuberculosis. The occurrence may pose a diagnostic problem in differentiating it from carcinoma of the pancreas. Clinical examination, laboratory data and imaging are all non-specific. Diagnosis is frequently misguided towards neoplasia requiring surgical intervention. We present one case of isolated pancreatic tuberculosis that was diagnosed by CT guided fine needle aspiration cytology (FNAC) illustrating the value of FNAC in such a situation, thus obviating the need for unnecessary surgery (laparotomy / laparoscopy) with its accompanying morbidity. The patient’s response to antituberculous drugs (quadruple therapy) was excellent. TB should be considered in the differential diagnosis of a pancreatic mass and most patients have an excellent response to standard antituberculous regimen. Thus, maintaining a high index of suspicion can assist in avoiding unnecessary laparotomies. We report this case as it is rare along with review of relevant literature.

KEY WORDS: antituberculous regimen, fine needle aspiration, Mycobacterium tuberculosis

INTRODUCTION

Tuberculosis (TB) is a major health problem with an increasing case load of both its pulmonary and extra-pulmonary forms worldwide\(^\text{[1,2]}\). TB is common in developing countries but that affecting the intra-abdominal organs is relatively uncommon\(^\text{[1,2]}\). The incidence varies from country to country\(^\text{[1,2]}\). In general hospital admissions, the percentage of patients admitted for abdominal tuberculosis has been reported as a 0.8% in Delhi, and 0.28% in Beirut\(^\text{[3]}\). Abdominal TB commonly affects the spleen, liver, ileocecal region, peritoneum and lymph nodes\(^\text{[4]}\). Pancreatic and peripancreatic TB seem to be rare and poses diagnostic dilemma to the attending physicians\(^\text{[3-5]}\). Most published papers are in the form of case reports\(^\text{[5]}\). TB of the pancreas is considered a rare entity in developed countries mostly in the setting of acquired immune deficiency syndrome (AIDS) epidemic or immunosuppression for transplantation with wide spread use of immunosuppressant drugs\(^\text{[4]}\). Nevertheless there has been an increase in the number of cases reported involving immunocompetent patients, originating mostly from developing countries\(^\text{[4]}\). In a large proportion of these cases there is neither concomitant disease elsewhere, nor evidence of miliary dissemination\(^\text{[3 - 5]}\).

We report here a case of isolated primary pancreatic TB in a 28-year-old man from Kuwait and also review the relevant literature.

CASE REPORT

A 28-year-old male citizen of Kuwait was admitted to our department with acute upper abdominal pain, vomiting and jaundice of few days duration. There was a history of weight loss of around 10 kg over the previous three months without fever, respiratory or abdominal symptoms. His past medical history was unremarkable for chronic disease or hospitalization. He denied any foreign travel and had no risk factors for human immunodeficiency virus (HIV) infection. His physical examination revealed jaundice and mild tenderness in the right hypochondrium, but otherwise was unremarkable with clear chest and no palpable abdominal masses. He was afebrile with normal vital
signs. Stigmata of hepatic insufficiency were not seen. His hemoglobin was 120 g/l, his white blood cell count was 7.5 x 10^9/l and erythrocyte sedimentation rate (ESR) was 120 mm/hr for the first hour. He had a biochemical picture of obstructive jaundice with raised alkaline phosphatase (ALP) 160 IU/l, total bilirubin 58 ummol/l, direct bilirubin 36 umol/l, total protein 70 g/l, albumin 36 g/l, alanine transaminase (ALT) 252 IU/l, aspartate transaminase (AST) 144 IU/l and gammaglutaryl transpeptidase (GGT) 390 IU/l. He showed a normal kidney function and normal coagulation profile. His X-ray chest was normal. Abdominal ultrasound showed a hypoechoic irregular mass 40 x 33 mm in the head of the pancreas with compression of the distal third of the common bile duct (CBD) as well as dilatation of the common hepatic duct (CHD) and intra-hepatic bile duct (IHBD) (Fig. 1). His gall bladder (GB) was normal with no calculi. Computed tomography (CT) scan of the abdomen (Fig. 2) confirmed the presence of a necrotizing mass in the head of pancreas with tiny retropancreatic lymph nodes. Tumor markers CA19-9, CEA and AFP were normal. An endoscopic retrograde cholangio pancreatography (ERCP) (Fig. 3) done, showed a stricture of the distal CBD with dilatation of the biliary tree above it. A papillotomy done with brush cytology was reported as benign. Percutaneous CT guided fine needle aspiration...
in 1981 conceived of the development of abdominal TB in India over 12 years and found no involvement in only 4.7% of 297 autopsies on patients rare
rate of pancreatic involvement in 256 patients with miliary tuberculosis[6]. Bhansali reviewed 300 cases of abdominal TB in India over 12 years and found no case of pancreatic TB[8]. Franco-Paredes et al reported two cases of pancreatic TB and reviewed the current literature involving pancreatic TB among non-immune suppressed individuals[9]. The authors documented 50 cases of pancreatic TB between 1980 and 2002[10]. Eric and colleagues identified 25 additional cases of pancreatic TB that presented as pancreatic masses[10]. In the Chinese language literature there are more than 70 cases of pancreatic TB described[8]. Abdominal TB in its diverse forms still affects the indigenous as well as expatriate population of Kuwait[11-12]. The pathogenesis of pancreatic tuberculosis is inconclusive because most cases are in the absence of any detectable lesions in other parts of the body[13]. It is speculated that the tubercle bacilli reach the pancreas through: 1) pancreatic involvement during miliary disease, 2) hematogenic dissemination from an occult site elsewhere (possibly the lungs) and 3) direct spread from contiguous lymph nodes[14]. Stock et al in 1981 conceived of the toxic allergic reaction to generalized tuberculosis as a theoretical mechanism[15]. However, there is little in the literature to support this view[16]. Pancreatic TB could present with protean clinical manifestations, including upper abdominal pain, pyrexia of unknown origin, ascites, abdominal mass, obstructive jaundice, acute or chronic pancreatitis, upper gastrointestinal hemorrhage due to splenic vein thrombosis, diarrhea, weight loss and colonic perforation[17-18]. Our patient, presented with vague upper abdominal pain, vomiting, obstructive jaundice and weight loss. The nonspecific clinical and laboratory investigations in combination with pancreatic mass on CT scan frequently lead to an erroneous primary diagnosis of a carcinoma, cystadenocarcinoma, or pseudocyst[19,20]. In china, Feng et al reviewed literature and revealed several characteristics of pancreatic TB as follows: 1) pancreatic TB is mostly found in young people, especially females (our patient was a young male) while pancreatic tumor is most common in old person, 2) some patients have a history of TB in the past and most often come from areas having high incidence of active TB (our patient had no history of tuberculosis in past and also did not travel to an endemic zone, as well, he was a citizen of Kuwait which is a non-endemic area for TB), 3) the patients often present with epigastric pain, fever and weight loss, (our patient presented with epigastric pain, vomiting, weight loss and obstructive jaundice) and 4) ultrasound and CT scan show pancreatic mass and peripancreatic nodules (as was seen in our patient), some with calcifications. Sinan et al reviewed the CT characteristics of abdominal TB and the most common features were peritoneal involvement and lymphadenopathy[14]. In contrast to noninvasive techniques, invasive diagnostic techniques can be used to obtain tissue for microbiological and pathological
cytology (FNAC) (Fig. 4) was done which showed a granulomatous inflammation with necrosis, necrotic debris, clusters of epithilioid cells, multinucleated giant cells, lymphocytes and polymorphs. Smear for acid fast bacilli (AFB) were negative for Mycobacterium tuberculosis. Cultures sent for six weeks confirmed the diagnosis of Mycobacterium tuberculosis. A tubercle skin test was carried out and was strongly positive. In view of the previous findings, antituberculous treatment in the form of pyrazinamide 0.5 g three times daily, rifampicin 600 mg once daily, ethambutol 400 mg three times daily, isoniazid 300 g once daily for two months was prescribed and further therapy with ten additional months of isoniazid and rifampicin at the previous doses was recommended. The patient did well and his symptoms were relieved. Five months later, a repeat CT scan of the abdomen revealed a complete resolution of the pancreatic lesion (Fig. 5). At a six-year follow-up, the patient is living a normal life free of symptoms and has regained his lost weight.

**DISCUSSION**

Although TB often occurs in the lungs, primary abdominal TB is not uncommon. However, the prevalence of abdominal TB in developing countries has been estimated to be as high as 12%(1-2). The development of abdominal TB is independent of pulmonary disease in most patients[3], with the repeated incidence of coexisting disease varying from 5% to 38%(4). However, the involvement of pancreas is rare[5]. Auerbach reported in 1944 a rate of pancreatic involvement in only 4.7% of 297 autopsies on patients with miliary tuberculosis[6]. Paraf et al reported a 2.1% rate of pancreatic involvement in 256 patients with miliary tuberculosis[7]. Bhansali reviewed 300 cases of abdominal TB in India over 12 years and found no

![Follow-up CT scan of the abdomen was done six years later showing total resolution of the pancreatic lesion](image)

**Fig. 5:** Follow-up CT scan of the abdomen was done six years later showing total resolution of the pancreatic lesion.
Techniques for biopsy include endoscopic ultrasound guided biopsy, CT / ultrasound guided percutaneous FNAC and surgical biopsy (laparotomy or laparoscopy). Unfortunately, in most cases in the literature, the diagnosis of pancreatic TB was made only after exploratory laparotomy or at necropsy. Fine needle aspiration of the mass to obtain a proof for tubercle bacilli by Ziehl-Neelsen stain showed to be positive only in 33 - 41% of cases of abdominal TB. (It was negative in our case). That is why, prolonged culture for 4 – 6 weeks is required and is positive in 60 - 70% of cases. Even in a nonendemic region like Kuwait, pancreatic TB should be considered in the differential diagnosis of a mass in the head of pancreas causing obstructive jaundice, especially in the young. Once the diagnosis has been made, the management rests on the medical treatment. In most literature, medical management of pancreatic TB generally consists of isoniazide and rifampicin with pyrizinamide and ethambutol. The response to therapy is predictable and complete. The recommended duration of therapy is 6 - 12 months. Our patient received treatment in the form of pyrizinamide, rifampicin, ethambutol, and isoniazid for two months and completed therapy with ten additional months of isoniazid and rifampicin. He did well, with relief of symptoms. Five months later, a repeat CT scan of the abdomen revealed a complete resolution of the pancreatic lesion. In one series, the mean time to radiologic resolution was 132 days. Longer duration of treatment results in higher costs and exposes patients to more side effects. Usually no surgical intervention is necessary and recurrences are rare. Even after six years our patient was doing well, living a normal life, free of symptom and has regained lost weight. However, patients with evidence of biliary obstruction would need either endoscopic or surgical intervention to relieve the obstruction as the ductal narrowing might persist despite treatment with antituberculous drugs. Our patient had endoscopic retrograde cholangio-pancreatography (ERCP) with sphincterotomy to relieve the obstruction and a brush cytology that was benign. This case report adds one more to the small number of cases of isolated pancreatic TB diagnosed by percutaneous CT guided FNAC and treated effectively with antituberculous drugs without any recurrence after six years.

CONCLUSION

Isolated pancreatic TB is rare and the diagnosis is challenging. However, the clinician’s high index of suspicion, its clinical feature and the conduct of more diagnostic modalities such as endoscopic ultrasonography guided, or percutaneous CT / ultrasonography guided FNAC of the pancreatic lesion can confirm the diagnosis. Thus, unnecessary exploratory laparotomy or pancreatic resection can be avoided. In addition, the disease can be effectively treated with antituberculous drugs.

REFERENCES


Case Report

Twin Pregnancy with a Complete Hydatidiform Mole and Surviving Co-Existing Fetus: A Case Report

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ABSTRACT

A 27-year-old woman conceived following six cycles of ovulation induction with clomiphene citrate. Successive ultrasound (US) examinations documented a normally growing live fetus with a normal placenta and an additional intrauterine echogenic mass with features of molar pregnancy. Follow-up serum β-hCG estimation and genetic amniocentesis was done. Fetus revealed normal female 46XX karyotype. The pregnancy was continued till 28th weeks. Labor was induced at 28 week gestation due to vaginal bleeding, which resulted in the delivery of a live normal female infant and two adjoining placentas. One placenta was normal and the other placenta was composed of vesicles of various sizes. Microscopic examination of the abnormal placenta documented complete hydatidiform mole (HM). The baby was well and serial maternal serum β-hCG levels showed a declining trend and were undetectable by 8 weeks after delivery. The prenatal diagnosis of twin pregnancy with complete HM and coexistent fetus was based on US findings, abnormally elevated β-hCG levels and normal fetal karyotype (46XX). The pregnancy should be continued with close follow-up to detect potential maternal and fetal complications.

