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EDITORIAL

REVIEW ARTICLE

ORIGINAL ARTICLES

CASE REPORTS

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KUWAIT MEDICAL JOURNAL (KMJ)
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INTRODUCTION

Formerly known as 'The Journal of the Kuwait Medical Association', the Kuwait Medical Journal (KMJ) was established in the year 1967. It is the official publication of the Kuwait Medical Association and published quarterly and regularly in March, June, September and December.

AIMS AND SCOPE

KMJ aims to publish peer-reviewed manuscripts of international interest. Submissions on clinical, scientific or laboratory investigations of relevance to medicine and health science come within the scope of its publication. Original articles, case reports, brief communications, book reviews, insights and letters to the editor are all considered. Review articles are solicited. Basic medical science articles are published under the section 'Experimental Medicine'.

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Book chapter

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

Weblinks

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

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Editorial

Questioning Keeps Science Alive!

Belle M Hegde
The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*
Manipal University, Manipal India**
The Middlesex Medical School, University of London, UK#
Northern Colorado University, USA##

Kuwait Medical Journal 2013; 45 (3): 189 - 191

"An expert is a person who has made all the mistakes that can be made in a very narrow field."

Niels Bohr

Progress is looking at the same thing from different angles. If we keep looking at something from the same angle that our forefathers were looking at, without questioning them, we would never progress. Change is progress and science is change. We have burnt our fingers in the past without change but do not seem to have learnt our lessons. Galen's idea of the humours as the cause of illnesses was followed without question for nearly 2500 years with disastrous consequences. Bloodletting, purging, and vomiting were the routine for any illness. Bloodletting had killed even President George Washington when applied for his typhoid fever. We ignored the free controlled studies of the poor, who could not pay the doctors, surviving with the help of their immune system[1]. Even today, the poor do not have the ravages of the expensive modern medical quick fixes!

Science can progress only if we try and understand nature. That is called bio-mimicry. One example will suffice. The North American native black bear (*ursidae*) goes into hibernation for months together. They sleep all the while. They do not eat or drink, neither do they pass urine or stool. But when they wake up months later they are healthier than before. Their blood urea nitrogen is so low, creatinine normal; they have fine lean body mass, stronger bones, no thrombotic illnesses and no atherosclerosis, no muscle wasting and bone loss. They are ready for an attack as soon as they wake up or an enemy disturbs them. This will be a nice case for our great nephrologists to study to understand chronic kidney failure treatment better[2]. Instead we make animal models of rats, dogs, pigs, *etc*. and study them with disastrous consequences! Learning from nature is better science.

"Shake a tree full of theorists, and twenty ideas will fall out" says Adam Riess of the Space Telescope Science Institute in Baltimore, USA. Albert Einstein's general and special relativity theories made the astonishing assertion that time, space and matter could be squeezed and stretched like India rubber. "But he might have been a bit too hasty." Some sort of antigravity force - the "dark energy" (Einstein's cosmological term) was needed to make his mathematical formulae work. He was greatly relieved in the 1920s when the theory of expanding Universe was formulated and it was thought that anti-gravity did not exist. The new discovery now has almost confirmed the presence of the "dark energy" as real. Astronomers however, would like to see a few more distant supernovas just to be sure, though.

The best assessment of western science comes from one of its own herd. Paul Feyerabend was the professor of Science philosophy at London School of Economics and later at Chicago and Zurich. In his classic, Against Method, he develops the thesis that "Any ideology, if not counterbalanced by other systems, is detrimental to society and stifles intellectual development. Science's incontrovertible position in society today is due not to any inherent correctness in its methodologies nor to the mass of documented results stemming from these methods, but to mere chance that no serious competitors developed and the generations that followed were educated as such." He argued that "science should have been only a stage in the development of society, a tool to overthrow other ideologies, then itself be overthrown (or at least questioned) by a new system. Instead, science today is taught as incontrovertible fact not unlike the religious facts taught earlier during the then dominant religious ideologies"[3].

"Recently scientists made a powerful case that Einstein's blunder may actually have been another Nobel-worthy prediction," wrote Michael Lemonick in

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the Los Angeles Times on October 11th, 2011. "Tens and billions of years from now, our Milky Way galaxy will find it alone in empty space with its nearest neighbours too far away to see. In the end, the stars will simply wink out - and the Universe will end not with a bang but with the meekest of whimpers, he wrote." Two science teachers Harry Collins and Trevor Pinch, in their book The Golem, so beautifully show how most, if not all, theories of science till to date have not been validated by laboratory experiments unequivocally! They think, and I agree with them, that science is only a Golem, kind of a scarecrow[4].

Let us allow people to think freely and not restrict their thinking by our rigid narrow views of science. Condemning anything that does not fit in with our tunnel vision need not be always right. Wisdom does not belong to scientists only! Some thinking would, per force, be wrong. That does not mean that we should not let people think at all. That would be throwing the bath water out of the window with the baby inside.

Someone wrote the correct history of medicine thus: (author not known)

- 2000 B.C. — Here, eat this root
- 1000 A.D. —That root is heathen, say this prayer
- 1850 A.D. —That prayer is superstition. Here, drink this potion
- 1940 A.D. — That potion is snake oil. Here swallow this pill
- 1985 A.D. — That pill is ineffective. Here, take this antibiotic
- 2000 A.D. — That antibiotic is dangerous. Here, eat this root

More and more scientists are realizing the futility of reductionist science. Dr. Mariette Gerber of the National Institute of Medical Research in France believes that such research methods, which attempt to isolate and examine the effects of a specific nutrient, are too narrowly focussed. In particular, single-agent studies may miss synergistic effects whereby different nutrients interact to lend increased disease fighting benefits. "There is no guarantee that a nutrient like vitamin 'C' exhibits the same behaviour, when consumed alone, as it may when consumed as a tomato," wrote Mariette Gerber. The report from her institute issued in June 2001 states that "Holistic approach to research may provide new insights into science."

I have been writing about this for decades but no one took note. Instead, they ridiculed me! I am sure they would now sit up and take note that it has come out in the World Cancer Research Journal. There is a lot more in this universe than what meets the reductionist scientists' eyes and tools. The following studies would throw a lot more light on what I have been writing and saying so far. I hope deeper thinking and holistic research would unravel many more mysteries of this universe. Human chromosomes contain just about 25,000 human genes but trillions of germ genes, which have become a part of us. The meta-genome thus contains more germ genes than human genes. Evolution, therefore, is more environmental than gene related. Lamarck was, after all, right. Let us get released from Darwin's followers' clutches. Genetic engineering and *in vitro* stem cell research needs to understand the meta-genome which today is not understandable! Studies have shown that the human body can produce its own stem cells *in vivo* when needed - a wonderful healer inside.

Coronary heart disease, claimed to be the "Ace killer" in this century, was linked to life style risk factors such as smoking, high-fat diet, sedentary habits and non-adherence to medical advice. These have had multi-billion dollar business built around them in the last five decades. There have, however, been pointers even as far back as the 1950s that certain behaviour patterns might have a bearing on its incidence too. The latter was mostly swept under the carpet, as it did not generate business dollars! The largest MRFIT study, followed up for as long as 25 years has now shown that the risk factors are not what they were thought to be. While one could alter the "so called" risk factors with drugs *etc*., one cannot change the real risk of precocious death! After spending millions of dollars and working hard for 25 years the researchers found that the MRFIT study has turned out to be a boondoggle. As far as that study goes, there are no real risk factors. MRFIT has been the largest study to date[5].

A wealth of well-designed animal and human studies now has shown the direct link between behaviour and coronary disease. The notable feature is that these behavioural factors predict future coronary heart disease events independently of the influence of life style risk factors that are made much of.

Max Planck feels that consciousness is fundamental. All matter is derived from there. Human body is immaterial - spiritual and mental. Energy and Matter are but the two faces of the same coin! This boils down to mind being the same as the body. Naturally the body suffers when the mind feels bad!

Future interventions should concentrate on these factors more than all the life style risk factors being sold to the gullible public. Two new studies ENRICHD and SADHART are looking into this and their results could alter our management strategies in coronary heart disease.

Newer studies have shown that atherosclerotic blocks (blocks seen in the angiograms) get worse with job stress. Psychosocial factors adversely affect the coronary arteries. Episodes of acute anger could bring on a heart attack. In patients with coronary disease and hostile personality, episodes of anger could bring on left ventricular dysfunction and heart failure. Similarly, in everyday life, intense anger and stressful mental activities could provoke anginal pain and even infarct. Hostility has been discovered to be the "toxic" factor

in human behaviour; it has several components such as aggressive and irritable feelings about others, and hostile thoughts about others. A recent meta-analysis revealed that hostility potential was the best predictor of all-cause mortality! [6-11].

Coupled with this, is the data emerging from many new studies to show how time-honoured interventions like prayer could be of use in sickness. I am sure our "scientists" would be terribly angry at these studies! But remember that anger is the worst risk factor for coronary heart disease, as shown above in many elegant scientific studies. William Harris and his colleagues at the Mid-American Heart Institute and the University of California in San Diego have shown, in an elegant randomized, controlled, prospective study with impeccable study design, that "remote, intercessory (praying for others) prayer was associated with lower Coronary Care Unit scores. These results suggest that prayer might be employed as an adjunct with significant benefit in the management of heart attack patients in the acute stage[12].

The earlier report about Vitamin C and tomato is a good example to show how the whole need not (usually is not) necessarily be the sum total of the bits. Nothing, in my opinion, that is complicated, becomes less complicated when looked at more carefully. On the contrary, new angle of research would bring out hidden facets of the mystery. Progress could, therefore, come from an open mind. Closed minds have no place in serious science. The new Indo-European etymological root of the word science is skei, which simply means to cut into. I feel that the only genuine scientist is an innocent child that explores anything given to it. Grown up scientists, who could keep a child's heart in their adulthood, would be wonderful scientists too! Otherwise science would go after money and prestige, although many claim that scientists do what they do for the passion. Passion makes some of the best observations, but might draw, at times, wretched conclusions.

Money was the driving force in the reductionist sciences even from the very beginning. A glance at the early history of chemistry would show how! Alchemy was the forerunner of the modern chemistry and the former was used to fool all people all the time or to make it big by turning base metals into gold! However, chemistry could go back to its origin in the Khimi region (the land of black earth) on the Nile Delta some 4000 years ago. The first discovery was the finding that minerals when heated could result in the isolation of metals and glasses with useful properties. Those could be sold for profit! This science of chemistry spread gradually from the Arab world to Asia - gaining en route the secrets of gunpowder manufacture from the Chinese. Gunpowder did make lots and lots of money. The foundation of the Nobel Prize owes its existence to gunpowder, right?

I strongly feel that more than the outwardly, intellect-based, objective education, a good scientist needs inwardly, and intuition-based, subjective education as well. The two together, in a balanced fashion, could bring forth real good scientists in the future, who have their own minds rather than the borrowed minds that cannot look at the same object from different angles. Science, like any other human endeavour, should be for the good of humankind. It should make man love man.

"Learn from yesterday, live for today, hope for tomorrow. The important thing is to not stop questioning."

Albert Einstein, Relativity:
The Special and the General Theory

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Review Article

In Vitro Flow Visualization of the Pulmonary Circulation

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ABSTRACT

Flow field of the pulmonary circulation has been investigated by *in vitro* pulsatile and steady flow visualization in simulation models. A couple of counter-rotating secondary flows were symmetric about the centerline in the normal valve. As the pulmonic valve became more stenotic, the two counter-rotating secondary flows in both the left pulmonary arteries (LPA) and right pulmonary arteries (RPA) were no longer symmetric. With a normal Hancock porcine aortic valve inside the extracardiac conduit, the flow of the proximal conduit was spiral, and that of the distal portion was axial. In stenosed Hancock porcine aortic valve loaded conduit, the flow was a continuous spiral. Studies on cavopulmonary connection models showed that energy savings were more evident at the 50:50 right / left pulmonary artery ratio, and the energy losses increased in proportion to total flow rates. A 60º to 90º anastomotic angle between the subclavian artery and the graft of Blalock-Taussig shunt could result in favorable pulmonary artery flow distribution and peak pressure. Simulations in the Norwood circulation model showed that larger shunts rendered an increased cardiac output to the lungs. In order to determine the idealistic cardiac surgical technical conditions, *in vitro* flow visualization study is a primarily useful tool in optimizing the flow and diminishing the energy losses.

KEYWORDS: cardiac surgical procedures, congenital, heart defects, pulmonary circulation, pulsatile flow

INTRODUCTION

Flow visualization is a technique to display the flow structures by a graphical representation of the paths that the tracing particles go and by a measurement of the flow velocities. It is widely used as an important experimental means in the natural sciences especially in hydrodynamics, aerodynamics, and geology, *etc*. Cardiovascular flow visualization experiments started from research on the flow in an evenly straight tube, followed by series studies of the geometric distortion of flow dynamics as regards the curvature, bifurcation, gradual narrowing and stenosis[1,2].

In order to highlight the hemodynamics of the systemic circulation as well as the etiologies of atherosclerosis, *in vitro* simulation models of the arterial segments including the carotid bifurcation, thoracic aorta, coronary arteries, abdominal aorta, common iliac arteries and femoral arteries were established, and the steady and pulsatile flow visualization studies were conducted[3-7]. Shear stress has been evidenced of a predisposing factor in the pathogenesis of the atherosclerotic plaque and formation of the thrombus, in particular when the shear stress is oscillatory[8].

Many congenital heart defects are associated with pulmonary hypertension or stenosis of the main pulmonary artery (MPA), left and right pulmonary artery (LPA and RPA), with pulmonary circulation findings as their principle pathological features[9]. Thus, the pulmonary circulation posed an important question for flow visualization and became one of the goals of an advanced research[10]. *In vitro* investigations as well as computer flow modeling have been increasingly utilized to study the cardiovascular system and, specifically, to examine the hemodynamic effects of a number of surgical operations so as to improve the hemodynamic status of the surgical techniques, reduce complications and enhance outcomes.

MATERIAL AND METHODS

A thorough literature retrieval of the *in vitro* flow visualization of the normal and stenotic pulmonary arteries and right heart surgical models (right ventricular outflow tract conduit, total cavopulmonary connection, Blalock-Taussig shunt and Norwood procedure) was made in MEDLINE database and Google and Highwire Press search engines. The

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secondary references cited in the articles obtained from the MEDLINE and the search engines were screened.

The pulmonary arteries

In vitro pulsatile flow visualization of the MPA, LPA and RPA in a pulmonary valve stenosis model revealed the flow pattern of the stenotic valve was jet-like, of the LPA was helical, which was more severe than of the RPA, while the flow of the MPA was more disturbed and turbulent especially during the peak systole and deceleration phase[11]. Velocity measurements in the main, left and right branches of the pulmonary artery revealed that as the degree of pulmonic stenosis increased, the jet flow created by the stenotic valve hit the distal wall of the LPA, leading to more turbulent flow, and larger secondary flow motion in the LPA compared to the RPA[12]. Normally, there is an axial flow in the pulmonary artery. With varying degrees of valvular stenosis, the axial flow velocity patterns change dramatically in the MPA and the LPA more than in the RPA[13].

In an *in vitro* model of an adult pulmonary artery with varying degrees of valvular pulmonic stenosis, flow fields in the MPA, LPA and RPA of the pulmonary artery model were mapped by using a two-dimensional laser Doppler anemometer (LDA) system. In the normal pulmonic valve model, a pair of counter-rotating secondary flows with a clockwise trajectory along the centerline of the LPA and RPA were observed. However, the two counter-rotating secondary flows in both the LPA and RPA became asymmetric as the pulmonic valve became more stenotic. The secondary flow disturbances became strengthened with increasing degree of valvular stenosis. The increase of the secondary flows in the LPA was greater than in the RPA[14].

Particle flow visualization was used to examine the flow patterns in a series of pulmonary artery models manufactured out of glass. As the valve became stenotic, a jet-like flow was observed in the MPA deflecting away from the centerline and impinge on the roof of the dilated MPA. The deflected jet-like flow was along its radius of curvature with considerable pressure gradient. The secondary flows increased as the LPA and RPA became more stenotic with a more disturbed secondary flow in the LPA than in the RPA. Increasing valvular stenosis was associated with increasing tranvalvular energy loss, whereas, downstream flow was associated with decreasing energy flow[15].