KEY WORDS: hydatidiform mole, ovulation induction; serum β-hCG

INTRODUCTION

Hydatidiform mole (HM) co-existing with a fetus is an extremely rare phenomenon. Frequency rates have been reported to be between 1 in 22,000 to 100,000 pregnancies[1]. Traditionally, when a placenta displaying a live fetus and molar degeneration is seen, three possible conditions may be considered: (1) Partial molar pregnancy with triploid fetus (69 chromosomes; 46 paternal and 23 maternal), (2) Dichorionic twin pregnancy with normal fetus (46 chromosomes, 23 maternal and 23 paternal) and complete molar pregnancy (46 chromosomes, all are paternal), that is, complete HM and co-existent live fetus (CHMCF) and (3) Twin pregnancies, partial molar (69 chromosomes, 46 paternal and 23 maternal) with normal fetus (46 chromosomes, 23 maternal and 23 paternal) combination, which is extremely rare. Most cases suffer severe complications such as spontaneous abortion, preterm delivery, intrauterine fetal death, bleeding, preeclampsia and persistent trophoblastic disease (PTD). Delivery of a viable normal infant from this combination is even rarer[2]. Here we present a case of CHMCF because of its rarity. This is the first documented case in Kuwait and the second in the Middle-East succeeding a case reported by Piura et al[3] in Israel.

CASE REPORT

The patient was a 27-year-old woman, gravida 3, para 0, with previous two spontaneous abortions. The present pregnancy was achieved following six cycles of ovulation induction with clomiphene citrate. Successive ultrasound (US) examinations at 12 and 16 week gestation demonstrated a live fetus matching the age of gestation alongside a normal-looking placenta located at the anterior uterine wall and an additional echogenic mass which could be a cystic degenerated mass or HM located posteriorly adjacent to the normal looking placenta. Serum β-hCG level at 16 week gestation was >1000 IU/l. Tentative diagnosis of a...
twin pregnancy with CHMCF was made at this stage. The patient party was explained about the possible complications. However, they wished to continue the pregnancy. At 20 week gestation, a detailed US examination revealed a normal live female fetus with a normal-looking placenta and co-existent degenerated placenta with sonographic characteristics of a HM (Fig. 1). The subsequent follow-up Doppler (Fig. 2) and US (Fig. 3) at 25 week of gestation exhibited the normal fetal umbilical artery blood flow and well-grown fetal parts. Genetic amniocentesis at 20 week gestation was performed which showed normal female 46XX karyotype. Other laboratory investigations for thyroid function, blood pressure, proteinuria and chest X-ray were unremarkable. At 28 week gestation, labor was induced because of complicated vaginal bleeding, breech presentation and preterm uterine contractions. An 850 gm normal female infant, with Apgar score of 6 and 7 at one and five minutes respectively, was delivered. Both normal and molar placentas were separated manually from the uterus.

The normal placenta weighed 220 gm and measured 14 x 11 x 2 cm (Fig. 4A). The molar placenta was composed of vesicles of varying sizes (0.3 - 1.5 cm), measuring 15 x 11 x 6 cm and weighed 390 gm (Fig. 4B). On microscopy, the normal placenta showed well-developed chorionic villi with normal vascularization compatible with an early third trimester placenta. The molar vesicular soft tissue showed circumferential trophoblastic proliferation. The stroma was extensively edematous with cistern formation. Vessels were scanty or absent in the stroma. The features were consistent with complete HM (Fig. 4C and 4D). Maternal serum $\beta$-hCG level decreased from >1000 IU/l to 775 IU/l and 489 IU/l on 8th and 9th day after delivery respectively. Further measurements of maternal serum $\beta$-hCG level demonstrated a steady fall and remained undetectable, eight weeks after delivery.

**DISCUSSION**

There are, overall, about 200 cases of twin pregnancy with CHMCF documented to date in the literature. It is speculated that recent widespread use of ovulation induction in the treatment of infertility may increase the incidence of twin pregnancies with CHMCF. However, there are only 57 cases (including the current case) documented in the literature of twin pregnancy with CHMCF resulting in a live birth. Recent advances in US have enabled diagnosis of a HM and co-existent fetus in the first trimester. Prenatal fetal karyotyping plays a major role in deciding the continuation and prognosis of the pregnancy. A triploid karyotype indicates a triploid fetus which invariably would be severely malformed and therefore, termination of pregnancy is highly recommended. A diploid fetal karyotype [46 chromosomes, 46XX or 46XY], on the other hand, indicates a viable fetus with a normal placenta co-existing alongside a twin molar placenta. Continuation
of pregnancy is recommended in such cases, since literature documented about 30 - 35% chances to result in a normal live neonate\[6\]. However, the parents should be explained of the possible complications like hyperemesis gravidarum, early-onset pre-eclampsia, hyperthyroidism, vaginal bleeding, anemia, development of theca lutein ovarian cysts, respiratory distress because of trophoblastic embolization to the lungs, and PTD. Rare cases with complicated metastatic trophoblastic disease have been documented before the maturation or delivery of the live fetus\[8\]. In our present case there was no complication except for the vaginal bleeding which leads to induction of vaginal delivery at 28th week of gestation. The prenatal diagnosis of a twin pregnancy with CHMCF was made in our case by US and demonstrating a normal fetal 46XX karyotype by amniocentesis in the second trimester of the pregnancy. Later, after the delivery, the complete HM was confirmed microscopically by examination of the vesicular degenerated placenta.

Dolapcioglu et al documented live deliveries in 56 (35%) of a total of 159 CHMCF cases in literature\[6\]. The chances of a live birth for parents who desire to continue the pregnancy had been estimated to about 33%. The prevalence rates of associated complications like preeclampsia and PTD were shown to be about 31% and 30% in these cases\[6\]. All the PTD in the reported series attained complete recovery with chemotherapy. There was no maternal loss. As seen in the present case too, most of the cases were found to have been subjected for ovulation induction (43% of the cases)\[6\].

The optimal treatment for CHMCF pregnancies is unclear. Formerly, most of them were terminated with or without exact diagnosis. However, with the availability of recent advances in US and karyotyping, the treatment protocol has been changed. Continuation of pregnancy is recommended in case of a normal fetal karyotype, no fetal anomalies, no early preeclampsia and observance of declining trend of β-hCG. Inspite of all the aforementioned facts, the parents should be informed that the rate of having a chance of live delivery is about 33% and the risk of receiving chemotherapy due to PTD may rise to about 30%\[6\].

**CONCLUSION**

The prenatal diagnosis of twin pregnancy with CHMCF was based on US, abnormally elevated β-hCG levels and normal fetal karyotype (46XX). The

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**Fig. 4:** (A) The normal placenta weighing 220 gm and (B) hydatidiform mole showing multiple vesicles of varying sizes. (C and D) Photomicrograph of the complete hydatidiform mole exhibiting the markedly enlarged and hydropic villi with absence of vessels and proliferation of the trophoblastic cells (H&E stain x 40)
pregnancy should be continued with close follow-up to detect potential maternal and fetal complications.

REFERENCES


Case Report

Colpocephaly, a Wide Clinical Spectrum for One Cephalic Disorder: Three New Cases from Kuwait

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ABSTRACT

Colpocephaly is an abnormal enlargement of the occipital horns of both lateral ventricles; it is also described as persistence of the fetal configuration of the lateral ventricles. Since it was first described, colpocephaly has been found in association with several abnormalities of the brain. The spectrum of clinical presentation is wide, including mainly various degrees of mental retardation, seizures, and motor and visual abnormalities. Approximately 50 cases have been described in children. Herein we report three new cases of colpocephaly. One of the cases was associated with CHARGE syndrome. To the best of our knowledge, this is the first publication to report such an association.

KEY WORDS: CHARGE syndrome, lateral ventricles, occipital horns

INTRODUCTION

Colpocephaly is a congenital brain abnormality in which the occipital horns of the lateral ventricles of brain are larger than normal with normal frontal poles.

Colpocephaly is considered part of a global impairment in brain development with aberrant or arrested migration of the neuroblasts between one and four months of gestation, causing diminished thickness of the cerebral white matter in the posterior part with subsequent dilatation of the occipital horns of the lateral ventricles[1]. Therefore, any process that inhibits the normal neuronal migration from within the ventricle, and likewise the normal genesis of the corpus callosum, may result in this entity. However, not all patients with agenesis of the corpus callosum manifest isolated ventriculomegaly of the occipital horns[2].

Colpocephaly may also develop in later fetal life as a result of infarction and cystic degeneration of deep white matter of the posterior third of cerebral hemispheres rather than as a developmental disorder of neuroblast migration[3].

No single etiologic agent has been implicated, and there may be many causative factors. The essential element is perhaps the time rather than the type of insult to the nervous system[3].

Colpocephaly has been associated with diverse factors including intrauterine infection (e.g., gestational exposure to Toxoplasma gondii), perinatal anoxic-ischemic encephalopathy[4], chromosomal anomalies such as trisomy 8 mosaic, trisomy 9 mosaic[5] and deletion of 1p36.3[6] and maternal gestational ingestion of ethanol, oral contraceptive medications, corticosteroids, salbutamol and theophylline[4].

This cephalic disorder has been described in conjunction with different syndromes like Pierre-Robin syndrome[7], Zellweger syndrome[8], Larsen syndrome[9], and Aicardi syndrome[10] but not with CHARGE syndrome.

A familial occurrence of colpocephaly has been noted in few reports. Cerullo et al. described familial colpocephaly in two siblings from different fathers[11]. In addition, there is a report of colpocephaly in non-identical twins[12] and another one in identical twins[13], suggesting a possible genetic cause.

A number of central nervous system malformations have been found in association with colpocephaly including agenesis of the corpus callosum, neuronal migration disorders (lissencephaly, pachygyria), schizencephaly, hemimegalencephaly, microcephaly, meningomyelocele, and hydrocephalus[5,7]. Agenesis of the corpus callosum is the most frequently associated malformation[7].

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Other associations like cleft palate, hypoplastic nails, simian creases, periventricular leukomalacia, enlargement of the cisterna magna and cerebellar hypoplasia\textsuperscript{[7]} were also reported.

Colpocephaly may be diagnosed late in pregnancy, although it is often misdiagnosed as hydrocephalus. It may be more accurately diagnosed after birth when signs of mental retardation, microcephaly, and seizures are present\textsuperscript{[3]}. The clinical spectrum of the disease is so varied ranging from being asymptomatic to be severely handicapped\textsuperscript{[7]}.

CASE PRESENTATION

Case 1

This six-year-old boy was born after uneventful pregnancy and delivery and his birth weight was 3 kg. There was no maternal risk factor reported and no family history of epilepsy or febrile convulsions. He was first admitted to the hospital at the age of four years for the first attack of convulsions associated with fever and upper respiratory tract infection.

His family reported that the child had recurrent attacks of abnormal movement occurring during sleep few months back and these abnormal movements were affecting his left side of the body only and each lasted few seconds. These did not awaken him from sleep and were not accompanied by abnormal voice or facial affection. One week after discharge he developed afebrile convulsions associated with up rolling of the eyes that lasted for five minutes and aborted spontaneously. This was preceded by headache and vomiting. He was admitted to the ward one month later because of a generalized atonic episode. The patient was commenced on sodium valproate that controlled his fits. No obvious dysmorphic features were noted and his chest, heart, abdominal and neurodevelopmental examination were unremarkable.

An EEG revealed markedly abnormal record on account of repetitive giant-like short wave complexes over both occipital leads, more pronounced over the left one that is consistent with some form of benign occipital epilepsy of childhood.

An MRI brain showed colpocephaly, more pronounced in the right occipital horn. Multiple areas of small gray matter were also seen in the subependymal region of the occipital horns of both lateral ventricles, suggestive of nodular heterotopia (Fig. 1A &B). The child is still on sodium valproate with good control of his fits after 18 months of follow-up.

Case 2

This female child was first seen in the pediatric outpatient department at the age of 7 1/2 months because of delayed psychomotor development and lack of eye to eye contact. She was still unable to recognize her mother, did not show a social smile and was not able to sit with support or support herself on her lower limbs. Her parents reported that hearing was normal.

She was born at term after uneventful pregnancy and delivery and her birth weight was 3.2 kg. She was the

![Fig. 1 (A): MRI, T2 WI, Axial and Coronal views, of Case1 showing colpocephaly of the occipital horns of both lateral ventricles, more seen on the right side. Multiple small gray matters in the subependymal region in both occipital horns of both lateral ventricles, suggestive of nodular heterotopias (Block arrows). (B) MRI, Coronal view T2 WI, colpocephaly is well appreciated (arrow heads).](image-url)
first baby to first-cousin parents with unremarkable family history. On examination she appeared not to be interested in the surroundings with very brief eye to eye contact. Her weight was 7.1 kg (25th percentile), height 66 cm (25th percentile) and head circumference 45 cm (90th percentile). The cranial nerves appeared intact.

She was universally mild to moderately hypotonic with normal deep tendon reflexes. The Babinski reflex was flexor and no clonus could be detected. Systemic examination was otherwise unremarkable. The ophthalmologist reported normal eye media and fundus examination. Liver, renal and bone profiles as well as her blood picture were normal. Cerebral MRI showed colpocephaly and corpus callosum agenesis (Fig. 2). No evidence of neuronal migration defect could be detected. Chromosomal karyotyping reported normal 46, XX pattern.

**Case 3**

A nine-month-old male infant was born vaginally after uneventful pregnancy at 32 weeks of gestation to related parents. His birth weight was 1.6 kg. The Apgar score was 7, 8 at 1 and 5 minutes respectively. He developed respiratory distress soon after birth. He was admitted to the neonatal intensive care unit and connected to mechanical ventilation. He received two doses of surfactant as the chest X-ray showed hyaline membrane disease grade II. Extubation failed several times as the baby developed respiratory distress after each trial of weaning. A right-sided choanal atresia was confirmed by CT scan. He was operated upon twice for that reason at 1\(\frac{1}{2}\) and 4 months of age due to restenosis of the choana. The baby was extubated finally after the second operation. Echocardiography showed a small patent ductus arteriosus (PDA) and a small atrial septal defect (ASD). Other congenital anomalies included bilateral microophthalmia, low set
abnormal ears, micrognathia, bilateral simian creases, right foot syndactyly of 2nd, 3rd, and 4th toes, and bilateral undescended testes. He was sucking fairly well but developed recurrent attacks of choking and aspiration pneumonia due to swallowing dysfunction (consistent with cranial nerves IX and X palsy); the baby was fed through a nasogastric tube. Radioisotope milk scan revealed gastroesophageal reflux. An MRI brain at two weeks of age showed colpocephaly and agenesis of corpus callosum. (Fig. 3 A & B).

At the age of four months, the baby developed recurrent attacks of generalized tonic convulsions that were controlled with phenobarbitone. At nine months of age he was severely failing to thrive (weight 4.9 kg) with severe global developmental delay. He was inattentive and in a rather vegetative state. He had generalized hypertonia and hyperreflexia.

The baby remained in morbid condition on oxygen therapy due to partial restenosis of choana and recurrent aspiration pneumonia. He passed away due to pneumonia and sepsis at the age of nine months.

**CHARGE syndrome** was diagnosed clinically in this case according to the major and minor criteria of **CHARGE syndrome** as described by Blake *et al*.[14].

**DISCUSSION**

The clinical spectrum of colpocephaly is broad and that is reflected in our reported cases; while one patient presented with convolution and no developmental delay, the second one presented with marked global developmental delay and no convolution. On the other hand, the third case was associated with **CHARGE syndrome** and there was convolution, neurological symptoms and developmental delay as well. This is in accordance with the available literature[2-4,7,11-13].

Colpocephaly has been reported with different chromosomal disorders and syndromes[7-10], but not to the best of our knowledge, with **CHARGE syndrome**.

In 1998, the revised diagnostic criteria for **CHARGE syndrome** were set. Individuals with all four major characteristics or three major and three minor characteristics are highly likely to have **CHARGE syndrome**[14].

Our patient had all the four major characteristics (coloboma or microphthalmia, choanal atresia, characteristic ears and cranial nerve anomalies) and four of the minor characteristics that include cardiac malformation, genital hypoplasia, cleft lip / palate or trachea-esophageal fistula, distinctive **CHARGE** facies, growth deficiency and developmental delay.

In 2004, mutations on the CHD7 gene (located on chromosome 8) were found, making **CHARGE** an official “syndrome”. The test is very expensive and available only in two centers in USA. The diagnosis is still largely clinical[15].

Colpocephaly typically has been reported in association with various degrees of mental retardation, seizures, and motor and visual abnormalities. This is not surprising as some authors considered colpocephaly to represent the end result of diverse insults to the developing brain[16].

In a review of 36 cases reported in the literature, 13 patients had seizures, 12 were noted to have mental retardation and 13 were affected by mild to moderate movement disorders. Other reported deficits included poor vision, speech and language difficulties, deafness and chorioretinitis. Three of the 36 cases reviewed had completely normal neurologic and motor development[4].

Epilepsy is reported in 30% of cases and it might be severe and refractory to treatment. In children with colpocephaly, the age of onset of epilepsy is usually less than one year, and the frequency of seizures is higher in early-onset cases. The type of epilepsy is usually occipital with prominent autonomic symptoms such as nausea, vomiting, pallor, mydriasis, urinary and fecal incontinence, eye deviation, versive seizures, and focal motor seizures[16].

Children have been described with colpocephaly and nearly normal or borderline intelligence. However, mental retardation of varying severity, ranging from mild to severe degree, is more common[13].

Motor abnormalities, such as hemiparesis, diparesis, and dyskinesias, may be present. Patients may be hypotonic or hypertonic[17]. Visual abnormalities include chorioretinal coloboma, optic nerve atrophy, congenital fibrosis of extraocular muscles and a Marcus Gunn jaw phenomenon[18].

Colpocephaly may sometimes be detected by ultrasonography in the fetus in late gestation or in the neonatal period. An MRI scan may also reveal associated cerebral anomalies further disclosing the periventricular white matter abnormalities that indicate a perinatal etiology[19].

Prenatal cerebral MRI may confirm colpocephaly, if ultrasonic findings are non-specific. It may also be useful in suggesting specific pathologies, if there is abnormal morphology of the ventricles and demonstrating some additional cerebral anomalies such as late sulcation, migrational pathological conditions, and heterotopia[19].

Prenatal diagnosis should prompt search for associated anomalies, karyotypic abnormality, gestational viral exposure, and maternal toxin ingestion[19]. Currently, definitive treatment options for colpocephaly do not exist and it is mostly symptomatic. Anticonvulsant medications like sodium valproate can be taken to control seizures and some cases of refractory epilepsy may respond to oral antiepileptics such as clobazam and clorazepate[20].
Physiotherapy may help in preventing contractures. Some children may benefit from special education while associated conditions may require more specific treatments[3].

The prognosis for individuals with colpocephaly depends on the severity of the associated conditions and the level of abnormal brain development. Some patients have mild disability and can have an almost normal life; others have profound one, resulting in total lifelong disability, vastly reduced functional capacity, and sometimes death[21].

CONCLUSION

We suggest that the term colpocephaly should be used as a descriptive term rather than a specific disease entity of the central nervous system as it represent the end result of diverse insults to the developing brain and is part of many other diseases. Diagnosis of colpocephaly should prompt a search for underlying associations. More research needs to be done to detect, if there is any genetic basis for transmission of colpocephaly, as some cases are familial or with history of consanguinity.

ACKNOWLEDGEMENT

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REFERENCES

Case Report

Cuff Herniation with Laryngeal Mask Airway

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ABSTRACT

The laryngeal mask airway (LMA) is being widely used for securing the airway in patients undergoing elective surgery under general anesthesia. However, use of LMA may involve some medical problems associated with its technical performance as an airway device. We encountered an unusual and potentially serious problem. A 47-year-old, female patient diagnosed as breast cancer underwent wide local excision and sentinel lymph node biopsy under general anesthesia. After induction of anesthesia, a size 4 reusable classic LMA was inserted and the cuff was inflated with 40 ml of air. A few moments after insertion of the LMA, an audible leak was noted. The cuff was inflated with a further 5 ml of air. The audible leak decreased, but did not disappear completely. Anesthesia was maintained but after 20 minutes the audible leak increased and ventilation became difficult. The LMA was removed and another LMA size 4 was inserted again. At the end of the procedure the patient was allowed to recover and the LMA was removed. After 45 minutes patient was discharged from recovery room. An examination of the device showed that there was a LMA cuff herniation.

KEYWORDS: cuff herniation, laryngeal mask airway, sterilization

INTRODUCTION

Since Brain’s publication about the laryngeal mask airway (LMA) in 1983[1], the device has made a significant contribution to airway control. The LMA is popular because it is easy to position, it provides a secure airway for spontaneously breathing patients, and affords effective assisted ventilation in elective and emergency situations without requiring endotracheal intubation or visualization of the glottis. Complications associated with the LMA have been reported to occur at insertion, during anesthesia, and upon emergence; however, the difficulties are rare and usually minor[2].

CASE REPORT

A 47-year-old female patient diagnosed as breast cancer, with body weight 84 kg, ASA III, not expected difficult airway (Mallampati II, mouth opening 7 cm, thyromental distance 10 cm) underwent wide local excision of the breast mass and axillary sentinel lymph node biopsy under general anesthesia. The patient was preoxygenated for three minutes before intravenous induction with fentanyl 100 mcg and propofol 180 mg. A reusable size 4 LMA (Silicone laryngeal mask tube LMT - Standard, Fortune Medical instrument Corporation, Spain) was inserted without any difficulties. The mask was inflated with the recommended volume of air and the position was secured with tape and bite block. Anesthesia was maintained with nitrous oxide 66%, oxygen 33% and sevoflurane 1.5 to 2.0%. The patient was breathing spontaneously. A few moments later an audible leak was noted. A diagnosis of either LMA displacement and / or inadequate cuff inflation was made. The cuff was inflated with a further 5 ml of air. The audible leak decreased, but did not disappear completely. Vital signs of the patient remained stable (BP 130 – 110 / 80 – 60 mmHg, HR 70 - 80 beats per minute, oxygen saturation 100%), and peak airway pressure did not exceed more than 25 cm H₂O. After 20 minutes the audible leak increased and ventilation became difficult. The oxygen saturation decreased to 85%. Misplacement of the LMA was diagnosed. The LMA was removed. The depth of anesthesia was increased with propofol; another LMA size 4 was inserted. This resulted in restoration of a patent airway and a normal respiratory pattern. The patient was paralyzed with cisatracurium 8 mg and ventilated mechanically. The operation proceeded uneventfully. At the completion of the procedure, the inhaled anesthetic agent was discontinued and the patient was allowed to recover. When the patient opened his mouth on command,
the oral cavity was gently suctioned and the LMA was removed, partially deflated. After 45 minutes the patient was discharged from the recovery room with no apparent complications.

After surgery close examination of the first LMA showed that there was a cuff herniation that had not been detected at pre-use check. The revision of sterilization, autoclaving and pre-use check protocols found two serious problems; first that there was no record sheet about sterilization and autoclaving of the device and second, during pre-use check the LMA was not inflated with a volume of air 50% greater than the maximum inflation value recommended for this size. If this is not done, a cuff herniation might be missed during inspection (Fig. 1, 2).

**DISCUSSION**

Problems associated with the use of LMA in operating room are infrequent and may be divided into three main types: mechanical, traumatic, and pathophysiological. Mechanical problems relate to its technical performance as an airway device, traumatic problems relate to local tissue damage, and pathophysiological problems relate to its effects on the body’s systems. The most common problems encountered include inability to position the LMA correctly, coughing and gagging during placement and removal, laryngospasm, and postoperative sore throat. Brimacombe’s analysis of 1500 LMA uses revealed that on two occasions (0.13%) the LMA cuff slowly deflated during the operation secondary to a small leak. Verghese and Brimacombe found that only 44 critical incidents were documented with the use of LMA in 11,910 anesthetics (0.37%), and only 18 (0.15%) out of these incidents were related to the airway.

To date, there have been fewer reported problems with disposable devices. This may be due to their recent introduction, or to the fact that there is no potential risk for damage to materials during repeated sterilization. There have been a number of case reports related to mechanical problems with re-usable LMA including separation, transection and shattering of LMAs. Repeated sterilization was thought to have caused degradation of the silicone, resulting in brittleness, cracking, and in one case “the friability of cheddar cheese”. Christelis and Doolan reported a case with complete airway obstruction caused by cuff herniation of an overused laryngeal mask airway.

LMA North America warrants reusable LMA products against manufacturing defects for 40 uses or a period of one year from date of invoice, whichever comes first. At each instance a reusable airway is considered for use, it must be visually inspected for discoloration and breakage, blockage, aperture breakage, crazing and tested for elasticity. The integrity of the cuff ought to be verified by inflating with a volume of air 50% greater than the recommended maximum inflation volume. In order to obtain the best performance from LMA the recommendations of the manufacturer of the device as regards tracking, cleaning and sterilization procedures should be implemented in clinical practice.

**CONCLUSION**

The continued use of an LMA beyond 40 insertions increases the probability of device malfunction. In order to prevent the above discussed problem, we decided to implement the following measures; track the number of times an LMA has been used and autoclaved, and limit the number to recommended 40 uses; perform manufacturers’ recommended pre-use tests prior to each use; use the standard insertion and fixation technique and bite-block; provide availability of back-up equipment in case of failure; increase awareness...
about the single-use (disposable) LMA as a low-cost alternative or supplement to reusable laryngeal devices, in order to reduce risk of nosocomial infection. We decided to carry out training and education for medical staff involved in LMA use to further reduce the likelihood of adverse events.

REFERENCES

Neutropenia Induced by Ceftriaxone Sodium

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Ceftriaxone sodium is a third-generation cephalosporin antibiotic, which is used for a wide spectrum of infectious diseases. Neutropenia is a rare life-threatening, adverse reaction associated with more than 100 different drugs except for anticancer ones. The most common causes of neutropenia in adults are acquired and they are due to either decreased granulocyte production or increased destruction. The usual definition of drug-induced neutropenia or agranulocytosis excludes the use of known cytotoxic agents (e. g., cyclophosphamide, doxorubicin) or diseases (e. g., vitamin B12 deficiency, chronic liver disease) that can cause neutropenia, and requires that the drug must have been administered within four weeks of the onset of neutropenia[1]. Discontinuation of the drug generally results in correction of the neutrophil count within 30 days. We report the case of a patient with ceftriaxone-associated neutropenia due to a standard dose parenteral antibiotic therapy.