Right ventricular outflow tract (RVOT) conduit

The RVOT and MPA having curvatures with varying radii were mounted in on a one-month lamb pulmonary artery model for the *in vitro* pulsatile flow visualization study[16]. Nine flow conditions were taken including heart rates of 70, 100, and 140 bpm, and cardiac outputs of 1.5, 2.5 and 3.5 l/min with mean pulmonary pressures of 10, 20, and 30 mmHg, respectively. Vessel curvature increase may lead to quicker and further downstream formation of the flow separation region. Earlier forming and quicker growing flow separation regions at higher heart rates were seen, while flow reversal occurred later in the cardiac cycle at lower heart rates. The mean pulmonary pressure was a determination factor influencing the magnitude of reverse flow. An alternative study focused on the normal and diseased pulmonary arteries[17]. In the experiment, a simplified right heart mimic system driven by a permanent magnetic linear motor with a heart rate of 75 beats/min, a cardiac circle of 0.8 s, and an approximate LPA-to-RPA flow ratio of 50:50 was used. The flow visualization of the normal MPA was chiefly an axial flow with a flow separation in the sinuses and low axial flow region close to the branches during the acceleration phase (Fig. 1A), an increased axial components in the MPA during peak systole (Fig. 1B), and an attenuated axial flow in the MPA and an enhanced flow separation in the sinus during the deceleration phase (Fig. 1C). When the extracardiac conduit was loaded with a normally functioning Hancock porcine aortic valve prosthesis at its proximal end, the flow in the right ventricular cavity formed two vortexes, one was clockwise upside, and the other counterclockwise downside. Both vortexes flowed and mingled together at the exit of the right ventricle and entered into the conduit (Fig. 2A). In this condition, the secondary flow in the MPA was stronger than in the normal MPA without the conduit (Fig. 2B). With a normal Hancock porcine aortic valve inside the extracardiac conduit, the flow of the proximal conduit was spiral, and that of the distal portion was axial (Fig. 3A). With a moderately stenosed Hancock porcine aortic valve inside the conduit, the flow was a continuous spiral from the bottom to the top in the conduit with a strengthened force in the acceleration phase (Fig. 3B). A severe regurgitant flow was noted in the non-valved conduit (Fig. 3C). Recently, Dur *et al*[18] reported that 14, 16, 22, and 24 mm conduits for RVOT reconstruction were evaluated using an *in vitro* flow loop comprised of a pulsatile pump with cardiac output of 1.2 - 3.2 l/min. The average pressure drop over the valved conduits was 0.8 ± 1.7 mmHg. Computational fluid dynamics simulations demonstrated the flow skewness toward the major curvature of the conduit based on the pulmonic curvature. *In vitro* evaluation of the bicuspid valved polytetrafluoroethylene conduit coincided well with acceptable early clinical performance (mild insufficiency), with relatively low pressure drop, and intact valve motion independent from the conduit

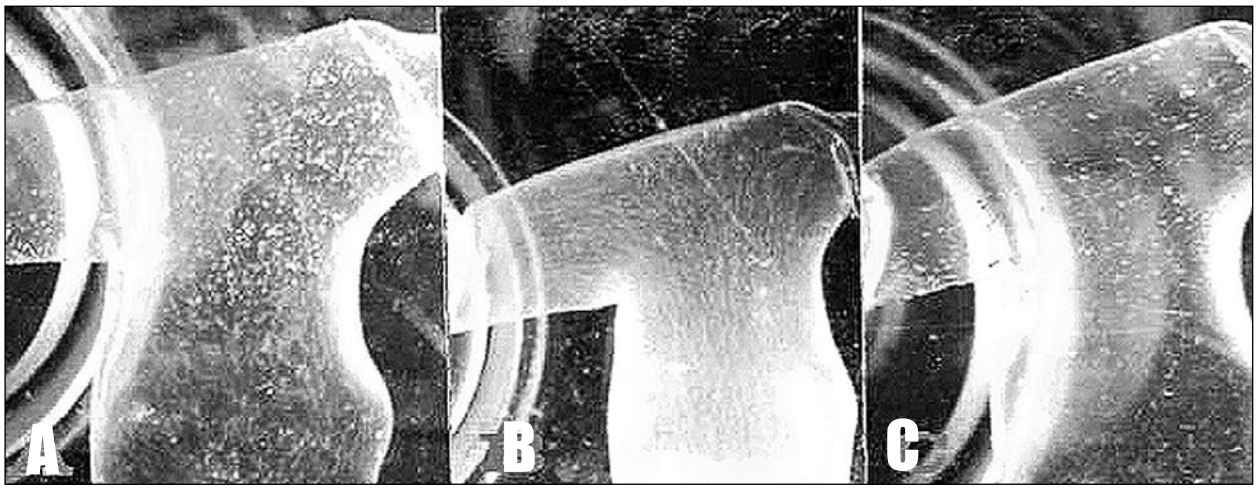

Fig. 1: Pulsatile flow visualization of the main pulmonary artery (MPA) with a normal pulmonary valve: (A) an axial flow with a flow separation in the sinuses and low axial flow region close to the branches during the acceleration phase; (B) an increased axial components in the MPA during the peak systole; and (C) an attenuated axial flow in the MPA and an enhanced flow separation in the sinus during the deceleration phase.

curvature, orientation or valve location, but at the expense of increased diastolic flow regurgitation.

Cavopulmonary connection

Kim *et al*[19] did *in vitro* flow visualization studies on five cavopulmonary connection models: Models I, II and III had the same position as the center of the anastomosis of the inferior vena cava with that of the superior vena cava, but Models IV and V had 10 mm offset between them. As well, the anastomotic junction angles were different (Models I and IV: 90°, Models II and V: 70°, Model III: 45°). These models were then connected to a flow loop for flow visualization

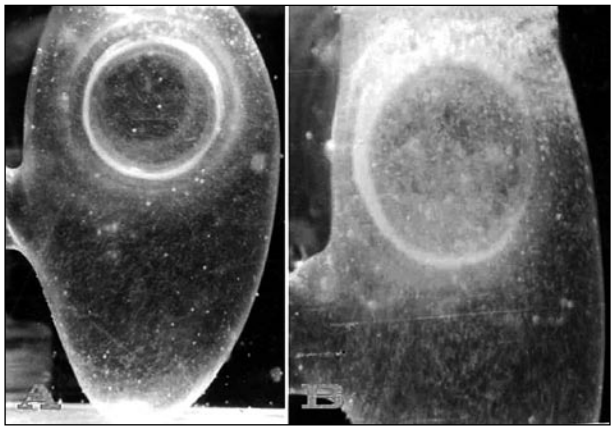

Fig. 2: The extracardiac conduit was loaded with a normally functioning Hancock porcine aortic valve prosthesis at its proximal end, and the flow in the right ventricular cavity formed two vortexes with diverse rotating directions: (A) both vortexes flowed and mingled together at the exit of the right ventricle and entered into the conduit; and (B) the secondary flow in the main pulmonary artery (MPA) was stronger than in the normal MPA without the conduit.

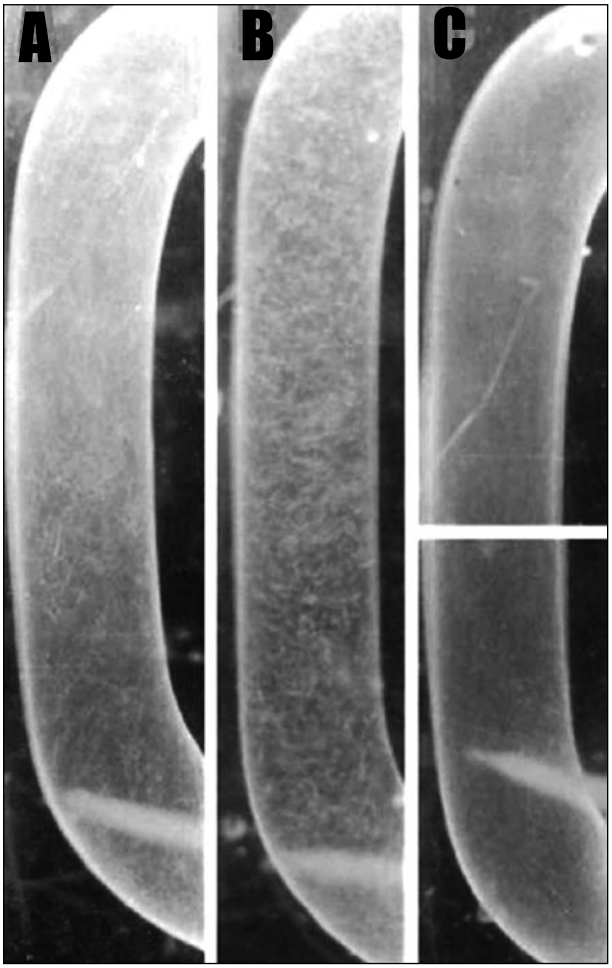

Fig. 3: Flow visualization of the right heart conduits: (A) the flow of the proximal conduit was spiral, and that of the distal portion was axial with a normal Hancock porcine aortic valve inside the extracardiac conduit; (B) the flow was a continuous spiral from the bottom to the top in the conduit with a strengthened force in the acceleration phase with a moderately stenosed Hancock porcine aortic valve inside the conduit; and (C) a severe regurgitant flow was noted in the non-valved conduit.

study. In Model I, no dominant vortex was seen in the central region of the junction, but a large unstable vortex was created in Models II and III. In Models IV and V, a significant stagnation region was created in the middle of the offset region. It also showed that the flow distribution from the inferior and superior venae cavae to the LPA and RPA depends more on the offset of the junction than on the anastomotic junction angle. The flow patterns in the cavopulmonary connection were complex and unsteady with high pressure drops and energy losses. These experimental results were fully supported by de Zelicourt *et al*[20], who found the asymmetric pulmonary diameters and the bulging intraatrial connection can be the underlying causes of flow unsteadiness and unbalanced lung perfusion, and a good agreement was shown between the experimental data of different research groups. Interestingly, the energy loss was always developed near the pulmonary artery wall, in particular the energy loss was even more in the accurate geometry vessel models[21].

When caval flow was matched that to the pulmonary artery, the curved model was an advantageous one, or else the energy losses were large, 56% greater for the curving than the flaring. Fully flaring without caval offset may reduce 45% of energy losses than without flaring, and may reduce 68% of energy losses in flaring with implemented caval offset on all sides than the non-flared model, implicating that caval curving could be optimal only under specific pulmonary flow conditions but not good for all clinical situations, and flaring of the anastomosis may conserve energy and could be an optimal choice of cavopulmonary connection[22]. In the study models, the caval connections were offset through a range of 0.0 to 2.0 diameters by 0.5 superior vena cava diameter increments. Flow ratios were fixed for superior and inferior venae cavae and varied for the RPA and LPA as 70:30, 60:40, 50:50, 40:60 and 30:70 to stimulate varying lung resistance. Pressure measurements and flow visualization were done at steady flows of 2, 4 and 6 l/min to simulate rest and exercise. The energy losses at the 0.0-diameter offset were double the losses of the 1.0 and 1.5 diameters, which had minimal energy losses. This result was attributable to chaotic patterns seen on flow visualization in the 0.0- diameter offset. Energy savings were more evident at the 50:50 RPA / LPA ratio, and energy losses increased in proportion to total flow rates. The results strongly suggest the incorporation of caval offsets in future total cavopulmonary connections[23].

Blalock-Taussig shunt

In vitro studies have proved that the 5 mm shunt was superior to the 4 mm and 3 mm shunts in terms of energy loss and smooth flow[24]. Angles of the anastomosis between the subclavian artery and the polytetrafluoroethylene of 60° to 90° resulted in favorable pulmonary artery flow distribution and the location of the peak pressure[25]. In the angled configuration, the flow in the RPA increased concomitant with increase of the flow through the shunt, while the flow in the LPA decreased at every caval venous pressure[26]. The glass model of the vessels was produced and investigated in a physical model of the cardiovascular system with an artificial ventricular device as the blood pump. Flow rate and hydrostatic pressure were measured at the inlet to and outlets from the glass model and in a few points within the system. Laser flow visualization was also performed. Computer simulations were done using the boundary conditions from the physical model. The opening of the modified Blalock-Taussig shunt changed flow distribution in all branches. A complex flow pattern with large eddies and channeling of the flow in the vicinity of the graft and within it was observed in flow visualization and in computer simulations. Because of that complexity the local measurements of hydrostatic pressure at the vessel wall could not predict the average flow rate. The reversed flow in the graft was observed during the systole. The channeling of the flow and the formation of large eddies may generate high shear stress and modify blood properties[27].

Norwood procedure

In a computational model of the Norwood circulation, influence of shunt diameter, systemic and pulmonary vascular resistance, and heart rate on the cardiovascular dynamics and oxygenation were studied. Simulations showed that larger shunts rendered an increased cardiac output to the lungs, resulting in poorer O_2 delivery, and a pulmonary-to-systemic blood flow ratio of one resulted in optimal O_2 delivery in all physiological states and shunt sizes[28].

DISCUSSION

Abnormal hemodynamics can impact on the pulmonary circulation in some of the pediatric patients with congenital heart defects, and eventually pulmonary hypertension may develop and lead to cardiovascular and pulmonary structural changes[29]. Surgical outcomes of the treatment options apparently depend on the hemodynamic status of the pulmonary circulation system caused by the underlying heart defects and pulmonary disease progression[30]. Therefore, in-depth hemodynamic studies of the normal and abnormal pulmonary circulation including RVOT reconstruction, Fontan procedure, cavopulmonary connection, and Blalock-Taussig anastomoses became demanding in order to find an optimal way of management.

The labeling of the motion track of the fluid was a key issue to be resolved in the early days of flow visualization. The flow is visualized by introducing

dye, smoke or pigment into the flow in the area under investigation[31]. Phillips *et al*[32] obtained optimal flow visualization effect by using amberlite resin particles rather than by pearl essence, and proposed that the candidates for tracing particles should be 0.5 mm in size with neutral floating force. Quartz iodide light and laser lighting were sources of choice for illumination on the flow field[32,33]. Traditionally used in momentum, heat, and mass transfer, dimensionless Reynolds number (Re) is an important parameter for assessing the dynamic similarity of the working fluid of flow visualization. In a close relation to the fluid properties of density and viscosity, it is calculated as proportional to { (inertial force) / (viscous force) }[34]. The Re can be used to determine if flow is laminar, transient or turbulent. The flow is laminar when Re < 2300, transient when 2300 < Re < 4000, and turbulent when Re > 4000[35]. Shear stress is the parallel force impact on an object. By calculation of shear stress, damage of the shear stress to the blood components could be evaluated *in vitro*[36]. *In vitro* flow visualization studies are usually carried out under either steady or pulsatile flow conditions. The experimental conditions of the former is simpler than the latter, but the flow characteristics observed under both the pulsatile and steady flow conditions were almost identical, with a maximum difference between the peak values of less than 4% when testing the artificial heart valves[37].

Yoganathan's research team[38] have contributed significantly to the domain of *in vitro* flow visualization of the pulmonary circulation. In 1990, they reported the flow field characteristics of normal pulmonary artery, and found a broad central flow in the MPA, and an axial flow in both branches in the distal portion but flow disturbances in the bifurcation plane toward the inner wall at the peak systole and during deceleration phase. The flow field of the pulmonary artery with a stenosed pulmonary valve showed narrower jet flow and more severe flow disturbance with a further downstream region impacted by the fluid flow in the LPA than in the RPA[11].

The surgical technique of RVOT reconstruction was firstly applied for the congenital heart defect repair due to anomalous coronary arteries, pulmonary artery discontinuity, or pulmonary atresia in clinical practice in the 1960's[39] aiming at palliative shunting to relieve hypoxemia during infancy and to permit full development of the pulmonary arteries for eventual total correction at a more optimal age. Regarding the conduit materials used, it was suggested that woven Dacron prostheses with a maximal tube caliber may benefit the fate of the conduits[40]. Long-term follow-up of RVOT conduit revealed an early mortality of 6.4% with four explantations due to endocarditis or conduit dilation, and 28.6% due to catheter interventions. Freedom from intervention at one and three years was 71 ± 6% and 53 ± 11%, respectively.

In order to highlight the flow features of the right heart conduit, Yuan *et al*[17] observed the flow field of the right heart system model with various conduits, and found two vortexes with diverse rotating directions in the right ventricular model with a RVOT conduit, whereas the vortexes were not seen in the right ventricular model without a RVOT conduit. The lateral angulation of the conduit and the centrifugal force of the fluid were considered two major factors responsible for the development of the two vortexes inside the ventricle with a right heart conduit. When the conduit valve was stenosed, the flow entering into the conduit became a turbulent jet, which was magnified in an even more distal portion. Meanwhile, a severe regurgitant flow was seen in the entire non-valved conduit. Miyazaki *et al*[41] designed a fan-shaped expanded polytetrafluoroethylene valved conduit and patch with bulging sinuses and used in 48 patients with less than mild regurgitation at 5.6 ~ 63.7 (mean, 20.8) month follow-up.

Atriopulmonary anastomoses at sharp angles may lead to great energy losses as tested by de Leval *et al*[42] and the importance of the streamline flow across the anastomostic site was emphasized. The energy loss of the atriopulmonary connections seemed to be reduced effectively in the 1.0- and 1.5-diameter offsets, which were associated with minimal caval flow interaction, and in a balanced flow split of the pulmonary artery branches[23]. However, flow increase into the lungs is an obvious drawback of the bidirectional cavopulmonary anastomosis and no significant differences occurred in the various models for either the angled or parallel configurations. Studies in the computerized numeric models revealed that the cavopulmonary connection was more efficient when the connection of the vena cava to the pulmonary artery was asymmetrical[43].

The classic Blalock-Taussig shunt is a common systemic-to-pulmonary artery shunt, which involves a direct anastomosis between the transected subclavian artery (or the innominate artery) and the pulmonary artery. The operation was performed on the side opposite the aortic arch to minimize kinking of the subclavian artery as it crosses over the aortic prominence. In addition, the longer innominate artery reduces kinking of the pulmonary artery. The modified Blalock-Taussig shunt is proposed to prevent the mutilating effects of the classic Blalock-Taussig shunt, and that pulmonary artery distortion is less likely than with classic Blalock-Taussig shunt. Excellent patency rates of 90% at age two years have been reported. Rare reported complications include leakage of serous fluid through the polytetrafluoroethylene in the chest and pseudoaneurysm formation, which can cause massive

fatal hemoptysis[44]. The Norwood procedure is the first stage palliative procedure for hypoplastic left heart syndrome. Traditionally the pulmonary circulation has been supplied *via* a modified Blalock-Taussig shunt. No difference was observed in the early hemodynamic profiles including mean arterial blood pressure, markers of pulmonary blood flow (PaO_2, $PaCO_2$ and PaO_2/FiO_2 ratio), or in markers of systemic blood flow (blood lactate and oxygen extraction ratio), or in estimated ratio of pulmonary : systemic blood flow (Qp:Qs) between patients undergoing a right ventricle-pulmonary artery conduit or a Blalock-Taussig shunt[45]. Computer simulations of the hemodynamics revealed that Norwood with a right ventricle-pulmonary artery conduit was more effective than that with a Blalock-Taussig shunt as the shunt size may influence the systemic blood flow and Qp / Qs ratio was higher for the latter[46].

In general, *in vitro* flow visualization provides a non-invasive study approach on the biomedical models. Observation of the flow patterns and measurement of flow velocities may help in the identification of ideal experimental conditions facilitating determination of optimal surgical conditions including pressure, conduit size, curvature, and angulations, *etc.* It is believed that *in vitro* flow visualization would be more and more broadly applied in the future for the examination of novel cardiac surgical techniques.

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Original Article

Urine Xanthine Oxidase and Myeloperoxidase Activity in Pediatric Urinary Tract Infections

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ABSTRACT

Objective: To investigate the relationships between urinary tract infection (UTI), and activity of antioxidant enzymes, xanthine oxidase (XO) and myeloperoxidase (MPO) in urine of children with UTI
Design: Prospective observational study
Setting: Department of Pediatrics, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Turkey
Subjects and Methods: A total of 115 random children admitted to our hospital for urinary symptoms, 61 girls and 54 boys, aged between 2 and 15 years (average 10 years) were included. Study subjects were divided into four groups: Group 1 consisted of 29 pyuria positive and urine culture negative children; Group 2 included 30 children with pyuria and positive urine culture; Group 3 included 26 pyuria negative and urine culture positive children and Group 4 included 30 with pyuria and negative urine culture. Measurement of urine XO and MPO activity were performed spectrophotometrically.
Intervension: Urine samples
Main Outcome Measures: Antioxidant enzyme activity levels in urine were examined in children with urinary tract infection.
Results: Urinary XO activities in Group 2 were significantly higher compared with other groups ($p < 0.001$, $p = 0.001$ and $p < 0.001$, respectively). Significantly different MPO activities were found between Group 1 and Group 2 ($p = 0.007$). However, no significant difference was found between Group 3 and 4.
Conclusion: Significantly increased MPO and XO enzyme activity was found in children with UTI. Measurement of MPO and XO activity may be useful in children with urinary symptoms to diagnose UTI, before obtaining a positive urine culture.

KEYWORDS: urine myeloperoxidase, urinary tract infection, urine xanthine oxidase

INTRODUCTION

Urinary tract infection (UTI) is common in childhood. Signs and symptoms of UTI vary in children and rarely with characteristic presentation such as dysuria, frequency and urgency. Frequently UTI is diagnosed during differential diagnosis of fever. Untreated UTIs in children may cause immediate and long-term morbidity including seizures, sepsis, hypertension and chronic renal failure[1].

Myeloperoxidase (MPO) demonstrates bactericidal activity of neutrophils. MPO catalyzes the conversion of hydrogen peroxide (H_2O_2) to hypohalous acid. It is synthesized in neutrophils and monocytes, packaged in azurophilic granules, and released either into the phagosome or the extracellular space. It is the most plentiful enzyme in the azurophilic granules, and plays a critical role in bacterial killing by neutrophils; for instance MPO-deficient cells need twice the time to kill bacterial pathogens *in vitro*[2-4]. Therefore, MPO is one of the indicators of leukocyte infiltration leading to the formation of free oxygen radicals. The mechanisms in halogenation catalyzed by MPO are formation of large amounts of O_2 initially in the oxygen–dependent MPO-H_2O_2-Cl system and then phagocytosis of bacteria or foreign bodies later on[5].

Xanthine oxidase (XO), a flavoenzyme, participates in purine metabolism and has a role in the release of free radicals and catalyzes the conversion of hypoxanthine to xanthine. XO is an important source for the formation of superoxide radicals[6].

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XO activity increases parallel to the increase in inflammation. In animal experiments, activation of the inflammatory cascade, through many different stimuli including lipopolysaccharide treatment, thermal injury, carcinogen exposure and inflammatory skin diseases, has been found to elevate the levels of XO. In addition, elevated XO activity increases both reactive oxygen species and uric acid generation[7-10].

To the best of our knowledge, biological variation of antioxidant enzymes XO and MPO activity in urine of children with urinary tract infection was not investigated in any previous studies. For this reason, we investigated urinary XO and MPO activity in children with UTI.

SUBJECTS AND METHODS

The present study included 115 children (61 boys, 54 girls; aged 2-15 years, average 10 years) with a suspicion of UTI. The criteria for suspecting UTI are dysuria, frequent urination, abdominal pain, hematuria and fever of unknown origin. These subjects were divided into four groups: Group 1 consisted of 29 pyuria positive and urine culture negative children; Group 2 included 30 children having both pyuria and positive urine culture; Group 3 included 26 children with negative pyuria and positive urine culture; and Group 4 consisted of 30 children with negative results for both pyuria and urine culture (Table 1). UTI diagnosis and physical examination were carried out by an experienced pediatrician (MD).

Ethical approval was obtained from the Institutional Ethics Board of Kahramanmaras Sutcu Imam University Medical Faculty in accordance with the Helsinki Declaration and informed consent was obtained from all patients and their parents.

Table 1: General characteristics of the study group

	Group 1	Group 2	Group 3	Group 4
Patients (n)	29	30	26	30
Boys/girls	13/16	16/14	12/14	17/13
Age (years; mean ± SD)	9.58 ± 3.33	10.1 ± 3.28	8.61 ± 2.99	9.73 ± 3.06

Urine samples

Urine samples were obtained from the patients by midstream catch or with urine bag under strict aseptic technique. These samples were divided into two portions for microbiological and biochemical analysis.

Microbiologic analysis

Urine samples were sent for urine culture. Gram-stained smears of unspun urine were examined for the presence of bacteria and leukocytes, as an indicator of the existence of infection. The urine was cultured quantitatively on MacConkey's and blood agar plates. Concentration of 10^5 and more bacteria per 1 ml of urine was considered as significant criteria for the diagnosis of UTI. When bacteria were isolated in cultures, further identification procedures were conducted.

Microscopic examination of centrifuged urine was performed and if five or more leukocytes were observed in every field this was accepted as pyuria.

Biochemical analysis

Spot urine samples were collected into 75 ml sterile containers (Kayline Plastics, The Barton, South Australia, 5031) which were diluted with 1:50 physiologic serum (0.9% NaCI) for biochemical analysis. XO activity was estimated spectrophotometrically with the method of Prajda and Weber, based on the formation of uric acid from xanthine. This increased the absorbance at 292 nm ($\varepsilon M = 9.2 \pm 103$). One unit of activity was defined as 1 μmol of uric acid formed each minute and data were expressed as U/l[6].

MPO activity was measured spectrophotometrically using 4-aminoantipyrine / phenol which is a substrate for MPO-mediated oxidation by H_2O_2. Absorbance was recorded at 510 nm, and the obtained data were expressed as U/l[11].

For calculating the urine concentration, data were normalized to urine creatinine concentration. Urinary creatinine was measured in spot urine samples by an auto analyzer (Dade Behring Dimension RXL, Germany).

Statistical analysis

The results were analyzed statistically using the Kruskal-Wallis test. Mann-Whitney U test was performed for two independent group comparisons. Statistical analysis was done by Statistical Package for Social Sciences (SPSS®) 11.0 software for Windows. Significance was accepted as $p < 0.05$.

RESULTS

Xanthine oxidase (XO) activity in the urine in Group 2 (pyuria positive, urine culture positive) (0.89 ± 0.42 U/l) was statistically significantly higher than other groups (Group 1 0.32 ± 0.52, Group 3 0.49 ± 0.23 and Group 4 0.10 ± 0.08 U/l; $p < 0.001$, $p = 0.001$ and $p < 0.001$) respectively. The second highest value for XO was found in Group 3 (urine culture positive, pyuria negative group). However, the difference in XO activity between Group 3 and Group 1 was not significant ($p = 0.28$). The difference in XO activity between Group 3 and Group 4 was found to be statistically significant ($p < 0.001$). XO activity was detected as the lowest in Group 4. The XO activities in all groups are presented in Fig. 1.

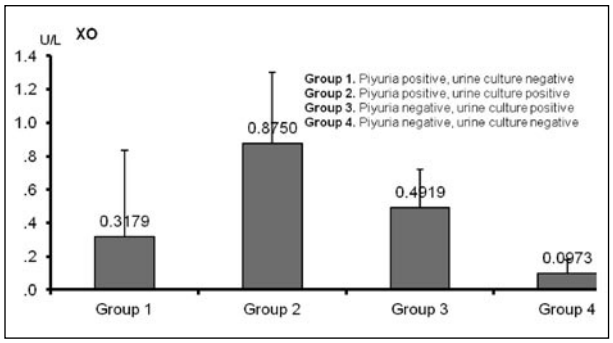

Fig. 1: Urine xanthine oxidase activity in study groups (U/l).

E. coli was the most commonly identified causative agent in urine culture (48.7%). *Enterococci, Klebsiella sp* and Proteus were other bacteria found in diminishing order.

MPO activity in Group 2 (3.57 ± 4.90 U/l) was significantly different when compared with MPO activities in other groups (Group 1: 1.30 ± 1.45, Group 3: 1.18 ± 0.84 and Group 4: 0.50 ± 0.36U/l; p = 0.007, p = 0.006 and p < 0.001) respectively. However, there was no significant difference between Group 3 and Group 4. The MPO activities in Groups 1 - 4 are presented in Fig. 2.

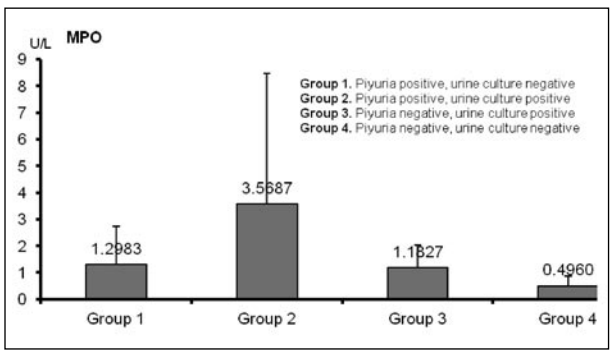

Fig. 2: Urine myeloperoxidase activity in study groups (U/l).

DISCUSSION

Oxidants generated by XO may cause endothelial damage directly or by triggering the accumulation of inflammatory cells[12,13]. Giler *et al* reported that urinary XO activity is related specifically to pathogenic urinary bacteria and the increased activity is detected only in the urine containing bacteria in amounts more than 10^5 / ml. They also pointed out that XO activity increased 2 - 3 folds in UTIs[14]. We also noticed that our cases with urinary tract infection in Group 2 had 3 - 4 times increased activity of XO compared with the other groups. However, XO level was also elevated in group 1 patients who had pyuria. We assume that the elevation in XO activity in Group 1 patients was due to increased inflammatory activity.

MPO enzyme is derived from the primary azurophil granules of neutrophils. Malle *et al* stated that MPO is able to directly react with superoxide and neutralize free radicals formed due to inflammatory response[15]. After conducting various studies of biological variation in sera, Fraser demonstrated that such variation did not depend on age, race, lifestyle and analytical procedures[16,17].

MPO was shown to be an important marker in diverse cases. Since its activity was found very high in patients who developed urinary tract infections after renal transplantation, Steinhoff *et al* claimed that MPO activity may be a new marker in diagnosing urinary tract infection following renal transplantation[18]. Also, Hillegass *et al* found that MPO activity in inflamed kidney was markedly more than that of control tissue[19]. Moreover, the increased activity of MPO was demonstrated in patients with experimental colitis and in diabetic patients who had UTI[20,21].

We found, two - three fold increased activity of MPO in our cases with UTI that was proved by both leukocyturia and positive urine culture. Therefore, urinary MPO can be used in the differential diagnosis of UTI in children.

CONCLUSION

Detection of increased activity of MPO and XO enzymes in children may be useful for the accurate diagnosis of UTI in children while waiting the urinary culture results. The fact that at least 24 - 48 hours are needed for obtaining a positive urine culture, urinary MPO and XO activity may be early markers for UTI in children.

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Original Article

Causes of Re-hospitalization of Patients with Peripheral Arteriosclerosis

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ABSTRACT

Objective: To evaluate readmissions as regards cardiac, peripheral vascular, neurological and renal vascular disorders in patients initially hospitalized for atherosclerosis
Design : Retrospective cohort study of the readmission of patients admitted into the vascular surgery service
Setting: Hospital de Base in São José do Rio Preto, Brazil
Subjects: Nine hundred and ninety-seven patients admitted to the vascular surgery service from 08/03/1999 to 10/09/2008
Interventions: Evaluate the main specialty-wise cause of re-hospitalization of each patient
Main Outcome Measures: Percentages of variables were analyzed using the Fisher exact test with significance defined as a p-value < 0.05
Results: A total of 251 patients initially with arteriosclerosis were readmitted with 10.99%, 29.79%, 6.38% and 52.84% of the re-hospitalizations being associated with neurological, cardiac, renal and vascular diseases, respectively. The in-hospital death rate was higher for cardiac disease than for vascular disease (Fischer exact test: p-value < 0.001).
Conclusion: Mortality is higher in this cohort for admissions for heart disease than for peripheral vascular disease.

KEY WORDS: atherosclerosis, mortality, neurological vascular disease, peripheral vascular disease, renal vascular disease

INTRODUCTION

Peripheral arterial disease (PAD), a major cause of disability, loss of work, and lifestyle changes in the United States, is defined as the obstruction of blood flow into an arterial tree excluding the intracranial or coronary circulations[1]. Atherosclerosis is now recognized as a chronic inflammatory disease occurring within the artery wall and ultimately responsible for myocardial infarction, stroke and peripheral vascular disease[2]. Critical limb ischemia is the end stage of peripheral arterial occlusive disease, with a profound impact on the patient's quality of life[3,4].

Estimates of the prevalence of intermittent claudication vary from 0.6% to nearly 10% depending on the population; the rate increases dramatically with age. Between 20% and 25% of patients will require re-vascularization, while fewer than 5% will progress to critical limb ischemia[5]. The goals of treatment are to prevent the progression of systemic atherosclerosis and its associated morbidity and mortality, to prevent limb loss, and to improve functional capacity of symptomatic patients[6].

Risk factors for atherosclerosis should be monitored beginning in childhood, even in asymptomatic patients. Modifiable factors (*e.g.*, blood pressure, smoking, serum lipids) and non-modifiable factors (*e.g.*, age, family history) are important in the overall assessment[7]. Patients have a good chance to improve the natural course of their disease by changing their lifestyle. In this regard, physical exercise, weight loss and smoking cessation should be mentioned first[8].

Re-vascularization is most beneficial for patients with lifestyle limiting symptoms, acute or chronic limb ischemia, with pain at rest or non-healing ulcers[9]. One study showed that the mortality rates linked to major leg amputation were 5.7% on the surgical ward, 15.7% within the first month after the procedure, 44% within the first year, 50% in the second and 72% in the sixth year after amputation. Additionally, the procedure seriously affected the quality of life of patients[10-12].

Inflammation is now considered to be a critically important determinant of outcome following acute injury to the central nervous system, potentially contributing to the development of secondary injury[13].

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Congestive heart failure, a complex clinical syndrome with impaired cardiac pump function, occurs as a consequence of mechanical deformities (pressure and volume overload), myocardial abnormalities (neurohormonal disorders, myocarditis, cardiomyopathies, inflammation and loss of cardiomyocytes) and rhythmic defects (conduction disturbances, fibrillation and tachycardia)[14].

Chronic kidney disease affects approximately 13% of the U.S. population and is associated with increased risk of cardiovascular complications[15].

Atherosclerosis is now generally accepted as an inflammatory disease, characterized by degenerative changes and extracellular accumulation of lipids and cholesterol. The evolving inflammatory reaction plays an important role in the initiation of atherosclerotic plaques and their destabilization, converting a chronic process into an acute disorder with an ensuing thromboembolism[16].

The aim of this study was to evaluate re-admissions associated with vascular diseases including cardiac, peripheral vascular, neurological and renal disorders in patients initially hospitalized for peripheral arterial disease.

SUBJECTS AND METHODS

In this retrospective cohort study, 997 patients with atherosclerosis according to the International Classification of Diseases (ICD) and admitted to the vascular surgery service of Hospital de Base in São José do Rio Preto from 08/03/1999 to 10/09/2008 were evaluated in a retrospective quantitative study. The reason for each re-admission, whether for heart, peripheral vascular, neurological or renal involvement or other diseases, was noted. Complications in the outpatient clinic were not evaluated. The age, gender and death during treatment were also recorded.

Data were input on an Excel spreadsheet and percentages of variables were analyzed using the Fisher exact test with significance defined as a p-value < 0.05.

The study was approved by the Research Ethics Committee of the institution (no 159/2008 – Protocol no 3190/2008).

RESULTS

A total of 251 patients who were readmitted for vascular diseases at least one time during this period were included in the study. Neurological disease (stroke and occlusion or stenosis of the carotid artery) accounted for 10.99% of the cases, cardiac (angina, myocardial infarction and congestive heart failure) for 29.79%, renal (chronic renal failure) for 6.38% and peripheral vascular disease (aneurysms, blood clots, thrombosis, gangrene and erysipelas) for 52.84% of cases initially hospitalized for atherosclerosis (Table 1). In-hospital mortality was higher for heart disease compared to peripheral vascular disease (Fischer exact test: p-value < 0.001) but no significant differences were identified as regards other diseases. The mean age and gender were important in respect to the reason for subsequent re-admissions (Table 2).

Table 1: The main reasons for hospitalization and in-hospital deaths

Reason for hospitalization	Readmissions n (%)	Deaths n (%)
Neurologic	31 (10.99)	3 (9.6)
Cardiac	84 (29.79)	18 (21.42)*
Renal	18 (6.38)	2 (11.1)
Peripheral vascular	149 (52.84)	5 (3.35)
Total	251 (100.00)	28

* Fisher exact test, P-value <0.001

Women had a higher chance that the first re-admission was related to heart disease (p-value = 0.003). Patients readmitted for renal disease were younger than those re-hospitalized for neurological disease (p-value = 0.0027). The mean age of women was higher than that for men (p-value = 0.03) and the mean age was higher for patients who died during the second re-admission (p-value = 0.04).

Table 2: Mean age and gender of different hospitalizations

Variables	Neurological	Peripheral vascular	Cardiac	Renal
Mean age (years)	67.96	64.29	65	57.16
Men %	54.84	67.78	47.62	88.8
Women %	45.16	32.22	52.38	11.2

The most common cause for the first re-hospitalization was peripheral vascular disease (64.14%), followed by heart (21.91%), neurological (9.16%) and chronic kidney disease (4.38%). Other causes (0.4%) were excluded from the evaluation. Table 3 lists the reasons for all re-admissions.

Table 3: Specialty-wise re-admission rate (as % of total)

Re-admission	Peripheral	Cardiac	Neurological	Renal	Others
1st	64.14	21.91	9.16	4.38	0.40
2nd	63.16	22.37	8.55	5.26	0.66
3rd	60.53	22.37	9.21	3.95	3.95
4th	50.00	30.43	6.52	10.87	2.17
5th	33.33	42.86	9.52	9.52	4.76
6th	44.44	44.44	-	11.11	-
7th	28.57	57.14	-	14.29	-

On comparing the reasons for the first and second re-admissions, a kappa coefficient of 0.43 was obtained. This affirms that the admissions of patients have a moderate agreement, *i.e.*, a moderate tendency to return to hospital for the same type of complaint in the first two re-admissions.

DISCUSSION

This study examined the leading causes of hospital re-admissions of patients with peripheral vascular disease. It did not consider however, the mortality and complications of outpatients or death during the first hospitalization. The objective of the study was to identify the sequence of arterial impairment involving peripheral sites, the heart, neurological sites and the kidneys and death related to these events after a first admission for PAD.