A 21-year-old patient was admitted to the emergency department with complaints of malaise, purulent discharge of sputum, cough and fever. He was having these symptoms for four days. On physical examination, the blood pressure was 120/80 mmHg, pulse was 92/min and body temperature was 38 °C. On auscultation, he had fine crackles and expiratory rhonchi at the lower left lung. All other systemic findings were normal. Laboratory results at admission revealed a total WBC count of 11,000 cells/μl with a differential of 90% neutrophils, 7% lymphocytes and 1% monocytes, 1% basophils and 1% eosinophils. The rest of the routine blood analyses and urine analyses were within the normal limits. On chest X-ray there were reticulonodular opacities on the left lower zones compatible with bronchopneumonia. The patient was hospitalized with a diagnosis of lobar pneumonia. No colonization was present in the sputum culture and direct microscopy for tuberculosis and bacterial infections. Treatment was started with ceftriaxone sodium 2 g/day intravenously. Ceftriaxone therapy was well-tolerated with normal hematological indices until day four, when the WBC count declined to 2000/mm3 and granulocyte count to 45%. There was no concurrent therapy prescribed, or over-the-counter medication exposure. Diagnostic tests for other possible causes of neutropenia, including viral tests for common respiratory pathogens, blood cultures and throat swabs for bacterial culture, Epstein–Barr virus, cytomegalovirus and HIV serology, were negative. As a result of these negative findings, the possibility of an undiagnosed infectious cause for neutropenia was considered highly unlikely. Ceftriaxone was considered the probable cause of neutropenia. Ceftriaxone sodium was stopped immediately and 400 mg of levofloxacin daily prescribed. On the seventh day of levofloxacin therapy the patient remained well with complete resolution of his symptoms and a normal WBC count.

Drug-induced neutropenia occurs as an adverse idiosyncratic reaction and is the second most common cause of neutropenia. The true incidence of drug-induced neutropenia is not known. Extensive data from randomized clinical trials confirm the efficacy of ceftriaxone in serious and difficult-to-treat community-acquired infections including meningitis, pneumonia and nonresponsive acute otitis media[2]. Unfortunately, the frequency of reported ceftriaxone-induced adverse events has been increasing over the last decade, but the frequency severe neutropenia is not known. In a systematic review of 980 case reports
of drug-induced agranulocytosis from 1966 - 2006, ceftriaxone was identified as a probable cause in five case reports[3]. This case reveals an extremely rare but serious potential complication arising from the use of a standard dose and duration of parenteral ceftriaxone in community acquired infection. In conclusion, medical professionals should be aware of hematological adverse events like neutropenia during ceftriaxone treatment and close follow-up of blood tests must be done for an early diagnosis.

REFERENCES

Schizophrenia is one of the most severe psychiatric diseases noted for its chronic and often debilitating processes, distinguished by a set of symptoms, which is characterized by hallucinations and delusions (positive symptoms), deficits in learning and memory (cognitive symptoms), depression and social isolation (negative symptoms). In addition, blockade of N-methyl-D-aspartate (NMDA)-type glutamate receptors (NMDARs) in normal people will induce behavior which is similar to the symptoms and cognitive deficits of schizophrenia and administration of non-competitive NMDAR antagonists could also increase positive, negative and cognitive deficits in schizophrenic patients. Therefore, the glutamate hypothesis is a robust model of schizophrenia.

Additionally, a loss of dendritic spines, particularly from cortical pyramidal neurons, could be consistent with the glutamate hypothesis of schizophrenia, as the NMDA subtype of glutamate receptor is present on their dendrites and probably dendritic spines. This is also verified by spine density measurements in schizophrenics or in the cortical area in normal people. Recently, a very interesting study shows that NMDAR dysfunction is more closely implicated in autism than in schizophrenia, which has deficits in all core domains of autism symptoms. Multiple abnormal behaviors have largely been interpreted in the context of schizophrenia. Mice lacking ProSAP1/Shank2 show autistic-like behaviors and hyperactivity as well as up-regulation of ionotropic glutamate receptors, such as NMDARs, at the synapse and exhibit fewer dendritic spines.

From the above mentioned facts, we know that some behaviors could be shared by schizophrenia and autism. Thus, it is reasonable to hypothesize that positive or negative symptom of NMDAR antagonists inducing schizophrenia may be related to the changes of the ProSAP1/Shank2 protein level at the synapses and modification of the dendritic spines plasticity, finally producing schizophrenia symptom.

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REFERENCES
Immunocytochemical Detection of Raf Kinase Inhibitor Protein and Human Papillomavirus Profiling of Normal and Abnormal Cervical Thinprep Samples

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Acta Cytol 2013; 57:259-265

**Objectives:** This study investigates the potential value of Raf kinase inhibitor protein (RKIP) as a marker of normal squamous cells in ThinPrep slides. RKIP was evaluated for its ability to distinguish between normal and abnormal cervical samples in the context of human papillomavirus (HPV) infections.

**Study Design:** A total of 316 ThinPrep samples were taken from women with normal and abnormal cervixes. ThinPrep slides were Papanicolaou stained and reported. Residual samples were used for RKIP immunostaining and HPV PCR-based sequencing.

**Results:** RKIP expression was seen in both nuclei and cytoplasm in 83.7% of samples. RKIP expression was highest (84.6%) in samples with a diagnosis of high-grade squamous intraepithelial lesion (HSIL) or worse; expression was lower in low-grade squamous intraepithelial lesions (73%) and was lowest in samples with normal cytology (p = 0.0023). A total of 74% of HPV-infected ThinPrep samples were immunopositive, and 67% of samples that did not harbor HPV were also immunopositive (p = 0.414). Sensitivity and specificity of RKIP were 84.6 and 34.6%, respectively, for the detection of samples with HSIL or worse.

**Conclusions:** This study showed that RKIP expression may be of some value as a marker for abnormal cervical cells. Combined RKIP expression and HPV testing could improve the identification of samples with abnormal cytology.

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Genetic and Immunohistochemical Characterization of Epstein-Barr Virus-Associated Diffuse Large B-Cell Lymphoma

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Acta Haematol 2013; 131:1-10

Epstein-Barr virus (EBV) has a pathogenic role in several lymphomas, including diffuse large B-cell lymphoma (DLBCL). EBV-associated genetic aberrations in DLBCL have not been fully characterized. The aim of this study was to investigate the prevalence of EBV infection in sporadic DLBCL cases in Kuwait and to evaluate their EBV status in relation to demographic data, the anatomical disease site, immunophenotypic features, particularly pertaining to the Choi’s DLBCL prognostic classification, and chromosomal aberrations. Using immunohistochemistry (IHC), in situ hybridization (ISH), nested polymerase chain reaction (nPCR) and comparative genomic hybridization techniques, formalin-fixed paraffin-embedded blocks of archived DLBCL cases were included and evaluated in the study. EBV was detected in 6.9, 18.2 and 25% of the studied cases using IHC, ISH and nPCR, respectively, indicating that nPCR is more sensitive in detecting EBV than IHC and ISH. EBV- DLBCL cases showed BCL6 protein expression more frequently than EBV+ DLBCL cases. The reported prevalence of EBV+ DLBCL cases in this study is similar to that reported in the literature using ISH results and higher using nPCR results. There was a significant inverse correlation between BCL6 protein expression and the presence of EBV (p = 0.01).
Increasing Prevalence and Incidence Rates of Multiple Sclerosis in Kuwait

Division of Neurology, Department of Medicine, Amiri Hospital, Kuwait

Mult Scler 2013 Sep 24 [Epub ahead of print]

Background: Kuwait was considered as low to intermediate risk area for MS.
Objectives: To determine the prevalence and incidence rates of MS among Kuwaiti nationals based on 2011 population census.
Methods: This cross-sectional study was conducted between October 2010 and April 2013 using the newly developed national MS registry in Kuwait. Patients with a diagnosis of MS according to 2010 revised McDonald criteria were identified. The crude, age- and sex-specific prevalence and incidence rates among Kuwaiti patients were calculated.
Results: 1176 MS patients were identified of which 927 (78.8%) were Kuwaitis and 249 (21.2%) were expatriates. Among Kuwaiti patients, female to male ratio was 1.8:1 with a mean age of 35.40 ± 10.99 years. The prevalence rate of MS was 85.05 per 100,000 persons (95% CI: 82.80 - 87.04). There was a peak in prevalence among patients aged 30-39 years. The incidence of MS was 6.88 per 100,000 persons (95% CI 5.52 - 8.55). Between 2003 and 2011, the incidence increased 3.22 and 2.54 times in women and men respectively.
Conclusion: Kuwait is considered a high-risk area for MS. The significant increase in prevalence and incidence rates may represent a true increase despite the improvement in case ascertainment and case definition.

Transcranial Doppler and Brain MRI in Children With Sickle Cell Disease and High Hemoglobin F Levels

Faculty of Allied Health Sciences, Department of Radiologic Sciences, Kuwait University, Safat, Kuwait


Background/Objective: While overt stroke and silent brain infarcts (SBI) are uncommon among Kuwaiti patients with sickle cell disease (SCD), there have been no previous transcranial Doppler (TCD) studies in this population. The main objective of this study is to determine TCD velocities in a group of Kuwaiti children with SCD and correlate same with brain magnetic resonance imaging (MRI) and angiography (MRA) findings.
Materials And Methods: Forty-three steady-state, pediatric patients with SCD aged 10.1 ± 3.9 years (21 SS, 19 Sβ0 Thal, and 3 SD) were studied. Twenty-six age-matched, normal siblings of the patients served as controls. TCD was performed using a General Electric (GE), Vivid 3 equipment and MRI/MRA with a GE Signa Excite HD 1.5 Tesla magnet. Complete blood count was with an electronic counter and Hb quantitation with cation-exchange high performance liquid chromatography (HPLC).
Results: The mean time-averaged mean of the maximum velocity (TAMV) was significantly higher in the SCD group than the controls, but was normal (<170 cm / second) in all. The mean values were comparable among the SS and Sβ0 thal groups. Five (11.1%) patients had SBI and all were between 12 and 16 years of age. There was no significant difference of TAMV in this group compared to those without infarcts. No patient showed evidence of stenosis or any other abnormalities in the circle of Willis vessels.
Conclusion: The mild phenotype among Kuwaiti patients with SCD is reflected in normal TCD velocities and a low prevalence of SBI in children with the disease.
Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013; 45 (4): 361 - 370

After All the Treatment: Delayed Effects of Disease & Treatment on Individuals Who Have Had Head & Neck Cancer
Jan 20, 2014
United Kingdom / London
Contact: Education and Conference Centre, Royal Marsden
Phone: 011-44-20-7808-2921 or 2924
Email: conferencecentre@rmh.nhs.uk

Orbital, Lacrimal & Ophthalmic Plastic Surgery
Jan 20 - 24, 2014
Malta / Valletta
Contact: European School for Advanced Studies in Ophthalmology
Phone: 011-41-91-921-1154

16th International Conference on Dialysis: Advances in Chronic Kidney Disease
Jan 22 - 24, 2014
United States / Nevada / Las Vegas
Contact: Ingrid Adelsberger, Renal Research Institute
Phone: 646-672-4059, Fax: 646-672-4174
Email: iadelsberger@rriny.com

9th International Conference on Cell Therapy for Cardiovascular Disease
Jan 22 - 24, 2014
United States / New York / New York
Contact: Cardiovascular Research Foundation
Phone: 646-434-4386

1st World Congress on Controversies in Multiple Myeloma
Jan 23 - 25, 2014
Thailand / Bangkok
Contact: Congress Secretariat, ComtecMed
Phone: 011-972-3-566-6166, Fax: 011-972-3-566-6177
Email: comy@comtecmed.com

2014 Progress and Controversies in Gynecologic Oncology Conference
Jan 24 – 25, 2014
Spain / Barcelona
Contact: prlME Oncology
Email: gyncongress2014@prlMEoncology.org

22nd Brussels Hand/Upper Limb Symposium: Tendon Disorder & Injuries at the Upper Limb: Basic Knowledge, Advances in Diagnosis & Treatment
Jan 24 - 25, 2014
Belgium / Brussels
Contact: Mrs L Ectors, Congress Secretariat, King Conventions
Phone: 011-32-9-235-2295, Fax: 011-32-9-233-8597
Email: info@kingconventions.be

Transoral Laser Microsurgery for the Management of Tumours of the Upper Aerodigestive Tract
Jan 25 - 27, 2014
United Kingdom / Liverpool
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

15th International Colorectal Forum
Jan 26 - 28, 2014
Switzerland / Verbier
Contact: Congress Organizer, M&S Event Services SA
Email: icf@ms-event.ch

Musculoskeletal MR Imaging
Jan 26 - 28, 2014
United States / California / Rancho Mirage
Contact: Office of Continuing Medical Education, University of California San Francisco
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