The data show that in the first re-admissions, the trend was to be readmitted for peripheral causes. The second most important reason was involvement of the heart. But as patients were readmitted for more times, there was a tendency that an inversion in respect to the main cause of re-hospitalization takes place with cardiac reasons becoming more common than vascular. About 52.8% of all re-hospitalizations were for peripheral vascular disease and about 29.8% for heart problems; this shows that cardiac involvement is a significant cause in these patients. The main reason of the first hospitalization was PAD which explains why most of these patients in subsequent re-admissions return for this reason. However, from the fifth re-hospitalization, heart problems become the most frequent reason, suggesting a progression of the arterial disease with the involvement of other important organs such as the heart.

After an initial re-hospitalization for kidney disease, re-admissions for renal complaints remained constant for these patients. However, the total number of re-admissions for renal disease increased as patients, initially re-hospitalized for other reasons, evolved with kidney failure.

The true concern however, is hospital mortality of these patients who have peripheral arterial insufficiency with involvement of the respective organs. In this case, mortality related to cardiac re-admissions was higher than for vascular hospitalizations. There were no significant differences in relation to other reasons for hospitalization.

Patients with neurological medical conditions are older than kidney disease patients, but in relation to the other causes of hospitalization the patients have similar ages. This suggests that peripheral arterial disease associated with renal disease is more severe than when associated with neurological diseases. Life expectancy in this geographic region is around 73 years, suggesting that patients with PAD and renal complaints, with a mean age at re-admission of 57.1 years, are the most affected as regards life expectancy.

Considering that these patients are hospitalized with critical ischemia and the evolution of PAD has a significant mortality rate, the prognosis is bad because of the involvement of other vascular structures such as the heart and the kidneys.

One study in the same vascular service reported that progression of chronic PAD is associated with a high procedure-related mortality rate as, major amputations and proximal re-vascularizations increase mortality (in press) as do complications related to infection[17]. Thus, aggravation with progression of PAD and the involvement of other vascular sites is associated with worse prognosis.

CONCLUSION

The re-admission of patients originally with PAD occurred in four major areas linked to arteriosclerosis; peripheral artery, cardiac, renal and neurological. The first re-hospitalizations were, in general, due to PAD, but with the progression of atherosclerosis, other important organs are also affected, in particular, the heart with a resulting high mortality rate.

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Competing interests: The authors declare that they have no competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) in relation to this manuscript.

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Original Article

Statin Use and Risk of Lung Cancer in Males: A Case-Control Study in Taiwan

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ABSTRACT

Objectives: To explore the association between statin use and lung cancer risk in men in Taiwan
Design: A nested case-control study
Setting: Data from the Taiwan National Health Insurance Program, 2000 to 2010
Subjects: Two thousand two hundred and ninety male patients aged 20 years or older with newly diagnosed lung cancer as cases and 9160 male subjects without lung cancer as controls
Main Outcome Measure: The association between statin use and lung cancer risk was estimated
Results: After adjustment for confounders including pulmonary tuberculosis, chronic obstructive pulmonary disease, asbestosis and tobacco use, multivariate logistic regression showed the adjusted odds ratio of lung cancer was 0.79 for the statins-use group (95% CI: 0.68, 0.91), when compared with no use of statins.
Conclusions: We found an association between statin use and lung cancer risk in men in Taiwan.

KEYWORDS: lung cancer, statin

INTRODUCTION

Lung cancer is one of the most frequent and fatal cancers worldwide. Globally, lung cancer was the first most commonly diagnosed cancer (1.61 million new cases, 12.7% of the total cases) and the first most universal cause of cancer death (1.38 million deaths, 18.2% of the total deaths) in 2008[1, 2]. In Taiwan (population, 23 million), lung cancer was the first leading cause of cancer death in 2010, with a mortality rate of 35.4 per 100,000 persons (8194 deaths)[3].

Statins (HMG-CoA reductase inhibitors) are commonly used for managing hypercholesterolemia and prevention of arteriosclerotic cardiovascular disease. So far, controversy exists about the role of statins on the risk of lung cancer. A case-control study by Khurana *et al* in the US showed that statin use for more than six months could decrease the risk of lung cancer by about half (odds ratio = 0.45, 95% CI: 0.42, 0.48)[4]. On the contrary, two case-control studies showed no association between statin use and lung cancer risk[5,6].

To date, little evidence is available about the association between statins and lung cancer risk in men in Taiwan. We conducted a case-control study to explore whether there is an association between statin use and lung cancer risk in men.

SUBJECTS AND METHODS

Data sources

We designed this case-control study using data from the National Health Insurance program in Taiwan. In brief, since March 1, 1995, this program is a universal health insurance system covering more than 99% of 23 million people of Taiwan. The program terms can be referenced from previous studies[7-10].

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Inclusion criteria

In this study, 2290 male subjects with newly diagnosed lung cancer were defined as cases (based on International Classification of Diseases 9th Revision-Clinical Modification, ICD-9 codes 162.X), who were aged 20 years or older on the date of diagnosis from 2000 to 2010. The index date was defined as the date of diagnosis of lung cancer for each case. For each lung cancer case, four male subjects without lung cancer were randomly selected as control subjects from the same dataset, who were frequency matched with age (per 5 years) and index date. In order to reduce confounding effect, subjects with lung cancer or any other cancer (ICD-9 codes 140-208) before index date were excluded.

Co-morbidities potentially associated with lung cancer risk before index date were defined as follows: obesity (ICD-9 codes 278.00 and 278.01), pulmonary tuberculosis (ICD-9 codes 010.X, 011.X, 012.X and 018. X), chronic obstructive pulmonary disease (ICD-9 codes 491.X, 492.X, 493.X and 496.X), pneumoconiosis (ICD-9 codes 500, 502, 503, 504 and 505), asbestosis (ICD-9 codes 501), and tobacco use (ICD-9 codes 305.1). In order to explore the effect of associated medications on potential lung cancer risk, statins and non-statin lipid-lowering drugs were included.

Statistical analysis

The Chi-square test, Fisher's exact test, and t test were used to compare the difference in age, co-morbidities and medications between lung cancer cases and control subjects. Multivariate logistic regression analysis was used to estimate odds ratio (OR) and 95% confidence interval (CI) for lung cancer risk. The probability value (p-value) < 0.05 was considered statistically significant (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Demographic and clinical characteristics of the study population

Table 1 compares the demographic characteristics, co-morbidities, and medications between lung cancer cases and controls. The cases had higher proportions of pulmonary tuberculosis (8.43% Vs 2.71%, $p < 0.0001$), chronic obstructive pulmonary disease (48.5% Vs 27.6%, $p < 0.0001$), asbestosis (0.13% Vs 0.01%, $p < 0.05$), and tobacco use (1.88% Vs 0.55%, $p < 0.0001$). There was no significant difference in mean duration of statin use between cases and controls (months, mean ± SD, 23.4 ± 41.0 Vs 20.5 ± 34.2, $p = 0.21$).

Association between co-morbidities, medications and lung cancer risk

After adjustment for confounders including pulmonary tuberculosis, chronic obstructive pulmonary disease, asbestosis and tobacco use, multivariate logistic regression showed the adjusted OR of lung cancer was 0.79 for the statins-use group (95% CI: 0.68, 0.91), when compared with no use of statins. Pulmonary tuberculosis (OR = 2.42, 95% CI: 1.98, 2.95), chronic obstructive pulmonary disease (OR = 2.30, 95% CI: 2.09, 2.54), asbestosis (OR = 12.2, 95% CI: 1.24, 120.6), and tobacco use (OR = 3.08, 95% CI: 2.02, 4.69) were significantly associated with lung cancer risk (Table 2).

Table 1: Demographic and clinical characteristics of lung cancer cases and control subjects

	Controls N = 9160		Cases N = 2290		
	n	%	n	%	p-value
Age group (years)					
20-39	130	1.4	33	1.4	0.75
40-59	1725	18.8	414	18.1	
60-79	5478	59.8	1367	59.7	
≥ 80	1827	20.0	476	20.8	
Age (Mean and SD, years) *	68.5	11.9	69.2	11.7	< 0.05
Co-morbidities prior to index date					
Obesity**	30	0.33	4	0.17	0.23
Pulmonary tuberculosis	248	2.71	193	8.43	<0.0001
Chronic obstructive pulmonary disease	2528	27.6	1111	48.5	<0.0001
Pneumoconiosis	88	0.96	28	1.22	0.26
Asbestosis**	1	0.01	3	0.13	< 0.05
Tobacco use	50	0.55	43	1.88	<0.0001
Use of medications prior to index date					
Statins	1259	13.7	280	12.2	0.06
Non-statin lipid-lowering drugs	921	10.1	208	9.08	0.16

Chi-square test, * t test and ** Fisher's exact test for comparing male cases and controls

Table 2: Odds ratios and 95% confidence intervals of lung cancer associated with statins use and covariates

Variables	Crude		Adjusted †	
	OR	(95%CI)	OR	(95%CI)
Age (per year)	1.00	(1.00, 1.01)	-	-
Co-morbidities prior to index date (yes Vs no)				
Obesity	0.53	(0.19, 1.51)	-	-
Pulmonary tuberculosis	3.31	(2.73, 4.02)	2.42	(1.98, 2.95)
Chronic obstructive pulmonary disease	2.47	(2.25, 2.72)	2.30	(2.09, 2.54)
Pneumoconiosis	1.28	(0.83, 1.96)	-	-
Asbestosis	12.0	(1.25, 115.5)	12.2	(1.24, 120.6)
Tobacco use	3.49	(2.31, 5.26)	3.08	(2.02, 4.69)
Medications prior to index date (use Vs non-use)				
Statins	0.87	(0.76, 1.00)	0.79	(0.68, 0.91)
Non-statin lipid-lowering drugs	0.89	(0.76, 1.05)	-	-

† Adjusted for pulmonary tuberculosis, chronic obstructive pulmonary disease, asbestosis and tobacco use; CI = confidence interval; OR = odds ratio

DISCUSSION

To date, only few clinical studies have explored the association between statin use and lung cancer risk. A case-control study by Suissa *et al* in the UK showed no association between statin use and lung cancer risk when the effect of time-dependent exposure of statins was taken into account (OR = 0.99, 95%CI: 0.85, 1.16)[5]. Another case-control study by Cheng *et al* in Taiwan showed no association between statin use and the risk of female lung cancer, no matter low or high cumulative defined daily dose[6]. In this present study, an association could be detected between statin use and lung cancer risk in men. Because this is only an observational study, we cannot make an extensive elaboration about our finding. Moreover, further studies are required to clarify the role of statins on the risk of lung cancer.

There may be some inherent limitations in the insurance dataset. In a published study by Wen *et al* in Taiwan, the prevalence of smoking in male adults was 46.8%[11]. Despite the fact that we have included tobacco use based on ICD-9 codes, only 1.88% cases and 0.55% controls were classified as tobacco users. This suggests that information on smoking was not available for a large portion of this study population. This also means that it is not possible to exercise control for the most important confounder of this association. However, this issue is particularly important because people who used statins might have higher cholesterol level and were at higher risk of cardiovascular diseases. Therefore, they might tend to quit smoking more than smokers with normal cholesterol. This might decrease the risk of lung cancer in statin users than in non-users. Thus, including tobacco use as 'ever versus never' would not cover this potential difference in risk.

CONCLUSION

We conclude that an association exists between statin use and lung cancer risk in men in Taiwan.

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Declaration: The first two authors equally contributed to this study.

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Original Article

Prevalence of Hepatitis C Virus Antibodies in Blood Samples Received at the Virology Laboratory of Mubarak Al-Kabeer Hospital, Kuwait

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ABSTRACT

Objectives: There is little information about the prevalence of exposure to Hepatitis C virus (HCV) in Kuwait in recent years. The aim of this study was to identify recent HCV antibody prevalence rates among Kuwaitis and non-Kuwaitis.
Design: Retrospective study
Settings: Serum bank of Virology Unit, Mubarak Al-Kabeer Hospital (MAKH), Kuwait
Subjects: A total of 2483 samples were collected from the serum bank at the MAKH, Virology Unit. Samples from patients with documented liver impairment were excluded. They were collected over a three-year period.
Intervention: Samples were screened for HCV antibodies by HCV version 3.0 (Abbott Laboratories, Germany) or ARCHITECT Anti-HCV (Abbott Laboratories, Germany) for the detection of antibodies against HCV structural and non-structural proteins
Main Outcome Measures: Prevalence rate of HCV antibody in Kuwait
Results: Results showed that the overall HCV antibody prevalence rate was 11% with non-Kuwaitis having a higher prevalence rate (13.5%) as compared to Kuwaitis (1.2%).
Conclusion: This significantly higher HCV antibody prevalence rate among non-Kuwaitis is thought to be mostly due to the relatively high male Egyptian expatriate population in our study group.

KEY WORDS: HCV, Kuwait, prevalence

INTRODUCTION

Hepatitis C virus (HCV) is an enveloped single stranded RNA virus, a member of the *Flaviviridae* family[1]. There are 180 million people who are infected globally with this virus. The general prevalence rate is estimated to be around 3%[1,2]. Out of those infected, 20% will recover spontaneously, while among the remaining 80%, about 20% will develop liver cirrhosis and 20% of those will develop liver cancer[1]. HCV is a major cause of chronic liver disease and mortality worldwide[1,2]. Chronic liver disease, due to HCV, is the main indication for liver transplantation[2]. HCV is mainly transmitted *via* blood or blood product with injection drugs being the most frequent route of transmission in the west[1,2]. However, there are HCV infected cases with unknown source of exposure[1]. A person is labeled as having HCV active infection if HCV antibodies and viral RNA or core antigen are detected in the blood[1,2]. Currently, there is no vaccine available against HCV[1]. Therefore, prevention is mainly by screening of blood and blood product, sterilization of reusable instrument, infection control measures and identification and counseling of at risk population[1]. Treatment of chronic HCV is mainly with peginterferon alfa and ribavirin[1,2]. Duration of treatment depends on the genotype of HCV[1,2].

The economical and social effects of HCV infection on a population are considerable. Screening of at risk population is advisable[1,2]. In 2005, the Kuwait Central Blood Bank (KCBB) estimated the HCV prevalence rate among first-time Arab blood donors in Kuwait to be 2.3%, with a higher exposure rate among non-Kuwaitis (5.4%) as compared to Kuwaitis (0.8%)[3].

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The virology unit at Mubarak Al-Kabeer Hospital (MAKH) is the main clinical virology center in Kuwait and therefore, patients are referred to it from many hospitals and medical centers in the country. Therefore, this provided an opportunity to investigate HCV prevalence rate among patients referred to this center for investigations, other than for viral hepatitis, and to compare the results with those of first-time blood donors.

SUBJECTS AND METHOD

A total of 2483 samples from different adult individuals were collected from the serum bank at the MAKH Virology Unit. Samples from patients with documented liver impairment were excluded. They were collected over a period of three years, between 2007 and 2009. These samples were screened for HCV antibodies. The total number of samples from Kuwaitis (as identified by their Civil ID card) in the study were 500, while, the total number of samples from non-Kuwaitis (as identified by their Civil ID card) were 1983.

AxSYM, HCV version 3.0 (Abbott Laboratories, Germany) or ARCHITECT Anti-HCV (Abbott Laboratories, Germany) was used for the detection of antibodies against HCV structural and non-structural proteins. AxSYM HCV version 3.0 detects antibodies against HCr43, c200, c100-3 and NS5, while the ARCHITECT anti-HCV detects antibodies against HCr43 and c100-3. Once a positive antibody result was detected by either technique the result was confirmed using INNO-LIA HCV score (Innogenetics N. V.). This is a supplementary test to confirm a positive result of the screening procedure, detecting antibodies against core region, the E2 hypervariable region (HVR), the NS3 helicase region, the NS4A, NS4B and the NS5A regions.

Our in-house HCV PCR using QIAgen 1 step RT-PCR kit was performed on 167 of the HCV antibody confirmed positive samples.

SPSS software (version 17.0 for Windows; SPSS, Chicago, IL, USA) was used for all statistical analyses. For categorical variables, χ^2-test or Fisher's exact test was used.

RESULTS

A total of 2483 blood samples were collected over a three year period. The total number of samples from females was 336 (13.5%) and the total number of samples from males was 2147 (86.5%). Five hundred samples were received from Kuwaitis and 1983 samples from non-Kuwaitis. Fifty-one percent (256 / 500) of the Kuwaitis were male and 48.8% (244 / 500) were female. In contrast, 95.4% (1891 / 1983) of non-Kuwaitis were male and 4.6% (92 / 1983) were female (Table 1).

The overall HCV antibody prevalence rate was 11% (274 / 2483) (p = 0.001; 95% CI: 9.84 - 12.35). The prevalence rate among Kuwaitis was 1.2% (6 / 500) as compared with 13.3% (263 / 1983) among non-Kuwaitis (p = 0.001; 95% CI: 10.41 - 14.22). HCV antibody prevalence rate was also calculated as 11.9% (255 / 2147) among males compared with 4.2% (14 / 336) among females (p = 0.001; 95% CI: 7.04 - 12.57). HCV antibody prevalence rate among Kuwaiti males and females was similar at 1.2% (3 / 256) and 1.2% (3 / 244), respectively (p = 0.725; 95% CI: -2.25 - 2.37). In contrast, HCV antibody prevalence rate among non-Kuwaiti males and females was 13.3% (252 / 1891) and 12% (11 / 92), respectively (p = 0.771; 95% CI: -5.74 - 9.01). There were 0.3% (5 / 1891) indeterminate HCV antibody results among non-Kuwaiti males (Table 2). Out of the 274 HCV antibody confirmed positive samples, 167 samples were processed for HCV RNA by PCR. Seventy-three percent (123 / 167) were HCV RNA PCR positive and 26.3% (44 / 167) HCV RNA PCR negative.

Table 1: Baseline characteristics of total samples collected

Gender	Nationality		
	Kuwaiti n (%)	Non-Kuwaiti n (%)	Total n (%)
Male	256	1891	
Within gender	(11.9)	(88.1)	2147 (86.5)
Within nationality	(51.2)	(95.4)	(100)
Female	244	92	
Within gender	(72.6)	(27.4)	336 (13.5)
Within nationality	(48.8)	(4.6)	(100)
Total	500 (100)	1983 (100)	2483 (100)

Table 2: Prevalence of HCV exposure among Kuwaiti sample group and non-Kuwaiti sample group in relation to gender

HCV antibody	Male n (%)	Female n (%)	Total n (%)
Kuwaiti			
Detected	3	3	6
Within gender	(1.2)	(1.2)	(1.2)
Within HCV antibody	(50)	(50)	(100)
Non-Detected	253	241	494
Within gender	(98.8)	(98.8)	(98.8)
Within HCV antibody	(51.2)	(48.8)	(100)
Total	256	244	500
Non-Kuwaiti			
Detected	252	11	263
Within gender	(13.3)	(12)	(13.3)
Within HCV antibody	(95.8)	(4.2)	(100)
Non-Detected	1634	81	1715
Within gender	(86.4)	(88)	(86.5)
Within HCV antibody	(95.3)	(4.7)	(100)
Indeterminate	5	0	5
Within gender	(0.3)	0	(0.3)
Within HCV antibody	(100)	0	(100)
Total	1891	92	1983

DISCUSSION

In this study, we found a significantly higher rate of HCV infection among non-Kuwaitis when compared to Kuwaitis referred to the Virology Unit at MAKH. Almost all of them were Egyptian by nationality. The rate of HCV infection among the Egyptian population is known to be one of the highest in the world and is estimated to be around 20%[4]. Although the study in 2005 on HCV prevalence rate among first time Arab donors[3] is not comparable to this one, there seemed to be an increase in the HCV infection rate in Kuwait from 2.3% to 11%. This is probably due to an increase in the Egyptian expatriate population in Kuwait[5]. The majority of the expatriate population in our study was male Egyptian which represents the current demographics in Kuwait[5]. It may be of interest to note that data from the Public Health Laboratories, Kuwait, estimated the prevalence of HCV infection rate in the population screened in Kuwait to be 8.3% (Trends in Infectious Diseases in Kuwait, March 2005). This figure is closer to the data presented in this study (11%) than that found among first-time blood donors in Kuwait (2.3%). Furthermore, previous studies from our laboratory suggested that prevalence of HCV among patients with chronic liver disease can be as high as 34.5 - 65%[6]. In 2011, our laboratory, conducted a study on common HCV genotypes in Kuwait and found that genotype 4 is by far the most predominant genotype[7].

This high HCV prevalence rate among the expatriate population could not be explained since HCV screening is mandatory for all non-Kuwaitis in order to get their residency application granted. However, HCV antibody screening in Kuwait started in March 1997 and HCV RNA screening by PCR started in March 2011 (Department of Public Health, Kuwait), therefore, this study might have included non-Kuwaiti individuals who have been in Kuwait prior to the implementation of HCV screening or could be due to the possibility of acquiring HCV infection after a negative HCV screening.

CONCLUSION

This study emphasizes the need for a well-designed comprehensive study that will estimate more accurately the total picture of HCV exposure and infection rate among the population in Kuwait.

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Original Article

The Importance of Serum Prostate Specific Antigen Levels in Demonstration of Potency between the Extent and the Degree of Aggressiveness of Inflammation in Patients with Asymptomatic Chronic Prostatitis

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ABSTRACT

Objective: To compare the extent and the degree of aggressiveness of inflammation on the total prostate specific antigen (t-PSA), free PSA (f-PSA), free / t-PSA ratio, and PSA-D values in patients with chronic prostatitis
Design: Retrospective, descriptive study
Setting: Yuksek Ihtisas Training and Research Hospital, Turkey
Subjects: Fifty-five patients with serum t-PSA levels higher than 4 ng/ml and with chronic prostatitis were included
Interventions: Transrectal ultrasound guided biopsy was taken from patients with serum PSA levels higher than 4 ng/ml. Histological sections of the prostatic tissues were scored using the extent and aggressiveness of inflammation seen, on a four point scale from 0 to 4.
Main Outcome Measures: Serum PSA levels in different inflammation grades were compared. Kruskal-Walls variance analysis was used for inter-group assessment.
Results: In both groups scoring; no patient was in grade 0. On the extent of inflammation group scoring; 2, 36, and 17 patients had grade 1, 2, 3, respectively. In this group, unlike the t-PSA values, the extent of inflammation was significant in PSA-D ($p = 0.004$) with a negative correlation in f / t PSA values. On the aggressiveness of inflammation group scoring; 18, 23, and 14 patients had grade 1, 2, 3, respectively. In this group, no statistical difference was found in terms of t-PSA, but statistical differences were monitored in terms of f-PSA, f / t PSA, and PSA-D values ($p = 0.03$, 0.002, 0.01, respectively).
Conclusion: High serum PSA levels in patients with asymptomatic chronic prostatitis may correlate with the degree of extent and aggressiveness of inflammation.

KEYWORDS: asymptomatic inflammation, benign prostatic hyperplasia, prostate specific antigen, prostatitis

INTRODUCTION

Prostatitis is the most frequent urological pathology seen in men aged below 50 years and it is the third most common uropathology in men above 50 years affecting 10 - 14% of male population[1-2]. In the USA, there are more than two million patients diagnosed as prostatitis and this number accounts for 8% of the outpatient applications[2,3]. Despite negative culture results, generally more than one antibiotic therapy is administered in most of the patients[4,5]. Prostate specific antigen (PSA) is the most appropriate serum marker for detecting prostate cancer and is used along with digital rectal examination (DRE)[6]. On the other hand, PSA is not cancer specific, but organ specific; hence, its levels may increase in benign prostatic hyperplasia (BPH), prostatitis, prostatic infarct, acute urinary retention, after prostate biopsy, after cystoscopy, after urethral catheterization, and after transurethral resection of prostate (TURP)[7]. In differential diagnosis of prostate cancer the patients with high PSA levels, particularly the ones with BPH and prostatitis, turns out to be the most difficult group. The PSA levels in 25% of the BPH patients are above 4 ng/ml and prostate biopsy is taken to exclude prostate cancer in this group[8].

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In patients with BPH, the factors that have the most important contribution to elevate PSA are the age and the prostate volume of the patient. Inflammatory prostatitis is commonly seen in histopathological examination of prostate tissue specimens obtained by surgery or biopsy regardless of clinical prostatitis[9]. In this study, we investigated the effects of the extent and the degree of aggressiveness of inflammation on t-PSA, free-PSA (f-PSA), free/total PSA and PSA-D values in asymptomatic chronic prostatitis patients diagnosed by biopsy.

SUBJECTS AND METHODS

The study was conducted in Yuksek Ihtisas Education and Research Hospital in Turkey. A total of 214 patients with elevated PSA levels of > 4 ng/ml underwent 12-core prostate biopsies between June 2008 and August 2009. Histopathological evaluations indicated prostate cancer in 62 patients (28.97%), while BPH was reported in 97 patients (45.33%), and BPH with chronic prostatitis was detected in 55 patients (25.70%). Then 55 patients whose biopsies were reported as chronic prostatitis were included in the study. Transrectal ultrasound-guided biopsy was taken from the patients whose serum PSA levels were higher than 4 ng/ml. The digital rectal examination (DRE) and transrectal ultrasonography (TRUS) findings were recorded. The PSA levels were determined by immunoassay testing using the Roche kit (Roche Diagnostics, Mannheim, Germany). Serum t-PSA and f-PSA levels were separately determined. A serum t-PSA level of 4.0 ng/ml or higher was considered high. For each patient, TRUS was performed in order to evaluate prostate morphology, prostate volume and to perform prostate needle biopsy. The ellipsoid formula was used to calculate the prostatic volume (ellipsoid formula: transverse diameter x anteroposterior diameter x cephalocaudal diameter x 0.52). All patients was administered a sedative, then streched out in the left lateral decubitus position and local anesthesia with 1% lidocaine using a spinal needle was given. Under TRUS guidance an 18-gauge biopsy needle was used to perform the biopsies and 10 core prostate biopsies were taken from each patient.

An enema was administered to each patient in the morning of the procedure. All patients received oral ciprofloxacin 500 mg twice a day for seven days, starting from the night before the biopsy. There was no bacteriuria and pyuria detected prior to the procedure in the urine analysis of any patient. The t-PSA and f-PSA were measured before rectal and urethral manipulations and ejaculations. PSA-D was obtained by dividing the total PSA value to the prostate volume. All biopsy materials were investigated in a blind manner with hematoxylin-eosin staining by a single pathologist working at the same hospital. Biopsy specimens were separately labeled and reviewed by the same pathologist.

Inflammation in the prostatic tissue was scored using a grading system designed by Irani *et al*[10] in terms of the extent and degree of aggressiveness. The extent of inflammation in this grading system was classified as follows: 0 = no inflammatory cells, 1 = dispersed inflammatory cell infiltration inside the stroma without lymphoid nodules, 2 = no merging lymphoid nodules, 3 = large inflammatory fields along with merging of lymphoid cell infiltration. The aggressiveness of inflammation was graded as follows: 0 = no contact between inflammatory cells and glandular epithelium (epithelium cells furnishing acini and ducts from the inside), 1 = contact is present between inflammatory cells and glandular epithelium (minimal epithelial dissociation is present but no destruction), 2 = interstitial inflammation along with distinct but limited glandular epithelium destruction (< 25% of material examined), and 3 = the presence of destruction in glandular epithelium in more than 25% of material examined. The t- PSA, f-PSA, f/t PSA and PSA-D values in groups were compared in terms of extent and agressiveness[10].

The patients who had clinical symptoms due to acute or chronic prostatitis or who had documented data (patients cards) related with prostatitis, carcinoma of the prostate (PCa) or prostatic intraepithelial neoplasia, previous prostate biopsy, radiotherapy, prostate surgery, usage of 5-alpha-reductase inhibitor, acute urinary retention, as well as patients who experienced urinary catheterization were excluded from the study. All patients included into the study experienced the prostate biopsy for the first time. Kruskal-Walls variance analysis was used for inter-group assessment. In data analysis, SPSS 11.5 was used. Statistically, $p < 0.05$ was accepted as significant.

Informed consent of all the patients was obtained. Formal approval was taken from the Ethics committee of the hospital.

RESULTS

A total of 55 patients whose mean age was 64.0 ± 6.21 (51 – 78 years), mean t-PSA was 9.6 ± 12.3 ng/ml (4 - 84.7), f-PSA was 1.77 ± 2.09 ng/ml (0.34 - 18.1) and prostate volumes were 55 ± 34.5 ml (20 – 175 ml) were included in the study. Prostate biopsies of all patients were scored in terms of the extent and the degree of aggressiveness of inflammation. According to the extent scoring; 2 patients had a score of grade 1 (group 1), 36 had grade 2 (group 2), and 17 had grade 3 (group 3). None of the patients had a score of grade 0. While the prostate volumes (p: 0.01) and f-PSA (p: 0.03), f/t PSA (p: 0.006), PSA-D values (p: 0.004)

Table 1: Distribution and characteristics of the patients according to the extent of inflammation

Extent	Age	t-PSA	f-PSA	f/t-PSA	Volume	PSA-D
Grade1						
Mean	69.5	10.78	2.22	0.20	93.5	0.18
SD	2.12	4.46	0.93	0.001	94.04	0.13
N = 2 (3.6%)						
Grade 2						
Mean	64.5	9.34	1.87	0.15	61.5	0.15
SD	6.26	6.05	1.15	0.06	34.06	0.13
N = 36 (65.5%)						
Grade 3						
Mean SD	64	12.7	1.67	0.10	40.0	0.27
N=17 (30.9%)	6.33	20.09	4.13	0.06	18.6	0.54
p-value	0.26	0.93	0.03*	0.006*	0.01*	0.004*

* : $p < 0.05$ is statistically significant

were statistically different among groups in terms of the extent of inflammation, there were no statistical differences between ages (p: 0.26) and t-PSA values (p: 0.93). A negative correlation was observed with the extent of degree of inflammation in terms of f/t PSA. A significant difference was found between groups in terms of PSA-D values (Table 1).

According to the degree of aggressiveness of inflammation; 18, 23, and 14 patients had grade 1, 2, 3, respectively. As in the extent scoring, the aggressiveness score of grade 0 was not seen in any of the patients. While age (p: 0.04), prostate volume (p: 0.02), f-PSA (p: 0.03), f/t PSA (p: 0.002) and PSA-D values (p: 0.01) were statistically different among groups in terms of the aggressiveness of inflammation, there was no statistical difference among t-PSA values (p: 0.56). While a positive correlation was observed with the aggressiveness of inflammation in terms of PSA-D values, a negative correlation was found among groups in terms of f-PSA and f/t-PSA values (Table 2). A positive correlation of 66.9% was found between extent and aggressiveness scores. This relationship was statistically significant ($p < 0.001$) (Fig. 1).

DISCUSSION

PSA is the most useful serum indicator for prostate cancer and is used along with DRE in early diagnosis of prostate cancer[11]. A great number of patients undergo prostate biopsy due to increased PSA levels, but prostate cancer is difficult to detect in most of them because the increased PSA levels may also depend on factors such as BPH, increased prostate volume and

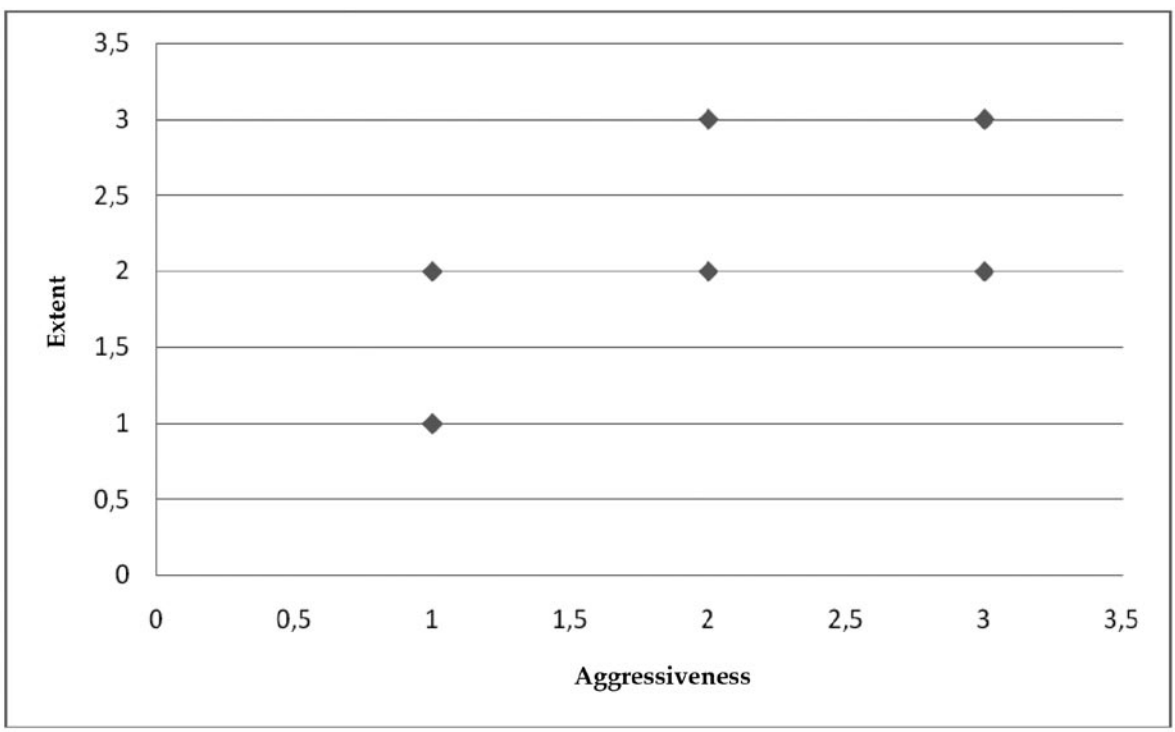

Fig. 1: Punctate distribution scheme of the extent and degree of aggressiveness of inflammation (Spearman correlation test)

Table 2: Distribution and characteristics of the patients according to the aggressiveness of inflammation

Aggressiveness	Age	t-PSA	f-PSA	f/t-PSA	Volume	PSA-D
Grade 1						
Mean	68	12.11	1.95	0.19	72.5	0.14
SD	6.01	6.25	1.41	0.05	46.6	0.06
N = 18 (32.7%)						
Grade 2						
Mean	64	9.61	1.84	0.14	60.0	0.20
SD	6.63	6.72	0.62	0.07	19.23	0.19
N = 23 (41.8%)						
Grade 3						
Mean	63.5	7.17	0.85	0.10	35.0	0.27
SD	4.41	22.06	4.60	0.04	15.8	0.59
N = 14 (25.5%)						
p value	0.04*	0.56	0.03*	0.002*	0.02*	0.01*

*: $p < 0.05$ is statistically significant

age[12,13]. In the diagnosis of non-tumoral situations, in which serum PSA levels are elevated, prostate biopsies may not always necessarily be required. According to National Institutes of Health (NIH) classification system, asymptomatic inflammatory prostatitis is described as the presence of inflammatory cells in prostatic secretions obtained or the presence of histological prostate samples (surgery or biopsy) compatible with NIH category-4 prostatitis[14]. Brawn *et al*[15] had concluded that inflammation causes an increase in serum PSA levels. Irani *et al*[10] has determined a correlation between the destruction of glandular epithelium and PSA as an indicator of the extent and aggressiveness of prostatic inflammation. Simardi *et al* has found that the extent of inflammation correlates with PSA levels[16]. Kwak *et al*[17] has modified the grading method formulated by Irani *et al* and showed that serum PSA levels were not related to either the extent or the degree of aggressiveness of the inflammation. Kandirali, *et al*[18] has classified the type of inflammation as glandular, periglandular, stromal, and perivascular and found that only perivascular inflammation was responsible for serious PSA increase. In another study by Li Gui-zhong *et al*[19] it was found that there was a positive correlation between the extent and degree of aggressiveness of the inflammation. In our study, the inflammation was categorized using the histopathological classification system described by Irani *et al* by a thorough analysis of the extent and degree of aggressiveness of inflammation and thus, the effect of prostatic inflammation on serum PSA levels, f/t PSA and PSA-D was attempted to be specified.

We could not find a significant correlation between the extent and degree of aggressiveness of prostatic inflammation with t-PSA values. It is our assumption that this was due to the fact that there was no homogenity between patients in terms of prostate volumes and ages among the groups. İn this pilot study, although the number of patients in the subgroups was small in the early period results, we suppose that the late period results of the study would provide an important contribution to the literature. In the two studies which were compared, no significant difference was noted between the mean f-PSA values in the patient groups with and without inflammation[20,21]. However, in other studies it was reported that prostatic inflammation reduces the free / total PSA ratio[22-24]. Schatteman *et al*[25] did not find a statistically significant correlation between PSA-D and the extent of inflammation but they showed a significant correlation between PSA-D and the aggressiveness of inflammation. In another study, no correlation could be shown between the extent of inflammation and PSA-D levels[26]. Kwak *et al*[17] were unable to find a correlation between the extent or aggressiveness of inflammation and PSA-D. However, we were able to show that there was a positive correlation between the degree of the extent and aggressiveness of inflammation and PSA-D values.