MRI of the Joints
Jan 27 - 31, 2014
Austria / Vienna
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<td>Jan 27 - 31, 2014</td>
<td>United States / Massachusetts</td>
<td>Department of Continuing Education, Harvard Medical School</td>
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<td>Jan 30 - 31, 2014</td>
<td>Switzerland / Geneva</td>
<td>Abcam Events Team</td>
<td>Phone: 011-44-12-2369-6000 Email: <a href="mailto:events@abcam.com">events@abcam.com</a></td>
</tr>
<tr>
<td>Endoscopic Ultrasound in the Diagnosing &amp; Staging of Lung Cancer</td>
<td>Jan 30 - Feb 1, 2014</td>
<td>Denmark / Copenhagen</td>
<td>European Respiratory Society</td>
<td>Fax: 011-41-21-213-0100 Email: <a href="mailto:school@ersnet.org">school@ersnet.org</a></td>
</tr>
<tr>
<td>USICON 2014: National Conference of Urological Society of India (USI)</td>
<td>Jan 30 - Feb 2, 2014</td>
<td>India / New Delhi</td>
<td>Prof. Dr. D. Ramesh, Honorary Secretary, USI</td>
<td>Phone: 011-91-80-2218-3065 Email: <a href="mailto:usisecretary@gmail.com">usisecretary@gmail.com</a></td>
</tr>
<tr>
<td>33rd Annual Advanced Nephrology: Nephrology for the Consultant</td>
<td>Jan 31 - Feb 2, 2014</td>
<td>United States / California / San Diego Nephrology</td>
<td>Kevin Bentz, Meeting Planner, UC San Diego Continuing Medical Education</td>
<td>Phone: 619-543-7602, Fax: 619-543-7610 Email: <a href="mailto:ocme@ucsd.edu">ocme@ucsd.edu</a></td>
</tr>
<tr>
<td>Hot Topics and Practical Approaches in Mental Health</td>
<td>Jan 31, 2014</td>
<td>Canada / British Columbia / Vancouver</td>
<td>University of British Columbia</td>
<td>Phone: 604-875-5101, Fax: 604-875-5078 Email: <a href="mailto:cpd.info@ubc.ca">cpd.info@ubc.ca</a></td>
</tr>
<tr>
<td>Radiology Errors</td>
<td>Jan 31, 2014</td>
<td>United Kingdom / London</td>
<td>Education Events, British Institute of Radiology</td>
<td>Phone: 011-44-20-3668-2220, Fax: 011-44-20-3411-6354 Email: <a href="mailto:conference@bir.org.uk">conference@bir.org.uk</a></td>
</tr>
<tr>
<td>Innovations in Advanced Therapeutic Endoscopy &amp; Endoscopic Resection Techniques</td>
<td>Feb 1 - 3, 2014</td>
<td>United States / Florida</td>
<td>Christopher Black, Continuing Medical Education, University of Florida</td>
<td>Phone: 352-273-9475 Email: <a href="mailto:blackcm@medicine.ufl.edu">blackcm@medicine.ufl.edu</a></td>
</tr>
<tr>
<td>5th Advanced Course in Knee Surgery</td>
<td>Feb 2 - 7, 2014</td>
<td>France / Val d’Isère</td>
<td>Frédéric Cretin / Gaëlle Busi, Centre de Congres et de Seminaires Henri Oreiller</td>
<td>Phone: 011-33-4-7906-2123, Fax: 011-33-4-7906-1904 Email: <a href="mailto:knee2014@valdisere-congres.com">knee2014@valdisere-congres.com</a></td>
</tr>
<tr>
<td>Neurology and Pain Management Australia &amp; New Zealand Cruise</td>
<td>Feb 2 - 16, 2014</td>
<td>Australia / Sydney</td>
<td>University at Sea, Continuing Education, Inc.</td>
<td>Phone: 800-422-0711, 2014</td>
</tr>
</tbody>
</table>
34th Annual Meeting of Society for Maternal-Fetal Medicine (SMFM)
Feb 3 - 8, 2014
United States / Louisiana / New Orleans
Contact: SMFM
Phone: 202-863-2476, Fax: 202-554-1132
Email: smfm@smfm.org

Geriatrics and Rheumatology: Practical Topics in Overlapping Specialties
Feb 3 - 7, 2014
United States / Florida / Sarasota
Contact: Tara Esteves, Live CME Administrator, American Medical Seminars, Inc.
Phone: 866-267-4263 (TOLL FREE) or 941-388-1766, Fax: 941-365-7073
Email: testeves@ams4cme.com

Head & Neck MRI
Feb 3 – 7, 2014
Belgium / Brugge
Contact: Mrs. Valérie Schotte, Department of Radiology, A.Z. St.- Jan Brugge
Fax: 011-32-50-452-146
Email: erasmuscourse2014@telenet.be

Medical Retina
Feb 3 – 7, 2014
Switzerland / Lugano
Contact: European School for Advanced Studies in Ophthalmology
Phone: 011-41-91-921-1154

Musculoskeletal MRI of the Joints
Feb 3 – 7, 2014
Austria / Vienna
Contact: H. Fischer, I. Fischer, Chr. Arnecker
Fax: 011-43-1-40-400-4898
Email: erasmus-course-vienna@meduniwien.ac

Short Course on Abdominal Ultrasound in Infectious Diseases & Tropical Medicine
Feb 3 - 14, 2014
Italy / Pavia
Contact: Silvia Bensi, Ms, University of Pavia
Fax: 011-39-3-8250-2296
Email: shortcourse@tropicalultrasound.org

25th International Congress on Anti-Cancer Treatment
Feb 4 - 6, 2014
France / Paris
Contact: Valérie Caillon, Organisation Committee, International Medical Events
Phone: 011-33-1-4743-5084, Fax: 011-33-1-4743-2226
Email: valerie.caillon@im-events.com

7th International Conference on Advanced Technologies & Treatments for Diabetes
Feb 5 - 8, 2014
Austria / Vienna
Contact: Tammy Lessick, Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: attd@kenes.com

3rd Systemic Sclerosis World Congress
Feb 6 – 8, 2014
Italy / Rome
Contact: Organizing Secretariat, AIM Congress – Rome Office
Phone: 011-39-6-330-531, Fax: 011-39-6-330-532-49
Email: ssc2014.reg@aimgroup.eu

72nd All India Ophthalmological Conference
Feb 6 – 9, 2014
India / Agra
Contact: Prof. S.K. Satsangi, Chief Organizing Secretary, AIOC-2014, Sarojini Naidu Medical College
Phone: 011-91-562-645-0597
Email: aioc2014agra@gmail.com

Endovascular Aneurysm Repair (EVAR) Planning for Endovascular Surgeons
Feb 6 - 7, 2014
United Kingdom / Edinburgh
Contact: Education Section, Royal College of Surgeons of Edinburgh
Phone: 011-44-13-1527-1600
Email: education@rcsed.ac.uk

Thromboprophylaxis in General Medicine and Obstetrics
Feb 6, 2014
United Kingdom / Leeds
Contact: Hartley Taylor Medical Communications Ltd
Phone: 011-44-15-6562-1967
Email: office@hartleytaylor.co.uk

11th International Winter Arrhythmia School
Feb 7 – 9, 2014
Canada / Ontario / Collingwood
Contact: Linda Liu, Organizer, University of Toronto
Phone: 416-480-6100 ext. 7537
Email: winterarrhythmia@sunnybrook.ca

2014 Electives in Hand Surgery
Feb 7 - 8, 2014
United States / Louisiana / New Orleans
Contact: American Society for Surgery of the Hand
Phone: 312-880-1900, Fax: 847-384-1435
Email: meetings@assh.org
Forthcoming Conferences and Meetings December 2013

**Rheumatology and Musculoskeletal Medicine for Primary Care**
Feb 7 - 9, 2014
United States / California / Palm Springs
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 or 303-798-9682, Fax: 303-798-5731
Email: info@mer.org

**Diagnosis & Treatment of Myofascial Pain Syndromes: An Introductory Course**
Feb 8 - 9, 2014
United States / New Mexico / Albuquerque
Contact: Continuing Medical Education, University of New Mexico
Phone: 505-272-3942, Fax: 505-272-8604
Email: CMEWeb@salud.unm.edu

**Hand and Upper Extremity Update**
Feb 8, 2014
Canada / Ontario / Toronto
Contact: Continuing Education & Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info@cepdtoronto.ca

**11th International Symposium on GnRH: Hypothalamic-Pituitary-Gonadal Axis in Cancer & Reproduction**
Feb 9 - 11, 2014
Austria / Salzburg
Contact: Ronit Eisenbach, APM, Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: gnrh@kenes.com

**Current Concepts in Neuro and Musculoskeletal Imaging**
Feb 9 - 14, 2014
United States / Hawaii / Kohala Coast
Contact: Office of Continuing Medical Education, University of California San Francisco
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

**2014 Neuro/ENT at the Beach**
Feb 10 - 13, 2014
Florida / Palm Beach
Contact: Wendy Ryals, Office Manager, IICME
Phone: 205-467-0290, Fax: 205-467-0195
Email: wryals@iicme.net

**25th Jagelman / 35th Turnbull International Colorectal Disease Symposium**
Feb 11 - 16, 2014
United States / Florida / Fort Lauderdale
Contact: Sandy Ronnenberg, CME Project Manager, Cleveland Clinic Florida, CME Department
Phone: 954-659-5490, Fax: 954-659-5491
Email: ronnens@ccf.org

**10th Asia Pacific Congress of Hypertension**
Feb 12 - 15, 2014
Philippines / Cebu City
Contact: Shidah Isa, APM, Kenes Asia
Phone: 011-65-6292-4710, Fax: 011-65-6292-4721
Email: apch2014@kenes.com

**37th Annual Advanced Ultrasound Seminar: Obs/Gyn**
Feb 12 - 15, 2014
United States / Florida / Orlando
Contact: American Institute of Ultrasound in Medicine
Phone: 800-638-5352 or 301-498-4100, Fax: 301-498-4450
Email: ddelanko@aium.org

**Asian American MultiSpecialty Summit VI: Laparoscopy & Minimally Invasive Surgery**
Feb 12 - 15, 2014
Australia / Lorne
Contact: ASN Events Pty Ltd
Phone: 011-61-3-9329-6600
Fax: 011-61-3-9329-1777
Email: rafeltra@cos-sco.ca

**26th Lorne Cancer Conference**
Feb 13 - 15, 2014
Canada / British Columbia / Whistler
Contact: Rita Afeltra, CRS
Phone: 613-729-6779 ext. 300
Email: rafeltra@cos-sco.ca

**3rd Global Congress for Consensus in Pediatrics & Child Health**
Feb 13 - 16, 2014
Thailand / Bangkok
Contact: Karen Davidson, Conference secretariat, Paragon Conventions
Phone: 011-41-22-533-0948, Fax: 011-41-22-580-2953
Email: cip@cipediatrics.com

**20th Annual Advances in Diagnosis & Treatment of Sleep Apnea & Snoring**
Feb 14 – 15, 2014
United States / California / San Francisco
Contact: Office of Continuing Medical Education, University of California, San Francisco
Phone: 415-476-4251; Fax: 415-476-0318
Email: info@ocme.ucsf.edu
27th Annual State-of-the-Art Echocardiography
Feb 14 – 18, 2014
United States / Arizona / Scottsdale
Contact: American Society of Echocardiography
Phone: 919-861-5574, Fax: 919-882-9900
Email: registrar@asecho.org

14th Annual International Symposium on Congenital Heart Disease
Feb 15 – 18, 2014
United States / Florida / St. Petersburg
Contact: Allison Madden, CME Coordinator, All Children’s Hospital
Phone: 727-767-2525
Email: allison.madden@allkids.org

2014 Advances in Abdominal, Cardiac, Musculoskeletal & Neuro Imaging
Feb 15 – 18, 2014
Bahamas / Paradise Island
Contact: Department of Radiology, Duke University School of Medicine
Phone: 919-684-2711

2014 Clinical Hematology and Oncology
Feb 15 – 18, 2014
United States / California / San Diego
Contact: Scripps Conference Services
Phone: 858-652-5400
Email: med.edu@scrippshealth.org

American College of Surgeons Thyroid & Parathyroid Ultrasound Skills-Oriented Course
Feb 15 – 16, 2014
United States / Hawaii / Honolulu
Contact: Office of Continuing Medical Education, University of California San Francisco
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

2014 Lorne Genome Conference
Feb 16 – 19, 2014
Australia / Lorne
Contact: ASN Events Pty Ltd
Phone: 011-61-3-5983-2400
Email: participation@asnevents.net.au

Infectious Diseases in Clinical Practice: Update on Inpatient & Outpatient Infectious Diseases
Feb 16 – 21, 2014
United States / Hawaii / Kauai
Contact: Office of Continuing Medical Education, University of California San Francisco
Phone: 415-476-4251, Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Internal Derangements of Joints: Advanced & Intensive MR Imaging Course
Feb 16 – 20, 2014
United States / California / San Diego
Contact: Wendy Ryals, Office Manager, IICME
Phone: 205-467-0290, Fax: 205-467-0195
Email: wryals@iicme.net

Medical CBT: Ten-Minute Techniques for Real Doctors (cognitive behavior therapy)
Feb 17 – 19, 2014
United States / Hawaii / Honolulu
Contact: Greg Dubord, MD, CME Director, CBT
Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

10th Annual Update in Nuclear Cardiology
Feb 18, 2014
United States / Pennsylvania / Philadelphia
Contact: Cardiovascular Institute of Philadelphia
Phone: 215-389-2300, Fax: 215-389-5450
Email: cvi.markhartnett@verizon.net

2014 Sarcoma and GIST
Feb 18 – 19, 2014
Italy / Milan
Contact: Nicole Bullo, Conference Secretariat, European Society for Medical Oncology
Phone: 011-41-91-973-1939, Fax: 011-41-91-973-1918

13th Genoa Meeting on Hypertension, Diabetes and Renal Diseases
Feb 20 – 22, 2014
Italy / Genoa
Contact: Organizing Secretariat, aristeia
Phone: 011-39-10-55-3591, Fax: 011-39-10 55-35970
Email: genoameeting@aristeia.com

19th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)
Feb 20 – 23, 2014
China / Macau
Contact: Ruthi Yahav, Secretariat, CongressMed
Phone: 011-972-73-706-6950, Fax: 011-972-73-706-6959
Email: cogi@congressmed.com

2014 Kyoto Breast Cancer Consensus Conference (KBCCC)
Feb 20 – 22, 2014
Japan / Kyoto
Contact: David Graham, Secretariat, KBCCC
Phone: 011-81-75-761-5751, Fax: 011-81-75-761-5718
Email: info@kyoto-breast-cancer.org
3rd International Meeting on **Cardiac Problems in Pregnancy**  
Feb 20 – 23, 2014  
*Italy / Venice*  
Contact: Shirley Dinenson, Conference Secretariat, Paragon Conventions  
Phone: 011-41-22-533-0948, Fax: 011-41-22-580-2953  
Email: secretariat@cppcongress.com

17th Annual Conference of Indian Association of **Cardiovascular Thoracic Anaesthesiologists**  
Feb 21 – 23, 2014  
*India / Mumbai*  
Contact: Dr. Uday Gandhe, Organising Secretary, Variance Conference and Events Private Limited  
Phone: 011-91-22-2494-0518, 011-91-77-3879-6785, Fax: 011-91-22-2494-0517  
Email: REGISTER@IACTA2014.COM

17th Annual Women’s Imaging: Advances in **Gynaecologic Imaging & First Trimester Ultrasound**  
Feb 21 – 23, 2014  
*Canada / Ontario / Toronto*  
Contact: Elizabeth Gan, CME Administrative Course Director, Dept. of Ob/Gyn, University of Toronto - Dept. of Ob/Gyn and the Dept. of Medical Imaging  
Phone: 416-586-4800 ext. 2489, Fax: 416-586-5958  
Email: egan@mtsinai.on.ca

19th ESRA Cadaver Workshop  
Feb 21 – 22, 2014  
*Austria*  
Contact: Rachel Zablow Katzir, APM, Kenes International  
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140  
Email: esra-congress@kenes.com

2014 **Pathology Update**  
Feb 21 – 23, 2014  
*Australia / Melbourne*  
Contact: Eve Propper, Events and Sponsorship Manager, Royal College of Pathologists of Australasia  
Phone: 011-61-2-8356-5806  
Email: evep@rcpa.edu.au

Active Surveillance for Low Risk **Prostate Cancer**  
Feb 21 – 22, 2014  
*Netherlands / Amsterdam*  
Contact: European School of Oncology  
Phone: 011-39-2-854-6451  
Fax: 011-39-2-854-6454  
Email: eso@eso.net

**Neurology/Psychiatry** for Primary Care  
Feb 21 – 23, 2014  
*United States / Nevada / Las Vegas*  
Contact: Medical Education Resources, Inc.  
Phone: 800-421-3756 or 303-798-9682, Fax: 303-798-5731  
Email: info@mer.org

**Primary Care Geriatrics Review** Hawaiian Islands Cruise  
Feb 22 - Mar 1, 2014  
*United States / Hawaii / Honolulu*  
Contact: Continuing Education, Inc., Meeting Planner, Continuing Education, Inc.  
Phone: 800-422-0711, Fax: 727-522-8304  
Email: contactus@continuingeducation.net

11th Annual **Critical Care Conference**  
Feb 25 – 28, 2014  
*Canada / British Columbia*  
Contact: Zena Davidson, Conference Coordinator  
Phone: 604-834-9362  
Email: Zena.davidson@vch.ca

2014 Combined Spine Conference of Canadian Spine Society (CSS), New Zealand Orthopaedic Spine Society & Spine Society of Australia  
Feb 25 - Mar 1, 2014  
*Canada / Alberta / Lake Louise*  
Contact: Jennifer Edwards, CSS  
Phone: 519-986-1459  
Email: css@spinecanada.ca

9th Annual **Biomarkers Congress**  
Feb 25 – 26, 2014  
*United Kingdom / Manchester*  
Contact: Danielle Dalby, Marketing Executive, Oxford Global  
Email: d.dalby@oxfordglobal.co.uk

2014 **Blood and Marrow Transplantation (BMT) Tandem Meetings**  
Feb 26 - Mar 2, 2014  
*United States / Texas / Grapevine*  
Contact: BMT Tandem Meetings  
Email: bmttandem@cs.com

9th International **Breast Cancer Congress**  
Feb 26 – 28, 2014  
*Iran / Tehran*  
Contact: 9th International Breast Cancer Congress, Breast Cancer Congress, Shahid Beheshti University of Medical Sciences Tehran, Iran  
Phone: 011-98-21-2274-8001 ext. 2  
Fax: 011-98-21-2272-4090  
Email: crc@sbmu.ac.ir

**Cellular Heterogeneity in the Tumor Microenvironment**  
Feb 26 - Mar 1, 2014  
*United States / California / San Diego*  
Contact: American Association for Cancer Research  
Phone: 215-440-9300, Fax: 215-351-9165  
Email: aacr@aacr.org
Infant, Child and Adolescent Medicine  
Feb 26 - Mar 1, 2014  
United States / California / Indian Wells  
Contact: American Academy of Family Physicians  
Phone: 800-274-2237 or 913-906-6000  
Fax: 913-906-6075

2014 Chronic Total Occlusion and Left Main Summit  
Feb 27 - Mar 1, 2014  
United States / New York / New York  
Contact: Cardiovascular Research Foundation  
Phone: 646-434-4386

2nd International Conference on Heart & Brain  
Feb 27 - Mar 1, 2014  
France / Paris  
Contact: Ronit Eisenbach, APM, Kones International  
Phone: 011-41-22-908-0488  
Fax: 011-41-22-906-9140  
Email: heart-brain@kenes.com

6th Advances Against Aspergillosis  
Feb 27 - Mar 1, 2014  
Spain / Madrid  
Contact: Hartley Taylor Medical Communications Ltd  
Phone: 011-44-15-6562-1967  
Email: derry@hartleytaylor.co.uk

Non-Melanoma Skin Cancer Meeting  
Feb 27, 2014  
United Kingdom / London  
Contact: Conference and Event Services, British Association of Dermatologists  
Email: conference@bad.org.uk

Sexuality and Learning Disabilities  
Feb 27, 2014  
United Kingdom / Bristol  
Contact: Association for Child & Adolescent Mental Health  
Phone: 011-44-20-7403-7458  
Email: membership@acamh.org

2014 Excellence in Diabetes  
Feb 28 - Mar 2, 2014  
Qatar / Doha  
Contact: Patrizia Schmid, Account Manager, EI Congresses & Communications UK Ltd  
Phone: 011-44-20-3384-0657, Fax: 011-44-20-8326-5726  
Email: patrizia.schmid@2eic.com

2014 Masters Experience Knee: Patellofemoral  
Feb 28 - Mar 1, 2014  
United States / Illinois / Rosemont  
Contact: Arthroscopy Association of North America  
Phone: 847-292-2262, Fax: 847-292-2268  
Email: info@aana.org

Cool Topics in Neonatology  
Feb 28 - Mar 2, 2014  
United States / California / San Diego  
Contact: Office of Continuing Medical Education, UCLA  
Phone: 310-794-2620, Fax: 310-794-2624

Multi-parametric MRI of the Prostate: Paradigm Shift in the Management of Prostate Cancer  
Feb 28, 2014  
United Kingdom / London  
Contact: Education Events, British Institute of Radiology  
Phone: 011-44-20-3668-2220, Fax: 011-44-20-3411-6354  
Email: conference@bir.org.uk

Treating the Addictions Psychiatry  
Feb 28 - Mar 1, 2014  
United States / Massachusetts / Boston  
Contact: Department of Continuing Education, Harvard Medical School  
Phone: 617-384-8600, Fax: 617-384-8686  
Email: hms-cme@hms.harvard.edu

Beyond LDL Cholesterol: Risk Assessment & Biomarkers in Special Populations  
Mar 1, 2014  
United States / Illinois / Chicago  
Contact: Blair Parker, Center for Continuing Medical Education, University of Chicago  
Phone: 773-834-5418  
Email: bparker@medicine.bsd.uchicago.edu

Orthopaedic Thromboembolic Day  
Mar 4, 2014  
United Kingdom / London  
Contact: Hartley Taylor Medical Communications Ltd  
Phone: 011-44-15-6562-1967  
Email: Julie@hartleytaylor.co.uk

2014 Diabetes UK Professional Conference  
Mar 5 – 7, 2014  
United Kingdom / Liverpool  
Contact: Conference Team, Diabetes UK  
Phone: 011-44-20-7424-1000, Fax: 011-44-20-7424-1080  
Email: conferences@diabetes.org.uk

2014 Faculty of Forensic Psychiatry Annual Conference  
Mar 5 – 7, 2014  
United Kingdom / Belfast  
Contact: Royal College of Psychiatrists  
Phone: 011-44-20-7977-6657  
Email: calc@rcpsych.ac.uk
6th UK Thromboprophylaxis Forum Annual Meeting  
Mar 5, 2014  
United Kingdom / London  
Contact: Hartley Taylor Medical Communications Ltd  
Phone: 011-44-15-6562-1967  
Email: kristy@hartleytaylor.co.uk

Essential Medical Dermatology  
Mar 5 – 7, 2014  
United Kingdom / London  
Contact: Conference and Event Services, British Association of Dermatologists  
Email: conference@bad.org.uk

Targeted Anticancer Therapies  
Mar 5 – 7, 2014  
United States / District of Columbia / Washington  
Contact: Monique de Brabander, Project Manager, Congress by design  
Phone: 011-31-88-089-8101  
Email: debrabander@congressbydesign.com

2nd International Symposium of Probiotics & Prebiotics in Pediatrics  
Mar 7 - 9, 2014  
Turkey / Antalya  
Contact: IS3P Organizing Secretariat, Serenas Group  
Phone: 011-90-312-440-5011, Fax: 011-90-312-441-4562  
Email: is3p@serenas.com.tr

9th International Symposium on Pneumococci and Pneumococcal Diseases  
Mar 9 – 13, 2014  
India / Hyderabad  
Contact: Alizah Davis, APM, Kenes International  
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140  
Email: isppd@kenes.com

21st Annual Echocardiographic Workshop on 2-D & Doppler Echocardiography at Vail  
Mar 10 – 13, 2014  
United States / Colorado / Vail  
Contact: CV CME, Education, Mayo Clinic  
Phone: 507-266-6703, Fax: 507-266-7403  
Email: cvcme@mayo.edu

1st Immunotherapy of Cancer Conference  
Mar 12 – 14, 2014  
Germany / Munich  
Contact: Riitta Kettunen, Registrations Coordinator, European Cancer Organisation  
Phone: 011-32-2-775-0205  
Email: riitta.kettunen@ecco-org.eu

2014 Asian Pacific Association for the Study of the Liver  
Mar 12 – 15, 2014  
Australia / Brisbane  
Contact: Sarah Perrott, Gastroenterological Society of Australia  
Email: apasl2014@gesa.org.au

2014 Gulf Thoracic Congress  
Mar 13 – 15, 2014  
United Arab Emirates / Dubai  
Contact: Hassan S. Alorainy BsRC, RRT, FAARC, Executive Director, GulfThoracic Congress  
Phone: 011-966-5-199-4114  
Email: halorainy@gmail.com

2014 UK Chronic Lymphocytic Leukaemia Forum  
Annual Scientific Day  
Mar 14, 2014  
United Kingdom / London  
Contact: Hartley Taylor Medical Communications Ltd  
Phone: 011-44-15-6562-1967  
Email: office@hartleytaylor.co.uk

4th Macula & Retina Congress  
Mar 14 – 15, 2014  
United States / Florida / Miami  
Contact: Josephine Gordon and Hannah Duncan, EuroLam Secretariat  
Phone: 011-44-78-3022-1032, Fax: 011-44-70-9287-7237  
Email: info@euro-lam.org

2014 Nephrology  
Mar 16 – 21, 2014  
United States / Massachusetts / Boston  
Contact: Department of Continuing Education, Harvard Medical School  
Phone: 617-384-8600  
Fax: 617-384-8686  
Email: hms-cme@hms.harvard.edu

16th Annual Conference of the International Society for Bipolar Disorders  
Mar 18 – 21, 2014  
South Korea / Seoul  
Contact: Raquel Louis, APM, Kenes International  
Phone: 011-41-22-908-0488  
Fax: 011-41-22-906-9140  
Email: isbd@kenes.com

34th International Symposium on Intensive Care & Emergency Medicine  
Mar 18 – 21, 2014  
Belgium / Brussels  
Contact: Intensive Care Department, Erasme University Hospital, Université Libre de Bruxelles  
Fax: 011-32-2-555-4555  
Email: sympicu@ulb.ac.be
10th World Congress on Brain Injury
Mar 19 - 23, 2014
United States / California / San Francisco
Contact: Margaret Roberts, MCC Association Mgt.
Phone: 703-960-0027, Fax: 703-960-6603
Email: mjroberts@aol.com
Website: http://www.internationalbrain.org/congress-page-tenth-world-congress-on-brain-injury/