CONCLUSION

High serum PSA levels in healthy men do not always indicate a malignant disease of the prostate. High levels of serum PSA may also show direct correlation with the extent and aggressiveness of inflammation in patients with asymptomatic chronic prostatitis. This study demonstrates that we should consider any decrease in f/t-PSA and increase in PSA-D values as a strong indication to be associated with the extent and degree of aggressiveness of prostate inflammation. However, this is only a pilot study. It only gives an insight about the factors affecting PSA and related measures. Prospective randomized trials with larger patient groups needs to be carried out in order to be able to make a precise conclusion.

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Declaration: The authors have no conflict of interest to declare.

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Original Article

Comparison of Laparoscopic Vessel Sealing Devices in a Porcine Model: Turkurolap Group Study

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ABSTRACT

Objective: To compare the effectiveness of different electrosurgical devices used during laparoscopic surgery in Turkey
Design: Retrospective study
Setting: Gulhane Military Medical Academy, Experimental laboratory, Turkey
Subject and Methods: Six large White-Landrace-Pietrain pigs, with a mean weight of 63 ± 3.61 kg, were used in 2011.
Interventions: Laparoscopic Vessel Sealing Devices
Main Outcome Measures: Sealing time, demarcation, destruction, sticking, and burning effects of laparoscopic electrosurgical devices were investigated in blood vessels and ureters
Results: Sealing process was significantly shorter with LigaSure Atlas (LS-10 mm and LS-5 mm), Plasma Trissector Gyrus (PTG) and Harmonic Scalpel (HS) in gonadal vessels. The shortest superficial demarcation was provided with HS. The sticking effects of the LS-5 mm and PTG were lower in ureters. The superficial demarcation was shorter with PTG than LS-5 mm, LS-10 mm and HS in ureters.
Conclusions: HS stands out a bit more among devices with electrosurgical effects and fewer side effects to surrounding tissues than other devices in our study. Electrosurgical device should be selected according to necessity of the kind of dissection.

KEY WORDS: electrosurgery, experimental model, laparoscopy, medical devices

INTRODUCTION

Hemostasis has a key role in laparoscopic surgery and affects the course of the operation. The vision of the surgeon is impaired by inadequate or failed hemostasis and surgical dissection becomes difficult. In addition, blood loss which can be life-threatening may occur and the inevitability for open surgery may increase. An adequate hemostasis will increase the success and quality of the laparoscopic operation.

When hemorrhaging occurs, the surgeon must localize the source of the bleeding and injured vessel, and then use the most appropriate and effective method for hemostasis. Hemostasis can be provided by mechanical devices such as sutures, clips, staplers and hemostatic agents as well as fibrin-based and collagen-based hemostatic and / or electrosurgical devices. However, mechanical devices and hemostatic agents are limited to hemostasis in their scope of function, and are not cost-effective in many instances[1].

Rapid development in minimally invasive techniques has driven the need for concomitant advances in instrumentation[2]. Electrosurgical devices provide hemostasis by coagulating, cutting and ablating tissues. Currently available instruments with tissue sensing technology can seal blood vessels with supra-physiologic burst pressures equal to those obtained with surgical clips or ligatures[2,3]. Although the working principle of laparoscopic electrosurgical devices was described well, their basis has been poorly characterized. Laparoscopic surgeons can provide coagulation by reducing tissue tension and also can make the incision by increasing tissue tension with minimal hemostasis with the new generation electrosurgical devices. Therefore, success and usage

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of these devices depends also on training and the skills of surgeons[4].

In this retrospective study, we evaluated effectiveness of new electrosurgical vessel sealing devices; LigaSure Atlas (LS, Valleyleb, Boulder, CO, USA, 5 mm – 10 mm), Plasma Trissector Gyrus (PTG, Gyrus, USA) and Harmonic Scalpel (HS, Ethicon Endosurgery Incorporated, Cincinnati, OH, USA) by comparing the different parameters such as sealing time, demarcation, destruction, sticking, and burning effects in live porcine vessels and ureters.

MATERIAL AND METHODS

All experiments were conducted after obtaining full approval from institutional animal care and use committee that conformed to NIH Guidelines for animal experimentation. Six large White-Landrace-Pie train pigs with a mean weight of 63 ± 3 kg were used and the range of body weight was nearly similar. This retrospective study was performed in 2011, in Gulhane Military Medical Academy experimental laboratory, in Turkey.

Operating and surgical procedures

The pigs were fasted for 12 hours before anesthesia induction. All procedures were undertaken using aseptic precautions. General anesthesia was induced with 5 mg/kg propofol and continued with sevoflurane. They were installed in the dorsal supine position and sloped to the left at an angle of nearly 45°. After umbilical puncture with a 14-gauge Verres needle, pneumoperitoneum was created. The maximum intra-abdominal pressure was 12 - 14 mmHg. Four trocars were used: a 10-mm trocar positioned in the midline, 10 cm below the umbilicus, for introduction of the 30° laparoscope, and three operating trocars (out of which two were 5 mm and one was 10 mm), inserted under visual control of the laparoscope.

At first, the peritoneum was incised with scissors over the convexity of the kidney and reclined medially in order to release the anterior surface of the kidney. The vascular pedicle was dissected carefully without clamping, and the ureter was identified and also dissected. At the same time gonadal vessels were dissected. After dissection of kidney, ureter and gonadal vessels, iliac vessels appeared. Thereafter, dissection was extended carefully down to bifurcation of the aorta. The lateral, posterior, and inferior surfaces of the kidney were dissected in order to mobilize the kidney easily. The electrosurgical vessel sealing devices for ureter and gonadal vessels were applied according the study method. Finally, at the end of the surgical procedure the subjects were deeply anesthetized and sacrificed with a high dose of general anesthetic (halothane).

The following instruments were used with the manufacturer's recommended factory default settings:

LigaSure Atlas

LS is a bipolar electrosurgical device which uses low voltage, high current and also regulates current by permanent measurements of impedance. Elastin and collagen tissues are oppressed and denatured in the ends of the device. LS create cross-link forms by cooling-down when current cuts. In this way, vessels up to 7 mm can be sealed. There must be collagen and elastin in the vessel wall for the vessel sealing process. In this study, we used 5 mm and 10 mm end LS.

Plasma Trissector Gyrus

PTG consists of a combination of energy generator and handle parts and uses high current and low voltage. The energy generator creates packages of steaming tissue, so it provides to stamp tissues by using intermittent bipolar high energy. The intermittent energy provides to cool surrounding tissues and the device alarms and cuts the current when the jaws of the device touch each other forming a short-circuit by the inefficient energy current.

Harmonic Scalpel

HS works by transferring electrical energy to piezoelectric ceramic element which expands and shrinks very quickly and mechanical vibrations are created on one jaw of the device. Ultrasonic energy provides localized heat generation. The cutting process can be performed by vaporizing tissue and hemostasis can be made by coagulation.

Efficiency in Vessel Sealing During Laparoscopy

The effectiveness of vessel sealing in three devices were analyzed for gonadal (2 – 3 mm radius) veins and ureters during laparoscopic procedures. The maximum sealing effects were determined by an automatic signal that indicates the end of the procedure and is created by the device itself. This was accepted as the maximum sealing point. The maximum sealing effect was recorded in seconds with a standard digital stopwatch. The adequacy of the seal was graded as follows: dry seal; oozing that stopped spontaneously; oozing that required additional intervention. We also recorded separately the cases in which the first attempt was unsuccessful and a second attempt had to be performed. The sticking and burning effects on the vessel were analyzed on a four-leveled scale as a qualitative visual analysis by three experienced surgeons (LT, ASG and MA). Adhesion (sticking, adherence) effect was scaled as "0"; no adhesion, "1"; minimal adherence to one or both pedals (jaws) but easily releases the vessel,

Table 1: Sealing effects of energy sources for vessels with a radius of 2 - 3 mm (gonadal vessels) in laparoscopic porcine model

Parameter	Effect	Ligasure		Plasma Trisector	Harmonic Scalpel	p-value
		5 mm	10 mm			
Vessel	Effective (n = 13)	4	4	3	2	0.194
	Ineffective (n = 3)	0	0	1	2	
	Total (n = 16)	4	4	4	4	
Ureter	Effective (n = 21)	6	6	4	5	0.194
	Ineffective (n = 3)	0	0	2	1	
	Total (n = 24)	6	6	6	6	

"2" ; moderate adhesion with a moderate difficulty in releasing the vessels, "3"; relevant difficulty in releasing the vessel. Burning effect was scaled as: "0"; no burning on the tissue, "1"; minimal blackening of the tissue, "2"; moderate blackening of the tissue, "3"; relevant tissue burning. Carbonization and burning are assessed qualitatively. The results were same, so both were recorded as burning effects.

The sealed vessel was taken out of the body through one of the ports and the visible tissue distribution was measured with the help of a magnifying glass in terms of millimeters and recorded. Out of 48 ureters and vessel samples, 16 vessels and 24 ureters were involved in the study from six porcines. All devices were tested in 2 - 3 mm radius vessels and ureters.

Statistical analysis

All statistical analysis was done using SPSS 15.0 statistical package program and the results were evaluated according to significance level at 0.05. Paired samples t-test, and non-parametric Friedman tests were used for evaluating the dependency between categorical variables. The related descriptive statistics, test values and the corresponding p-values are presented in the relevant tables.

RESULTS

The vessels with a radius were 2 - 3 mm (gonadal vessels) and ureters were evaluated for the three devices in our study. The mean outcomes of the evaluation parameters for sealing are summarized in Table 1. The results are given in order of the sealed tissue types. Seals were achieved successfully in all vessel and ureter trials with these electrosurgical devices. There were no significant differences in sealing effects among the devices (Table 1).

2 - 3 mm radius vessels (gonadal vessels)

The sealing process was significantly shorter with LS-10 mm compared with LS-5 mm, PTG and HS in the gonadal vessels as shown in Table 2 ($p = 0.014$, $p = 0.001$, $p = 0.007$ respectively). In vessels, the shortest demarcation and the lowest destruction effects were provided with HS although not statistically significant (Table 2).

There was no significant difference either for qualitative seal assessment (Table 3) or for sticking effects among the electrosurgical devices (Table 4).

Ureter

Seals were achieved successfully for ureteral sealing with the electrosurgical devices (Table 1). There were no significant differences between sealing effects and sealing speed among devices (Table 1).

Sealing time and destruction effects were similar for all devices. However, longer demarcations on ureter were provided with HS than LS-5 mm, LS-10 mm and PTG ($p = 0.035$, $p < 0.001$, $p < 0.001$ respectively). Sticking effects of LS-5 mm and PTG were less than the other devices (Table 4) ($p = 0.002$).

Table 2: Vessel and ureteral sealing time, seal demarcation and destruction clarity

						p-values for pairwise comparisons					
						LS† - 5 mm			LS† - 10 mm		PTG††
Parameters		LS† - 5 mm	LS† - 10 mm	PTG††	HS†††	LS†10	PTG††	HS†††	PTG††	HS†††	HS†††
Sealing time	Vessel	9.25 ± 1.7	5.00 ± 0.00	12.50 ± 1.258	10.50 ± 1.91	0.014*	0.072	0.267	0.001*	0.007*	0.223
(mean. sn¶))	Ureter	7.66 ± 3.93	7.00 ± 0.63	10.50 ± 2.16	7.50 ± 5.2	0.544	0.151	0.745	0.004*	0.823	0.287
Demarcation	Vessel	0.90 ± 0.08	1.55 ± 0.05	1.00 ± 0.08	0.85 ± 0.19	<0.001*	N/A**	0.523	<0.001*	0.002*	0.119
(mean. cm¶¶)	Ureter	0.95 ± 0.2	1.00 ± 0.24	0.58 ± 0.24	1.33 ± 0.19	0.731	0.043*	0.035*	N/A**	<0.001*	<0.001*
Destruction	Vessel	1.12 ± 0.09	1.37 ± 0.09	1.15 ± 0.12	1.00 ± 0.14	N/A**	0.245	0.34	0.002*	0.04*	0.297
(mean. mm¶¶¶)	Ureter	1.76 ± 0.18	1.70 ± 0.3	1.73 ± 0.12	1.75 ± 0.08	0.428	0.470	0.847	0.884	0.741	0.21

¶: Second, ¶¶: centimeter, ¶¶¶: millimeter, *Statistically significant p-value, **N/A: Not assesed, †LS: LigaSure Atlas device, ††PTG: Plasma Trissector, †††HS: Harmonic Scalpel

Table 3: Burning effects of energy sources in laparoscopic porcine model

Parameter	Effect	Ligasure		Plasma Trisector	Harmonic Scalpel	p-value
		5 mm	10 mm			
Vessel	No-burning	2	0	1	1	0.318
	Minimum	2	3	3	3	
	Moderate	0	1	0	0	
	Relevant	0	0	0	0	
	Total (n = 16)	4	4	4	4	
Ureter	No-burning	3	0	3	1	0.261
	Minimum	3	6	1	4	
	Moderate	0	0	2	1	
	Relevant	0	0	0	0	
	Total (n = 24)	6	6	6	6	

Although there was no significant thermal destruction (coagulation necrosis) of the seal among devices in ureters, the shortest thermal destruction was provided with HS in vessels without statistical significance (Table 2).

DISCUSSION

Electrosurgery is a commonly used technique in laparoscopic surgery. Electrosurgical devices are being used in many medical subdisciplines in order to coagulate, cut, and ablate tissues and to provide hemostasis[4].

Hemostasis is very important for the course of the laparoscopic surgery. McGinnis *et al* reported using mechanical devices such as suturing, clips and laparoscopic staplers in laparoscopy[5]. The use of these devices in laparoscopic surgery is time-consuming[6,7]. Additionally, clips occupy a lot of space. Furthermore, clips and staplers are not cost-effective for hemostasis in small vessels[8,9]. Suturing is mostly used in urologic laparoscopic surgeries when ligating dorsal vessel complex in laparoscopic radical prostatectomy and for approximating tissues together in laparoscopic partial nephrectomy[10]. Although suturing is a basic technique for hemostasis, it is difficult to perform when surgeons have less experience in laparoscopic surgery and/or the space available is narrow. Timsit *et al* described the use of polyglactin tie added to clips to control arterial bleeding[11]. Some devices such as Endo GIATM can be used for tying in laparoscopic surgery but they are expensive and require more experience to use[12].

There are other hemostatic agents which are used in laparoscopic surgery besides mechanical and electrosurgical devices[13]. Fibrin-based, collagen-based, hydragel, glutaraldehyde-based, methyl cellulose-based and Ankaferd bloodstopper® were described earlier[14-19]. All of these hemostatic agents may provide significant advantages for hemostasis in tissues which have intensive blood supply and wide surfaces such as renal parenchyma[18,19]. It should be kept in mind that hemostatic agents cannot stop bleeding. They only help to provide hemostasis by reducing bleeding.

The diversity and efficiency of electrosurgical devices has greatly improved in recent years due to advances in technoogy. Now electrosurgical devices are the most commonly used devices in laparoscopic surgery for hemostasis[20].

The term electrosurgery is used to describe the passage of high-frequency electrical current through different tissues to create a desired clinical tissue

Table 4: Sticking effects of energy sources in laparosccopic porcine model

Parameter	Effect	Ligasure		Plasma Trisector	Harmonic Scalpel	p-value
		5 mm	10 mm			
Vessel	No-sticking	2	0	0	3	0.137
	Minimum	1	3	3	1	
	Moderate	1	1	1	0	
	Relevant	0	0	0	0	
	Total (n = 16)	4	4	4	4	
Ureter	No-sticking	4	0	4	0	0.002*
	Minimum	2	3	1	2	
	Moderate	0	1	1	4	
	Relevant	0	2	0	0	
	Total (n = 24)	6	6	6	6	

*Statistically significant parameter

effect[21]. Electrosurgical devices generate electrical energy, which is able to both cut the target tissue and coagulate vessels, effecting hemostasis and thereby reduce postoperative bleeding compared to standard dissection methods[22]. Additionally, laparoscopic electrosurgical devices are commonly used to cauterize the tissue and seal the vessels[23].

In our study, we compared the vessel and ureter sealing effects of different electrosurgical devices. Although Harold *et al*, Lamberton *et al*, Landman *et al* and Campbell *et al* in their report stated that LS (5 mm and 10 mm) was more effective than PTG and HS for vessel sealing, in our study all of them had no statistically significant difference on sealing capacity in porcine model for vessels as well as for ureters[22-25]. Additionally, there are some differences among them in terms of their demarcations, sealing time and tissue destructions as shown in Table 2.

Moreover, our results revealed that sealing time was shorter with 10 mm LS, like the report of Landman *et al* and in contrast with the report of Lamberton *et al*[23,24]. Additionally, Lamberton *et al* reported that HS and PTG were faster than LS-10 mm for sealing vessels in bovine models[24]. Although we used the same devices as Lamberton *et al*, LS-10 mm was faster than HS and PTG in our study. These results may be due to the usage of vessels with 2-3 mm radius in our study but Lamberton *et al* used it for 5 mm vessels. If LS-10 mm was faster than other device for 2-3 mm radius vessels and if LS-10 mm was more effective than PTG and HS for vessel sealing as reported by Harold *et al*, Lamberton *et al*, Landman *et al* and Campbell *et al*, LS-10 mm may be well-suited for tissues like perirenal fatty and/or fascial tissues in which the vessels are not more than 2 - 3 mm in radius and faster dissection is needed and preferred[22-25].

As Lamberton *et al* reported, our study revealed that HS provided statistically shorter demarcation and destruction for vessels. According to these results, HS may be a safe choice for hemostasis with fewer side effects to surrounding tissues than other devices. Moreover HS should be preferred for the coagulation in 2 - 3 mm radius vessels or lymphatic tissues which are very close to major arteries in the hilar area. This is not only because of less thermal spread of HS as Landman *et al* reported, but also because of its optimal ergonomic design[23]. Tip design of HS allows the surgeon to use it in close proximity to heat-sensitive structures by precisely delivering current through the tip of the instrument. Thus, HS can retain the coagulation effect up to the tip of the device. There is decreased coagulation effect in 2 - 3 mm end of the tip of the LS-5 mm, LS-10 mm and PTG, because of their design (Fig. 1).

Ureter can be sealed in laparoscopic simple nephrectomy, radical nephrectomy and radical nephroureterectomy. Using electrosurgical devices for ureter sealing may reduce usage of clips. Additionally, PTG provided statistically significant demarcation in ureters but there were no significant differences for destruction of ureter among the devices. Long demarcation demonstrates efficiency of the device in

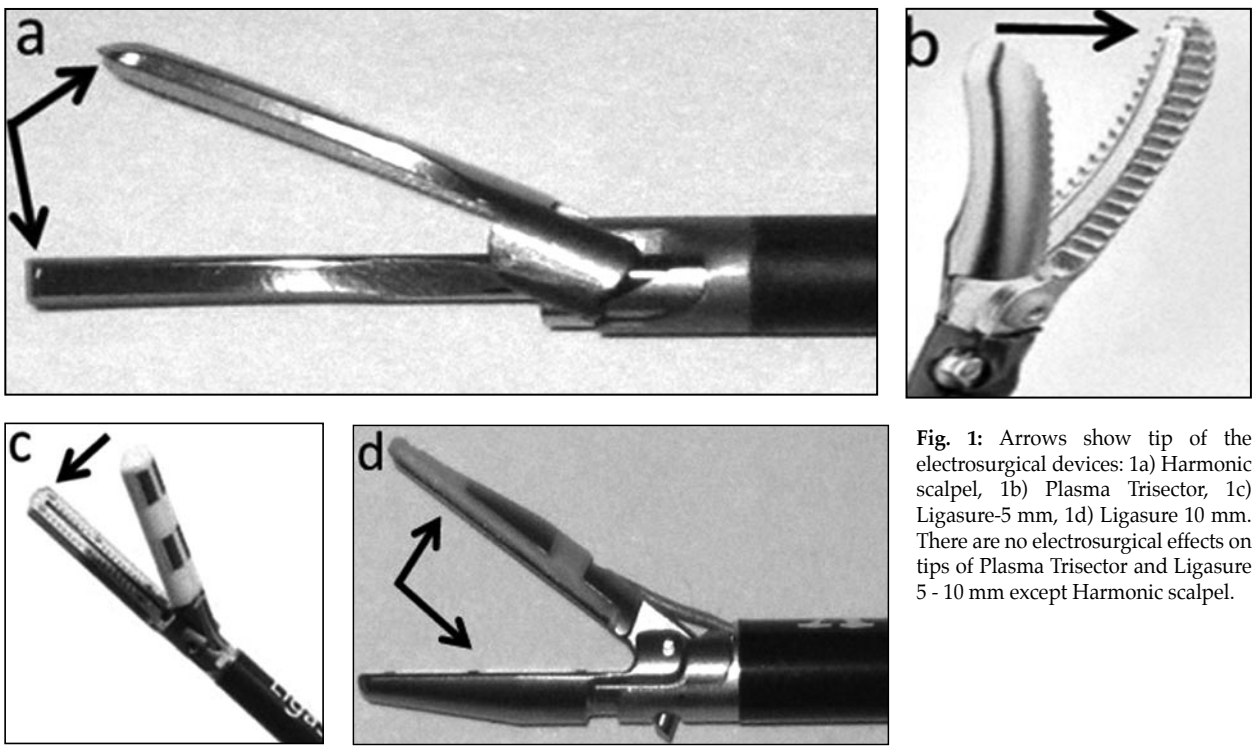

Fig. 1: Arrows show tip of the electrosurgical devices: 1a) Harmonic scalpel, 1b) Plasma Trisector, 1c) Ligasure-5 mm, 1d) Ligasure 10 mm. There are no electrosurgical effects on tips of Plasma Trisector and Ligasure 5 - 10 mm except Harmonic scalpel.

ureter sealing. Therefore, PTG may be more effective than other devices in ureters. However, there is not enough evidence about the effects of electrosurgical devices on ureter in literature. That is why, our results are unique.

Electrosurgical devices provide hemostasis by thermal tissue injury. Collagen melts at 45 ºC, and proteins are denatured at 60 ºC. Burning begins at 80 ºC, tissue dries and contracts. Cell injury occurs at 100 ºC. Protein oxidation occurs at 120 ºC. Burning effects may become important for nerve sparing laparoscopic radical prostatectomy. Although Ong *et al* and Carlander *et al* demonstrated neurovascular bundle injury with electrosurgical devices we have to be careful when performing nerve sparing laparoscopic radical prostatectomy with electrosurgical devices[26,27]. None of the three devices are superior to each other for burning effects in our results.

Sticking effect is an unwanted side-effect in laparoscopic operations because the device needs cleaning when tissues adhere to the device and this is time-consuming. Additionally, the effect of the device may be reduced. There was no significant difference in burning effects of all devices for vessels and ureters as well as for sticking effect for vessels. Sticking effect of LS-5 mm and PTG was statistically significantly lower than other devices in ureter. This result may support the clear effectiveness of LS-5 mm in vessels and ureters.

According to our results, the new laparoscopic electrosurgical devices have nearly the same effects in hemostasis in this experimental porcine model. Although these devices have some minimal differences among them, they can be used in nephrectomy, prostatectomy and nephroureterectomy safely[4,28,29]. Minimal differences in tissue effects may be used for hemostasis in particular tissues. Briefly LS-10 mm affected vessels and ureters in a short time but PTG has been more effective in ureters with shortest demarcation in our study. Additionally, as a clinical observation, LS-5 mm was more effective in sealing of renal pedicles whereas other devices were not so effective in our experimental porcine model. This may have been caused by burst pressure of a renal pedicle.

There are some limitations in this study. We have some missing data regarding vessel sealing in renal pedicles. So we compared the data of 2 - 3 mm vessel sealing. Tissues of 16 vessels and 24 ureters were included in the study. Standard monopolar and bipolar electrocautery may also be included in the study, but they have been well-described before and we wnated to compare new electrosurgical devices[30]. Additionally, the cost-effectiveness of each device should also be considered. There is no doubt that the prices of these devices will go down as technology develops. The bipolar electrosurgical device which is not included in our study seems to be the cheapest and has the longest life among devices. A further advantage of the bipolar device is that it is reusable[31].

CONCLUSIONS

The usage patterns and characteristics of the devices which are used should be well-known before surgery. Although the effects of all electrosurgical devices were similar, there were a few differences among them. Furthermore, HS can be preferred for dissection at a hilar area because of increased effectiveness on thin vessels and a less thermal spread. In addition, PTG may be more effective than other devices in ureters in porcine model. Although we have found similar effectiveness with the tested devices on the vessels, our experimental study showed that effectiveness of each device will be increased when they are used in accordance with recommendations and for appropriate tissues. Furthermore, HS stands out more among devices with the electrosurgical sealing effect on 2-3 mm radius vessels with fewer side-effects to surrounding tissues than other devices in our study. However, well-designed, standardized and large data-based studies are needed for developing new electrosurgical devices for hemostasis.

ACKNOWLEDGMENT

Conflict of interest: There is no conflict of interest.

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Case Report

Mesenteric Cystic Lymphangioma Complicated by Intestinal Volvulus: A Case Report

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ABSTRACT

Intestinal volvulus is an abdominal pathology which can affect the pediatric age group and may lead to catastrophic intestinal loss. The most common cause is malrotation but other etiologies are also reported. We report a case of intestinal volvulus in which the initial cause was mesenteric cystic lymphangioma.

KEY WORDS: abdominal lesion, cystic tumor, mesentery, volvulus

INTRODUCTION

Mesenteric cystic lymphangiomas (MCLs) are rare benign cystic tumors, most often seen in pediatric patients[1]. The clinical presentation is diverse, ranging from an incidentally discovered abdominal cyst to symptoms of acute abdomen[2]. MCLs are mostly congenital with male preponderance but acquired cases due to lymphatic obstruction were also documented[3]. Cystic mesenteric lymphangioma differs from mesenteric cysts in location, histological feature, and recurrence rate[4]. Also, it is reported to be more invasive and symptomatic[5]. In this report we present a case with mesenteric cystic lymphangioma (MCL) presenting as intestinal volvulus.

CASE REPORT

A four-year old child with no previous medical history presented to our emergency room (ER) with history of abdominal pain for three days and biliary vomiting and constipation for one day. The patient had previous history of a similar attack one year ago treated conservatively in a local hospital. Also, the mother reported frequent transient bouts of pain and vomiting of short duration and spontaneous relief throughout the last year.

Generally, the patient was hemodynamically stable, mildly dehydrated, malnourished and in pain. Upper abdominal distension was evident with mild tenderness and exaggerated intestinal sounds. The rectum was empty with anterior rectal tenderness. The nasogastric aspirate was biliary.

Hematological and biochemical data were within normal limits except for mild leucocytosis (15×10^9/l) and hypokalemia (3.4 mmol/l). A plain abdominal X-ray revealed fluid levels and dilated jejunal loops in upper left abdomen. On CT scan with IV contrast of abdomen, beside evidence of intestinal obstruction, the whirl sign of volvulus was present (Fig. 1). Also, a unilocular cystic mass impacted in the right side of pelvis was documented (Fig. 2). The cystic content was homogenous without septation.

After preparation and correction of fluid and electrolyte deficits, abdominal exploration was done. A volvulus was found at the base of the mesentery (Fig. 3) with congested vessels and edema. The volvulus was corrected in an anticlockwise direction and no intestinal ischemia was noted. Correction of volvulus revealed a cystic mass 6 × 5 × 5 cm in size engaged in the pelvis and attached to the ileal loop (Fig. 4). This mass was found to be the largest of about five cysts incorporated in mesentery and close to the mesenteric side of the affected loop. The cysts were variable in size, thickness of wall and color of content. There were no anatomical signs of malrotation and dudeno-jejunal junction was found left to vertebrae. Resection of the intestinal part carrying the cysts was done (Fig. 5)

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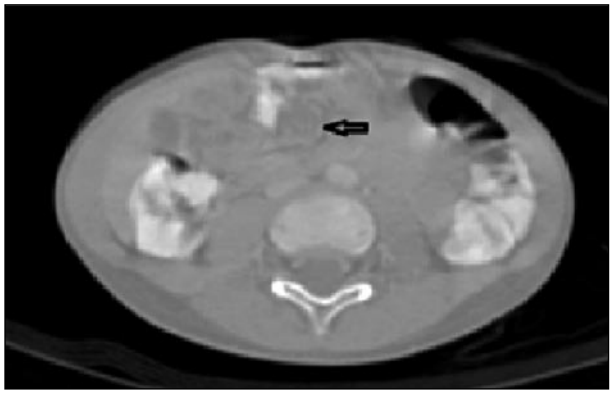

Fig.1: CT scan of abdomen with whirl sign (arrow)

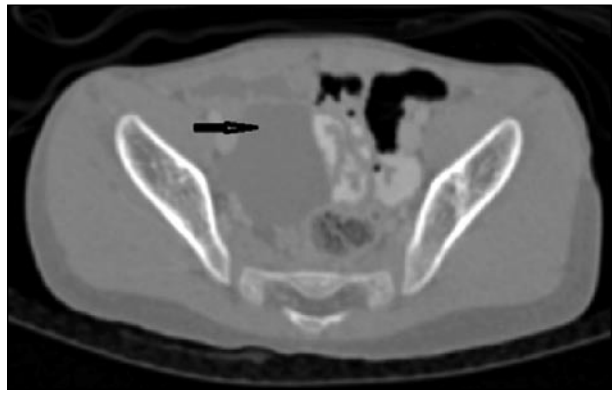

Fig.2: CT scan of pelvis showing cystic lymphangioma impacted in the right side of pelvis (arrow)

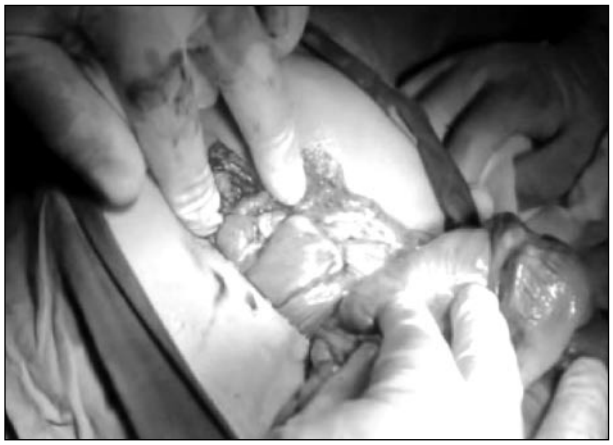

Fig.3: Volvulus of the intestine

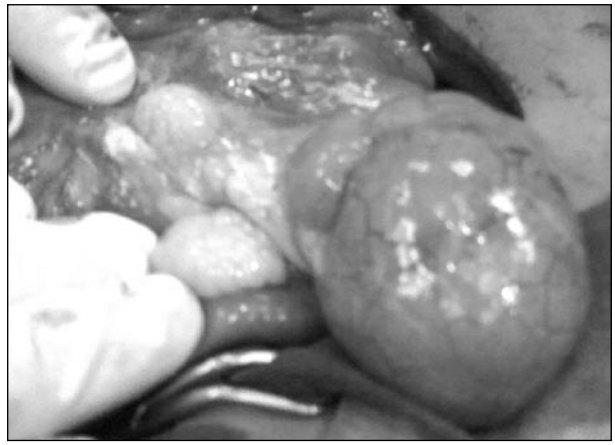

Fig.4: Multiple lymphatic cysts with the large one (arrow) which caused volvulus

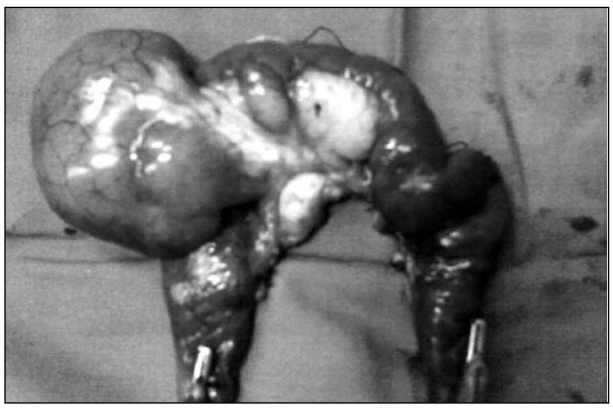

Fig.5: The resected intestinal segment carrying lymphatic cysts

with primary anastomosis. Postoperative course was uneventful with smooth recovery and resumption of normal oral intake and normal bowel movement in five days. The histopathology report was cystic lymphangiomas. Follow-up for one year was smooth and review CT scan of abdomen after one year did not reveal recurrence of cysts.

DISCUSSION

MCLs occur at all ages, though most (65%) are present at birth and nearly 60% are diagnosed before the fifth year of life[6]. They are rare, with fewer than 200 detailed reports published in the English-language literature[7]. Cystic lymphangiomas can be located in any part of the body except the brain[8]. They are most frequently single, but multiple lymphangiomatous cysts can affect a single organ, predominantly the spleen causing massive splenomegaly[9], a single region such as the abdominal or retroperitoneal cavity[10] or the disease can be generalized[11]. In the abdomen, less than 1% affects the mesentery (MCL)[12], while other abdominal sites include esophagus, diaphragm, and duodenum[13-15]. Pathogenesis of lymphangioma remains unknown, and many possible pathological processes have been proposed, including benign proliferation of ectopic lymphatics or obstruction of the lymphatics[16]. Also, sequestrations of fetal lymphatic sacs which lack proper connections with the venous system may make blind vessels to proliferate and dilate producing cystic lymphangioma[17].

The cystic spaces are lined with a single layer of endothelium. Presence of small lymphoid aggregates and smooth muscle fibers in the cyst wall distinguish MCL from simple cysts of the mesentery[18].

Complications of MCL include peritonitis by rupture, hemorrhage, or infection[19]. Malignant

transformation is possible but has been described only once[20]. Volvulus was recorded in literature as a complication of MCL but was mostly associated with malrotation and omental torsion[21,22]. In our case, no anatomical evidence of malrotation was present and the volvulus can be explained by torque effect of the large cyst. History of antecedent similar attacks denotes that volvulus was of the chronic variety. This was evidenced at surgery by congested mesenteric vessels and edema.

A cause and effect relation was discussed before for association of MCL and volvulus. Some advocated the primary presence of the cyst which leads to volvulus[21]. Others believed that chronic volvulus with lymphatic obstruction are the initial pathology which can end in acquired cystic lymphangioma[23]. Lymphatic permeation was recorded before in malrotation and chronic volvulus[24], and the presence of chylous ascites during hernia repair was attributed to asymptomatic malrotation[25]. In our case, malrotation criteria were absent and the cyst is mostly the cause of volvulus. Moreover, lymphatic obstruction secondarily led to cyst enlargement and engagement in pelvis.

A universal pathological classification of MCL was suggested and used to stratify different presentations. Type 1 is a pedicled MCL, which might cause volvulus of the intestine or undergo torsion and subsequent necrosis. It can be resected solely with preservation of intestine[7]. Type 2 is a sessile MCL located in the mesenteric boundaries. Such type is less mobile compared with Type 1 and surgical removal can alter the bowel's vascular supply and require bowel resection[2]. Type 3 has retroperitoneal extension with involvement of aorta and vena cava which makes complete removal of the lesion impossible[26]. Type 4 describes multicentric MCL with doubtful prognosis[27]. Our case can be categorized as combined type 1 and 2 as there was a big pedicled cyst and four sessile cysts on the mesenteric side of intestine. Resection of intestine in our case was mandatory due to anatomical location of cysts.

Complete resection with free microscopic edges is advised to prevent recurrence which would be 10%[28]. Invasion of potentially resectable abdominal organs like spleen or pancreas makes complete resection possible. Palliative surgical treatment methods have been used for invasive abdominal lymphangiomas[29], but were associated with complications such as hemorrhage, infection, lymphatic fistula and recurrence[30]. Use of sclerosing agents such as alcohol, dextrose, bleomycin, corn protein, and fibrin sealant was insufficient to permit definitive conclusions[7]. OK432 is the only agent that has been ultimately effective in a large number of lymphangiomas for which radical surgical treatment has proved impossible[31]. However, its use in MCL is not fully established.

CONCLUSION

MCL is a rare abdominal lesion. Volvulus is a possible risk and presence of malrotation is not an absolute prerequisite. Discovery of such lesion mandates its complete resection to avoid complications and recurrence.