30th International Congress on Clinical Neurophysiology
Mar 19 – 23, 2014
Germany / Berlin
Contact: Conventus Congress Management
Phone: 011-49-3641-311-6110, Fax: 011-49-3641-311-6241

5th World Congress on Controversies in Ophthalmology
Mar 20 – 23, 2014
Portugal / Lisbon
Contact: Congress Secretariat, ComtecMed
Email: cophy@comtecmed.com

9th Tuberculosis Symposium
Mar 20 – 21, 2014
United States / Alberta / Edmonton
Contact: Norma Jean Olivier, Event Coordinator, TB Symposium 2014
Phone: 780-988-0707
Email: tbconference@shaw.ca

2014 CHEST World Congress
Mar 21 – 24, 2014
Spain / Madrid
Contact: American College of Chest Physicians
Phone: 847-498-1400, Fax: 847-498-5460

11th World Congress of International Hepato-Pancreato-Biliary Association: IHPBA World Congress 2014
Mar 22 – 27, 2014
South Korea / Seoul
Contact: IHPBA 2014 Seoul Secretariat, InSession International Convention Services
Phone: 011-82-2-3452-7260, Fax: 011-82-2-521-8683
Email: ihpba2014@insession.co.kr

Football Medicine Strategies for Joint & Ligament Injuries
Mar 22 - 23, 2014
Italy / Milan
Contact: Bologna Isokinetic Srl
Email: conference@isokinetic.com

2nd Asian Congress on Pain
Mar 27 – 30, 2014
Taiwan / Taipei
Contact: Debbie Tang, APM, Kenes Asia
Phone: 011-65-6393-0235, Fax: 011-65-6292-7577
Email: aafps2014@kenes.com

3rd International Conference on Prehypertension & Cardio Metabolic Syndrome
Mar 27 – 30, 2014
Poland / Warsaw
Contact: Gail Tito, Paragon Group
Phone: 011-41-22-533-0948
Email: secretariat@prehypertension.org

1st International Workshop Intensive Care of the Newborn
Mar 28, 2014
Italy / Verona
Contact: Organizing Secretariat, AIM Group
International – Florence Office
Email: verona2013@aimgroup.eu

40th Annual Meeting of the European Society for Blood & Marrow Transplantation
Mar 30 - Apr 2, 2014
Italy / Milan
Contact: Congress Organizer, MCI Suisse S.A.
Phone: 011-41-22-339-9581, Fax: 011-41-22-339-9631
Email: ebmt2014.reg@mci-group.com

5th New Directions in Leukaemia Research
Mar 30 - Apr 2, 2014
Australia / Noosa
Contact: Secretariat, SAPRO Conference Management
Phone: 011-61-8-8274-6054, Fax: 011-61-8-8274-6000
Email: ndlr2014@sapmea.asn.au

Cleft & Paediatric Plastic Surgery: Series 3, Course 2
Mar 31 Apr 1, 2014
United Kingdom / Manchester
Contact: British Association of Plastic, Reconstructive and Aesthetic Surgeons
Phone: 011-44-20-7831-5161, Fax: 011-44-20-7831-4041
Website:
Endoscopic Surgery of the Sinuses & Eustachian Tube
Mar 31 Apr 2, 2014
United States / Massachusetts / Boston
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600, Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

16th International Congress on Infectious Diseases
Apr 2 - 5, 2014
South Africa / Cape Town
Contact: International Society for Infectious Diseases
Phone: 617-277-0551
Fax: 617-278-9113
Email: info@isid.org
10th Australasian Lympiology Association Conference  
Apr 3 - 5  
New Zealand / Auckland  
Contact: Conference Office, Think Business Events  
Phone: 011-61-3-9417-1350, Fax: 011-61-3-8610-2170  
Email: ala@thinkbusinessevents.com.au

12th Anti-Aging Medicine World Congress  
Apr 3 – 5  
Canada / Monaco / Monte Carlo  
Contact: EuroMediCom  
Phone: 011-33-1-5683-7800, Fax: 011-33-1-5683-7805

2014 39th Annual Meeting of Society for Sex Therapy & Research (SSTAR)  
Apr 3 – 5, 2014  
United States / Pennsylvania / Pittsburgh  
Contact: SSTAR  
Phone: 847-647-8832  
Email: Lindag@sstarnet.org

2014 Pediatric Rheumatology Symposium  
Apr 3 – 6, 2014  
United States / Florida / Orlando  
Contact: American College of Rheumatology  
Phone: 404-633-3777, Fax: 404-633-1870  
Email: acr@rheumatology.org

2014 Peptides Congress  
Apr 3 – 4, 2014  
United Kingdom / London  
Contact: Ross McIvor, Senior Marketing Manager, Oxford Global  
Email: r.mcivor@oxfordglobal.co.uk

3rd International Congress on Epilepsy, Brain and Mind  
Apr 3 – 5, 2014  
Czech Republic / Brno  
Contact: Congress Secretariat, GUARANT International  
Phone: 011-420-284-001-444  
Email: ebm2014@guarant.cz

6th International Conference on Advances in Diabetes & Insulin Therapy  
Apr 3 - 5, 2014  
Serbia / Belgrade  
Contact: etouches European Headquarters  
Phone: 011-44-84-5077-2804

7th Annual Proteins & Antibodies Congress  
Apr 3 – 4, 2014  
United Kingdom / London  
Contact: Danielle Dalby, Marketing Manager, Oxford Global  
Phone: 011-44-18-6524-8455, Fax: 011-44-18-6525-0985  
Email: d.dalby@oxfordglobal.co.uk

Interstitial Lung Diseases  
Apr 3 – 5, 2014  
Germany / Heidelberg  
Contact: European Respiratory Society  
Fax: 011-41-21-213-0100  
Email: school@ersnet.org

Palliative Care for Hospitalists and Intensivists  
Apr 3 – 5, 2014  
United States / Massachusetts / Boston  
Contact: Department of Continuing Education, Harvard Medical School  
Phone: 617-384-8600, Fax: 617-384-8686  
Email: hms-cme@hms.harvard.edu

5th Congress of the Asia Pacific Initiative on Reproduction  
Apr 4 – 6, 2014  
Australia / Brisbane  
Contact: Malou Guervarra, APM, Kenes Asia  
Phone: 011-65-6292-4710, Fax: 011-65-6292-4721  
Email: aspirecongress@kenes.com

36th Charing Cross Symposium  
Apr 5 – 8, 2014  
United Kingdom / London  
Contact: BIBA? Medical Ltd.  
Phone: 011-44-20-7736-8788, Fax: 011-44-20-7736-8283  
Email: info@cxsymposium.com

9th Annual Musculoskeletal Ultrasound  
Apr 5 – 9, 2014  
United States / California / San Diego  
Contact: Wendy Ryals, Office Manager, IICME  
Phone: 205-467-0290, Fax: 205-467-0195  
Email: wryals@icmeme.net

5th International Congress on Physical Activity and Public Health  
Apr 8 – 11, 2014  
Brazil / Rio de Janeiro  
Contact: CCM Worldwide Medical Congresses  
Phone: 011-55-51-3028-3878, Fax: 011-55-51-3028-3879

8th World Congress for NeuroRehabilitation  
Apr 8 – 12, 2014  
Turkey / Istanbul  
Contact: Serenas Tourism  
Phone: 011-90-312-440-5011, Fax: 011-90-312-441-4563  
Email: info@wcnr2014.org
WHO-Facts Sheet

1. Rabies
2. Echinococcosis
3. Dengue and Severe Dengue

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013, 45 (4): 371 - 376

1. RABIES

Overview
Rabies is a zoonotic disease (a disease that is transmitted to humans from animals) that is caused by a virus. The disease affects domestic and wild animals, and is spread to people through close contact with infectious material, usually saliva, via bites or scratches.

Rabies is present on all continents with the exception of Antarctica, but more than 95% of human deaths occur in Asia and Africa. Once symptoms of the disease develop, rabies is nearly always fatal.

Rabies is a neglected disease of poor and vulnerable populations whose deaths are rarely reported. It occurs mainly in remote rural communities where measures to prevent dog to human transmission have not been implemented. Under-reporting of rabies also prevents mobilization of resources from the international community for the elimination of human dog-mediated rabies.

KEY FACTS
• Rabies occurs in more than 150 countries and territories.
• More than 55,000 people die of rabies every year mostly in Asia and Africa.
• 40% of people who are bitten by suspect rabid animals are children under 15 years of age.
• Dogs are the source of the vast majority of human rabies deaths.
• Wound cleansing and immunization within a few hours after contact with a suspect rabid animal can prevent the onset of rabies and death.

• Every year, more than 15 million people worldwide receive a post-exposure vaccination to prevent the disease – this is estimated to prevent hundreds of thousands of rabies deaths annually.

Symptoms
The incubation period for rabies is typically 1 – 3 months, but may vary from <1 week to >1 year. The initial symptoms of rabies are fever and often pain or an unusual or unexplained tingling, pricking or burning sensation (paraesthesia) at the wound site.

As the virus spreads through the central nervous system, progressive, fatal inflammation of the brain and spinal cord develops.

Two forms of the disease can follow. People with furious rabies exhibit signs of hyperactivity, excited behaviour, hydrophobia and sometimes aerophobia. After a few days, death occurs by cardio-respiratory arrest.

Paralytic rabies accounts for about 30% of the total number of human cases. This form of rabies runs a less dramatic and usually longer course than the furious form. The muscles gradually become paralyzed, starting at the site of the bite or scratch. A coma slowly develops, and eventually death occurs. The paralytic form of rabies is often misdiagnosed, contributing to the under-reporting of the disease.

Diagnosis
No tests are available to diagnose rabies infection in humans before the onset of clinical disease, and unless the rabies-specific signs of hydrophobia or aerophobia are present, the clinical diagnosis may be difficult. Human rabies can be confirmed intra-vitam and post
mortem by various diagnostic techniques aimed at detecting whole virus, viral antigens or nucleic acids in infected tissues (brain, skin, urine or saliva).

Transmission

People are usually infected following a deep bite or scratch by an infected animal. They are the source of infection in all of the estimated 50,000 human rabies deaths annually in Asia and Africa.

Bats are the source of most human rabies deaths in the Americas. Bat rabies has also recently emerged as a public health threat in Australia and western Europe. Human deaths following exposure to foxes, raccoons, skunks, jackals, mongooses and other wild carnivore host species are very rare.

Transmission can also occur when infectious material – usually saliva – comes into direct contact with human mucosa or fresh skin wounds. Human-to-human transmission by bite is theoretically possible but has never been confirmed.

Rarely, rabies may be contracted by inhalation of virus-containing aerosol or via transplantation of an infected organ. Ingestion of raw meat or other tissues from animals infected with rabies is not a source of human infection.

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis (PEP) consists of:

- local treatment of the wound, initiated as soon as possible after exposure;
- a course of potent and effective rabies vaccine that meets WHO recommendations; and
- the administration of rabies immunoglobulin, if indicated.

Effective treatment soon after exposure to rabies can prevent the onset of symptoms and death.

Local treatment of the wound

Removing the rabies virus at the site of the infection by chemical or physical means is an effective means of protection. Therefore, prompt local treatment of all bite wounds and scratches that may be contaminated with rabies virus is important. Recommended first-aid procedures include immediate and thorough flushing and washing of the wound for a minimum of 15 minutes with soap and water, detergent, povidone iodine or other substances that kill the rabies virus.

Recommended PEP

PEP depends on the type of contact with the suspected rabid animal (see table below).

All category II and III exposures assessed as carrying a risk of developing rabies require PEP. This risk is increased if:

- the biting mammal is a known rabies reservoir or vector species;
- the animal looks sick or has an abnormal behaviour;
- a wound or mucous membrane was contaminated by the animal’s saliva;
- the bite was unprovoked; and
- the animal has not been vaccinated.

In developing countries, the vaccination status of the suspected animal alone should not be considered when deciding whether to initiate prophylaxis or not.

Who is most at risk?

Dog rabies potentially threatens over 3 billion people in Asia and Africa. People most at risk live in rural areas where human vaccines and immunoglobulin are not readily available or accessible.

Poor people are at a higher risk, as the average cost of rabies post-exposure prophylaxis after contact with a suspected rabid animal is US$ 40 in Africa and US$ 49 in Asia, where the average daily income is about US$ 1–2 per person.

Although all age groups are susceptible, rabies is most common in children aged under 15. On an average, 40% of post-exposure prophylaxis regimens are given to children aged 5–14 years, and the majority are male.

Anyone in continual, frequent or increased danger of exposure to rabies virus – either by nature of their residence or occupation – is also at risk. Travellers with extensive outdoor exposure in rural, high-risk areas where immediate access to appropriate medical care may be limited should be considered at risk regardless of the duration of their stay. Children living in or visiting rabies-affected areas are at particular risk.

<table>
<thead>
<tr>
<th>Categories of contact with suspect rabid animal</th>
<th>Post-exposure prophylaxis measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I – touching or feeding animals, licks on intact skin</td>
<td>None</td>
</tr>
<tr>
<td>Category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding</td>
<td>Immediate vaccination and local treatment of the wound</td>
</tr>
<tr>
<td>Category III – single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membrane with saliva from licks, contacts with bats</td>
<td>Immediate vaccination and administration of rabies immunoglobulin; local treatment of the wound</td>
</tr>
</tbody>
</table>
Prevention
Eliminating rabies in dogs: Rabies is a vaccine-preventable disease. The most cost-effective strategy for preventing rabies in people is by eliminating rabies in dogs through vaccination. Vaccination of animals (mostly dogs) has reduced the number of human (and animal) rabies cases in several countries, particularly in Latin America. However, recent increases in human rabies deaths in parts of Africa, Asia and Latin America suggest that rabies is re-emerging as a serious public health issue. Preventing human rabies through control of domestic dog rabies is a realistic goal for large parts of Africa and Asia, and is justified financially by the future savings of discontinuing post-exposure prophylaxis for people.

Preventive immunization in people: Safe, effective vaccines can be used for pre-exposure immunization. This is recommended for travellers spending a lot of time outdoors, especially in rural areas, involved in activities such as bicycling, camping, or hiking as well as for long-term travellers and expatriates living in areas with a significant risk of exposure. Pre-exposure immunization is also recommended for people in certain high-risk occupations such as laboratory workers dealing with live rabies virus and other rabies-related viruses (lyssaviruses), and people involved in any activities that might bring them professionally or otherwise into direct contact with bats, carnivores, and other mammals in rabies-affected areas. As children are considered at higher risk because they tend to play with animals, may receive more severe bites, or may not report bites, their immunization could be considered if living in or visiting high risk areas.

2. ECHINOCOCCOSIS

Overview
Human echinococcosis is a zoonotic disease (a disease that is transmitted to humans from animals) that is caused by parasites, namely tapeworms of the genus Echinococcus. Echinococcosis occurs in four forms:
• cystic echinococcosis, also known as hydatid disease or hydatidosis, caused by infection with *Echinococcus granulosus*;
• alveolar echinococcosis, caused by infection with *E. multilocularis*;
• polycystic echinococcosis, caused by infection with *E. vogeli*;
• unicystic echinococcosis, caused by infection with *E. oligarthrus*.

The two most important forms, which are of medical and public health relevance in humans, are cystic echinococcosis and alveolar echinococcosis.

KEY FACTS
• Human echinococcosis is a parasitic disease caused by tapeworms of the genus Echinococcus.
• The two most important forms of the disease in humans are cystic echinococcosis (hydatidosis) and alveolar echinococcosis.
• Humans are infected through ingestion of parasite eggs in contaminated food, water or soil, or through direct contact with animal hosts.
• Echinococcosis is often expensive and complicated to treat, and may require extensive surgery and/or prolonged drug therapy.
• Prevention programs involve deworming of dogs, improved slaughterhouse hygiene, and public education campaigns; vaccination of lambs is currently being evaluated as an additional intervention.
• WHO is working towards the validation of effective cystic echinococcosis control strategies by 2018.

Transmission
The life-cycle of *Echinococcus granulosus* occurs between domestic or wild carnivores, such as dogs, foxes, wolves, jackals, hyenas and cats (definitive hosts), and sheep, goats, cattle, pigs, yaks or other farm animals (intermediate hosts). Cystic echinococcosis is principally maintained in a dog–sheep–dog cycle. Humans are accidental intermediate hosts and become infected through the ingestion of soil, water or food (e.g. vegetables) contaminated with the parasite’s eggs shed in the faeces of the carnivores. Humans can also be infected by hand-to-mouth transfer of eggs after contact with the contaminated fur of a carnivore (most commonly, a dog).

Carnivores become infected when they ingest the organs of intermediate hosts that harbour the larval stages of the parasite (hydatids, or hydatid cysts). In the carnivore, the cysts develop into adult worms and live in the intestines where they produce eggs that are passed in the faeces, contaminating the ground. Intermediate hosts ingest eggs in the contaminated ground, the eggs develop into cysts, and the cycle continues.

Transmission of *E. multilocularis* to humans occurs through ingestion of soil, food or water contaminated with the parasite’s eggs shed in the faeces of foxes and other canids, including domestic dogs and, to a lesser extent, cats. Humans may also become infected by hand-to-mouth transfer of eggs after contact with the contaminated fur of foxes, dogs or cats. Intermediate hosts are small mammals (rodents and lagomorphs).
Signs and symptoms

Human infection with E. granulosus leads to the development of one or more hydatids located mainly in the liver and lungs, and less frequently in the bones, kidneys, spleen, muscles, central nervous system, and eyes.

The asymptomatic incubation period of the disease can last many years until hydatid cysts grow to an extent that triggers clinical signs. Non-specific signs include anorexia, weight loss and weakness. Other signs depend on the location of the hydatid(s) and the pressure exerted on the surrounding tissues.

Abdominal pain, nausea and vomiting are commonly seen when hydatids occur in the liver. If the lung is affected, clinical signs include chronic cough, chest pain and shortness of breath.

Alveolar echinococcosis is characterized by an asymptomatic incubation period of 5 - 15 years and the slow development of a primary tumour-like lesion which is usually located in the liver. Clinical signs include weight loss, abdominal pain, general malaise and signs of hepatic failure.

Larval metastases may spread either to organs adjacent to the liver (e.g. the spleen) or distant locations (lungs, brain) following dissemination of the parasite via the blood and lymphatic system. If left untreated, alveolar echinococcosis is progressive and fatal.

Diagnosis

Ultrasonography is the imaging technique of choice for the diagnosis of both cystic echinococcosis and alveolar echinococcosis. This technique is usually complemented or validated by computed tomography (CT) and/or magnetic resonance imaging (MRI) scans.

Sometimes, cysts can be incidentally discovered by radiography. Specific antibodies are detected by different serological tests and can support diagnosis. Biopsies and ultrasound-guided punctures may also be performed for differential diagnosis of cysts from tumours and abscesses.

Treatment

Both cystic echinococcosis and alveolar echinococcosis are often expensive and complicated to treat, sometimes requiring extensive surgery and/or prolonged drug therapy.

Four options exist for the treatment of cystic echinococcosis:
- percutaneous treatment of the hydatid cysts with the PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique;
- surgery;
- anti-infective drug treatment;
- ‘watch and wait’.

The choice must primarily be based on the ultrasound images of the cyst, following a stage-specific approach, and also on the medical infrastructure and human resources available.

For alveolar echinococcosis, early diagnosis and radical (tumour-like) surgery followed by anti-infective prophylaxis with albendazole remain the key elements. If the lesion is confined, radical surgery offers cure. Unfortunately, in many patients the disease is diagnosed at an advanced stage, and palliative surgery, if carried out without or with incomplete anti-infective treatment, frequently results in relapses.

Health and economic burden

Both cystic echinococcosis and alveolar echinococcosis represent a substantial disease burden. Worldwide, there may be in excess of one million people living with these diseases at any one time. Many of these people will be experiencing severe clinical syndromes which are life-threatening if left untreated. Even with treatment, people often face reduced quality of life.

For cystic echinococcosis, there is an average 2.2% postoperative death rate for surgical patients and about 6.5% of cases relapsing after intervention that require prolonged recovery time. Present estimates suggest that cystic echinococcosis results in the loss of at least one million DALYs (One DALY [disability-adjusted life year] can be thought of as one lost year of “healthy” life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an
advanced age, free of disease and disability) annually and possibly up to three million.

Annual costs associated with cystic echinococcosis are estimated to be 3 billion US dollars for treating cases and losses to the livestock industry.

Alveolar echinococcosis results in the loss of about 650,000 DALYs annually, with most of the disease burden concentrated in western China.

Prevention and control

Cystic echinococcosis is a preventable disease as it involves domestic animal species as definitive and intermediate hosts. Periodic deworming of dogs, improved hygiene in the slaughtering of livestock (including proper destruction of infected offal), and public education campaigns have been found to lower and, in high income countries, prevent transmission and alleviate the burden of human disease.

Vaccination of sheep with an *E. granulosus* recombinant antigen (EG95) offers encouraging prospects for prevention and control. Small-scale EG95 vaccine trials in sheep indicate high efficacy and safety with vaccinated lambs not becoming infected with *E. granulosus*.

A program combining vaccination of lambs, deworming of dogs and culling of older sheep could lead to elimination of cystic echinococcosis disease in humans in less than 10 years.

Alveolar echinococcosis prevention and control is more complex as the cycle involves wild animal species as both definitive and intermediate hosts. Regular deworming of domestic carnivores that have access to wild rodents should help to reduce the risk of infection in humans.

Culling of foxes and unowned free-roaming dogs is applicable but appears to be highly inefficient. Deworming of wild and stray definitive hosts with anthelmintic baits resulted in significant reductions in alveolar echinococcosis prevalence in European and Japanese studies. Sustainability and cost–benefit effectiveness of such campaigns are however controversial.

3. DENGUE AND SEVERE DENGUE

Overview

Dengue is a mosquito-borne infection found in tropical and sub-tropical regions around the world. In recent years, transmission has increased predominantly in urban and semi-urban areas and has become a major international public health concern.

Severe dengue (previously known as Dengue Hemorrhagic Fever) was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Today, severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children in these regions.

There are four distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue.

**KEY FACTS**

- Dengue is a mosquito-borne viral infection.
- The infection causes flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue.
- The global incidence of dengue has grown dramatically in recent decades.
- About half of the world’s population is now at risk.
- Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas.
- Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.
- There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%.
- Dengue prevention and control solely depends on effective vector control measures.

Global burden of dengue

The incidence of dengue has grown dramatically around the world in recent decades. Over 2.5 billion people – over 40% of the world’s population – are now at risk from dengue. WHO currently estimates there may be 50 - 100 million dengue infections worldwide every year.

Before 1970, only nine countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. The American, South-east Asia and the Western Pacific regions are the most seriously affected.

Cases across the Americas, South-east Asia and Western Pacific have exceeded 1.2 million cases in 2008 and over 2.3 million in 2010 (based on official data submitted by Member States). Recently the number of reported cases has continued to increase. In 2010, 1.6 million cases of dengue were reported in the Americas alone, of which 49,000 cases were severe dengue.
Not only is the number of cases increasing as the disease spreads to new areas, but explosive outbreaks are occurring. The threat of a possible outbreak of dengue fever now exists in Europe and local transmission of dengue was reported for the first time in France and Croatia in 2010 and imported cases were detected in three other European countries.

An estimated 500,000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die.

**WHO/TDR/Stammers**

The *Aedes aegypti* mosquito is the primary vector of dengue. The virus is transmitted to humans through the bites of infected female mosquitoes. After virus incubation for 4 – 10 days, an infected mosquito is capable of transmitting the virus for the rest of its life.

Infected humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. Patients who are already infected with the dengue virus can transmit the infection (for 4 - 5 days; maximum 12) via *Aedes* mosquitoes after their first symptoms appear.

The *Aedes aegypti* mosquito lives in urban habitats and breeds mostly in man-made containers. Unlike other mosquitoes *Ae. aegypti* is a daytime feeder; its peak biting periods are early in the morning and in the evening before dusk. Female *Ae. aegypti* bites multiple people during each feeding period.

*Aedes albopictus*, a secondary dengue vector in Asia, has spread to North America and Europe largely due to the international trade in used tyres (a breeding habitat) and other goods (e.g. lucky bamboo). *Ae. albopictus* is highly adaptive and therefore, can survive in cooler temperate regions of Europe. Its spread is due to its tolerance to temperatures below freezing, hibernation, and ability to shelter in microhabitats.

**Characteristics**

Dengue fever is a severe, flu-like illness that affects infants, young children and adults, but seldom causes death.

Dengue should be suspected when a high fever (40 °C/104 °F) is accompanied by two of the following symptoms: severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands or rash. Symptoms usually last for 2 - 7 days, after an incubation period of 4 - 10 days after the bite from an infected mosquito.

Severe dengue is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Warning signs occur 3 - 7 days after the first symptoms in conjunction with a decrease in temperature (below 38 °C/100 °F) and include: severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness, blood in vomit. The next 24 - 48 hours of the critical stage can be lethal; proper medical care is needed to avoid complications and risk of death.

**Treatment**

There is no specific treatment for dengue fever.

For severe dengue, medical care by physicians and nurses experienced with the effects and progression of the disease can save lives – decreasing mortality rates from more than 20% to less than 1%. Maintenance of the patient’s body fluid volume is critical to severe dengue care.

**Immunization**

There is no vaccine to protect against dengue. Developing a vaccine against dengue/severe dengue has been challenging although there has been recent progress in vaccine development. WHO provides technical advice and guidance to countries and private partners to support vaccine research and evaluation. Several candidate vaccines are in various phases of trials.

**WHO/TDR/Crump**

At present, the only method to control or prevent the transmission of dengue virus is to combat vector mosquitoes through:

- preventing mosquitoes from accessing egg-laying habitats by environmental management and modification;
- disposing of solid waste properly and removing artificial man-made habitats;
- covering, emptying and cleaning of domestic water storage containers on a weekly basis;
- applying appropriate insecticides to water storage outdoor containers;
- using of personal household protection such as window screens, long-sleeved clothes, insecticide treated materials, coils and vaporizers;
- improving community participation and mobilization for sustained vector control;
- applying insecticides as space spraying during outbreaks as one of the emergency vector control measures;
- active monitoring and surveillance of vectors should be carried out to determine effectiveness of control interventions.

*For more information contact: WHO Media centre; Telephone: +41 22 791 2222.*
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