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Case Report

Cerebrovascular Accident following Carotid Arterial Dissection in a Child Abuse Case

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ABSTRACT

We present the case of a young boy who was physically abused in the form of a blunt trauma to the neck. The boy developed a dissection of his right internal carotid artery leading to a stroke few hours later. The literature regarding this entity in the pediatric population consists mainly of case reports and small series with a very limited clinical experience.

KEY WORDS: aphasia, blunt trauma, carotid artery, stroke

INTRODUCTION

Although the overall stroke rate in children is low carotid artery dissection is one of the major causes of stroke in this population[1]. To date the natural history, optimal management, and prognosis of pediatric carotid arterial dissection remain largely unknown. The most significant controversy in the treatment of carotid artery injuries is antithrombotic therapy. It is unclear from the literature whether the more risky anticoagulant treatment is mandatory or the less risky antiplatelet treatment is sufficient. Nearly all patients who present with a focal neurological deficit consistent with a stroke or transient ischemic attack (TIA) will prompt a workup which includes magnetic resonance angiography (MRA) to rule out carotid dissection. Carotid artery dissection should be considered in any child with gross neurologic abnormalities especially after blunt trauma to the head or neck. Though rare, child abuse should be suspected based on a meticulous history about the mechanism of injury and on physical signs.

CASE HISTORY

A 3-year-old boy was carried to the emergency department by his biological mother with the history of being found unresponsive at the bottom of stairs at home. On examination, his BP was 90/60 mmHg, pulse rate 112 b/m, respiratory rate 20 b/m, O_2 saturation 96% on room air and his temperature was normal. No bruises were found and his glasgow coma scale score (GCS) was 11/15. His pupils were equally reactive bilaterally and neurologically he had no localizing signs.

On auscultation he had bilateral lung crepitations which raised the suspicion of aspiration. Shortly after arrival to the emergency department the child vomited three times and started to bleed from his nose and mouth. At this time computerized axial tomography (CAT) scan of the head and neck showed normal results. Ultrasound (US) abdomen was negative and X-ray of the whole spine with skeletal survey was normal. The child was intubated shortly after presentation as he was not protecting his airway and was admitted to the intensive care unit under a provisional diagnosis of an isolated head injury.

The child's mother changed her story to a trauma to the head caused by his 5-year-old sister. Child protection services were involved as the change in the presenting story by the mother was supicious. Next day extubation was done as child's level of consciousness improved when sedation was discontinued. Few hours later, he started to develop a left-sided hemiparesis aphasia and difficulty swallowing. An urgent CAT scan brain was done. The result of the CAT scan was an acute infarction in the course of right middle cerebral artery (MCA) and its tributaries with a mass effect in the form of compression on the ipsilateral right lateral ventricle and a midline shift. Two days later, the child was intubated again for deterioration in level of consciousness and for having an unequal

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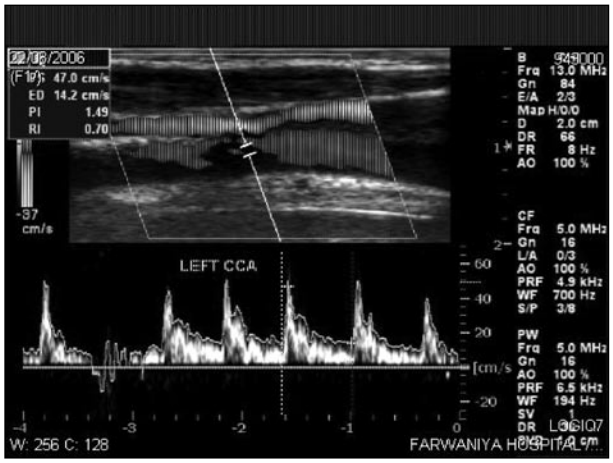

Fig. 1: Carotid duplex scan showing normal blood flow in the left internal carotid artery

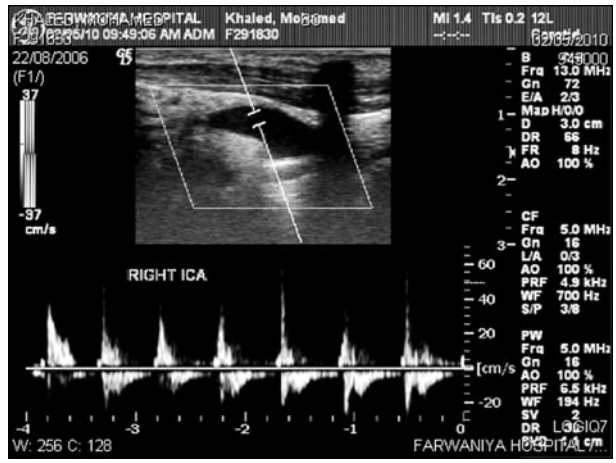

Fig. 2: Carotid duplex scan showing no blood flow in the right internal carotid artery

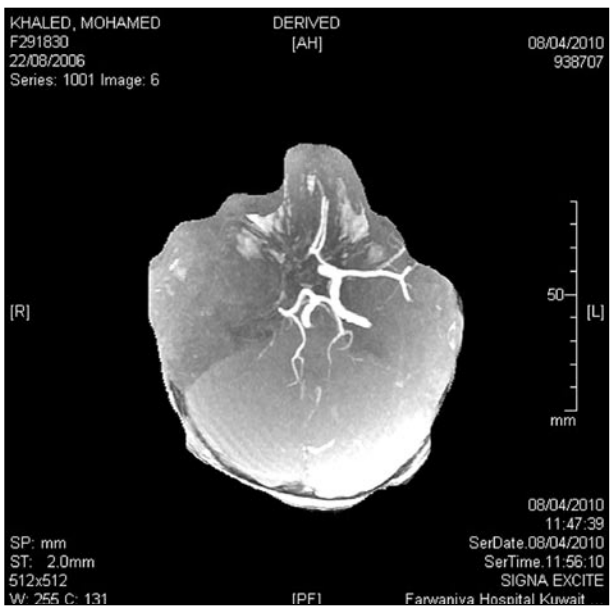

Fig. 3: MRA showing an occluded right internal carotid artery and middle cerebral artery.

size of pupils along with bradycardia (a HR of 62 b/m). A repeat CAT scan brain showed a diffuse cerebral edema with an increase in the mass effect and midline shift with a right uncal herniation and compression of the midbrain.

The child's mother changed her story again. This time she said that the aggressor was the child's father. Following that a duplex scan of the carotids was done which showed a total occlusion of right internal carotid artery (Fig.1, 2). A MRA of the carotids showed an occluded right internal carotid artery and middle carotid artery with carotid dissection as the only possible suggested diagnosis (Fig. 3).

An urgent neurosurgical consultation was made and a right frontoparietal decompressive craniotomy and durotomy procedure was done. Post surgery pediatric neurology and hematology consultation were done and both teams agreed to start the child on low molecular weight heparin and investigate for a possible underlying cause of stroke. These investigations were echo, coagulation profile, antithrombin III, factor V laden Protein, C S level activated protein C, lipid profile, lipoprotein A factor II level, antiphospholipid antibodies, transferin level and hemoglobin electrophoresis all of which showed normal results.

Two weeks later the ICU team was able to extubate the child. His condition post-extubation was aphasia, left-sided hemiparesis and difficulty in swallowing. On follow-up by the vascular team, antiplatelet therapy was also started as part of the treatment protocol. Patient was discharged home two-and-half months later as he only required physiotherapy and follow-up care.

DISCUSSION

Carotid artery injury due to blunt trauma to the neck is rare in any age group and is therefore not considered on initial presentation. In addition, often there is a delay in diagnosis, as in about 35% of patients the development of neurologic symptoms is later than 24 hours[2]. Moreover, the presence of head trauma can further obscure the underlying cause and contribute to delays in diagnosis, making the true incidence of carotid artery injury probably higher than reported[3,4].

There is a debate as to the benefits of aggressively perform vascular imaging for every patient presenting with head and neck trauma who have altered mental status. Studies showed that up to 1% will demonstrate blunt carotid injury[5,6]. However, such imaging has not yet been demonstrated to decrease the risk of symptoms such as stroke[6].

Carotid artery dissections can take the form of intracranial or extracranial dissections each differing from the other in clinical presentation. Intracranial dissection can predispose to subarachanoid hemorrhage while extracranial dissection most commonly present with ischemic signs and symptoms as in our case here. Spontaneous carotid artery dissection are more commonly intracranial while traumatic dissections are more commonly extracranial[7,8]. However, the overall incidence of extracranial dissections in the entire trauma population is 0.08% to 0.4[9,10]. Because in children the basilar skull is more mobile than adults due to incomplete ossification, carotid arteries generally dissect intracranially in children[11].

For children with a clinical presentation suggestive of carotid artery dissection, MRA is extremely useful whether initial imaging such as CAT scan or MRI shows evidence of cerebral infarction or not[12].

Carotid artery injury can take the form of a pseudo-aneurysm formation, carotid artery dissection, and/or thrombosis and occlusion of the vessel. Treatment options include observation, anticoagulation and endovascular stenting, and aggressive surgical repair of the injured carotid artery[11]. Surgical intervention for carotid artery dissection is reserved for patients with recurrent TIAs or progressive neurological deficits secondary to hypoperfusion or embolic phenomenon despite maximal medical therapy[13-15]. Experience in endovascular carotid stenting in children is very limited, and long term results of carotid stenting in children are unknown. Only nine cases of endovascular stenting in the pediatric population, have been reported for extracranial carotid artery injury. Eight out of these cases were trauma related, and the other two cases were idiopathic[7]. The indication for stenting in all these cases was pseudo-aneurysm formation. In our case, endovascular stenting was not performed because of the rapid neurological worsening of the condition. There was no pseudo-aneurysm formation and most important, the right carotid artery and the right MCA were thrombosed.

First line medical therapy is based on the premise that the majority of neurologic events are related to thrombus within the lumen and are potentially preventable with anticoagulation or antiplatelet drugs. The most recent aspect of the controversy on treating carotid artery dissection surrounds the role of antiplatelet therapy versus anticoagulation therapy. Complete anticoagulation is difficult to apply and regulate in children, whereas antiplatelet therapy is much easier to administer[1,16]. One study indicated that the presence of a large or expanding pseudoaneurysm, occurring in 1/3 of cases, is also an indication for surgical intervention.

Child abuse is under reported and majority of fatalities are among children less than five years old[11]. Awareness by physicians to possibly prevent occurrence is vital. Early intervention is also important. It is crucial to recognize potential cases and to involve child protection services as early as possible. Understanding the mechanism of injury can allow using modalities of treatment that could prevent clotting and therefore neurological complications.

CONCLUSION

We presented a case of child abuse in the form of trauma to the neck which resulted in carotid artery dissection with concomitant thrombosis which extended intra-cranially involving the ipsilateral MCA with extensive infarction of the brain. This report highlights the importance of suspecting a vascular insult early in children presenting with localizing neurologic signs.

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Case Report

Pseudo-Aneurysm of the Internal Maxillary Artery: A Case Report

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ABSTRACT

This report describes radiologic features and management of a case of pseudo-aneurysm of the right internal maxillary artery and a brief review of the literature. We report the case of an 18-year-old man who presented with right-sided sudden, severe nasal bleeding. He had sustained craniofacial trauma five months before the onset the bleeding. This resulted in multiple facial bone fractures for which he had undergone open reduction and internal fixation (ORIF). The pseudo-aneurysm was diagnosed by conventional angiography of the common carotid arteries and was successfully occluded.

KEY WORDS: craniofacial trauma, epistaxis, traumatic pseudo-aneurysm

INTRODUCTION

Pseudo-aneurysms (PA) are often caused by injuries that rupture the full thickness of the arterial wall. This leads to extravasation of blood into the surrounding tissue, pulsatile hematoma and a potential cavity that may expand and rupture causing a life-threatening hemorrhage[1]. There are very few previous reports of pseudo-aneurysm of the internal maxillary artery (PAIMA). We report the case of an 18-year-old man who presented with a right-sided sudden, severe nasal bleeding five months after craniofacial trauma.

CASE REPORT

An 18-year-old man presented to the casualty unit of the ENT department with a five-day history of severe, intermittent right-sided epistaxis. Rhinoscopy revealed no obvious source of bleeding. The bleeding stopped after anterior nasal packing but recurred after removal. Hence, a computed tomography (CT) scan of the nose-sinuses was done. It demonstrated the presence of a tubular enhancing lesion in the right maxillary sinus (Fig. 1a,b).

CT angiography of the right carotid artery was requested in view of the previous CT finding, the severity of the bleeding and a positive history of craniofacial trauma. The result confirmed the vascular nature of the tumor; it showed the presence of aneurysm of the IMA (Fig. 2a,b). Hence, this required a bilateral, diagnostic conventional angiography of the common carotid arteries. The latter showed a large pseudo-aneurysm of the distal part of the internal maxillary artery that was successfully occluded with histacryl (Fig. 3). Post-embolization angiogram showed complete occlusion and disappearance of the pseudo-aneurysm (Fig. 4). The post-embolization period was uneventful. The patient was thus discharged and there was no complaint on subsequent follow-ups.

The patient sustained craniofacial trauma as a result of road traffic accident five months before the onset of the nasal bleeding. He had multiple craniofacial bone fractures including bilateral infra-orbital, zygoma, left ramus and body of the mandible that required tracheostomy and ORIF. His blood work was normal.

DISCUSSION

Pseudo-aneurysm of the internal maxillary artery (PAIMA) is a rare[2-4] but a potentially life-threatening condition; if untreated it can lead to severe oronasal bleeding[3,4].

The most common cause of PAIMA is believed to be fracture of the maxilla. There have been reports of PAIMA secondary to infection, maxilla-mandibular surgeries and rarely due to post-radiation or neoplastic infiltration of blood vessels[4,5]. Ellens states that radiation induced carotid vasculopathy may present as steno-occlusive disease or less commonly as a pseudo-aneurysm[6].

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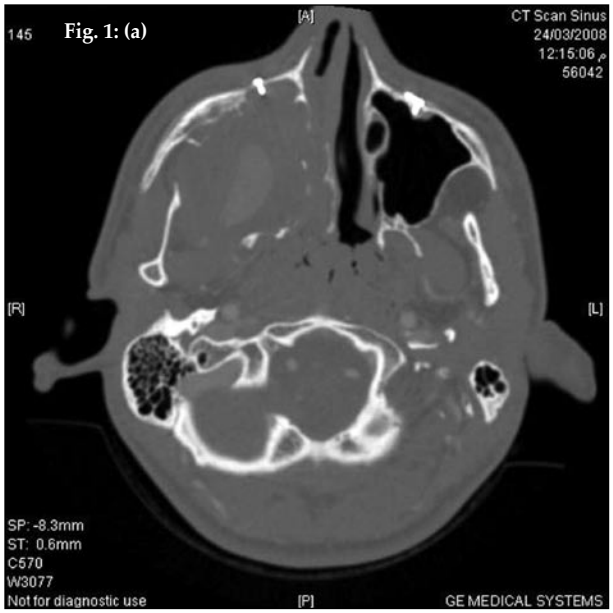


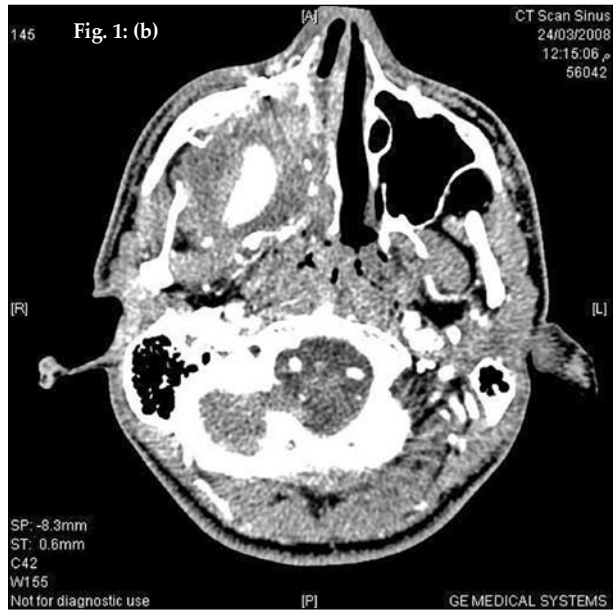


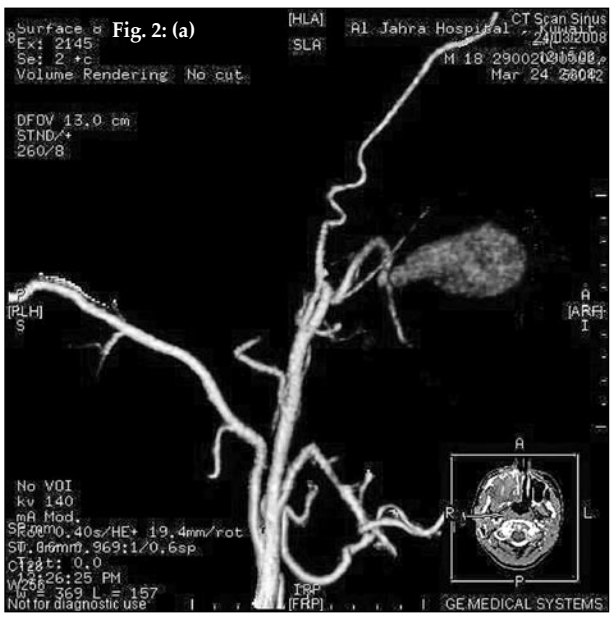
Fig. 1: (a) Pre and **(b)** post-contrast CT of the nose-sinuses demonstrating the presence of a tubular enhancing lesion in the right maxillary sinus

PA of the branches of the external carotid artery (ECA) is rare. This is due to the fact that the branches of the ECA are small and hence more susceptible to transection than laceration. Further, the deeper branches are protected by soft tissue. Among the branches of ECA, the most PA vulnerable include the superficial temporal, distal facial and distal IMA[3,7].

It is a potential cause of life threatening hemorrhage[7]. Massive epistaxis after a latent period of three weeks after trauma is highly suggestive of PA. Unruptured PA often presents with expanding pulsatile mass. Signs of adjacent nerve-arterial compression are also part of the clinical picture[3].

Its diagnosis is based on CT scan and angiography[5,6]. CT shows the extent of facial trauma and at times can directly visualize the PA, if it is larger than 1 cm[6]. Angiography is the standard imaging tool[3].

Initial treatment depends on blood transfusion and anterior nasal packing. The latter though is blamed for delaying the diagnosis and treatment[6]. Endovascular



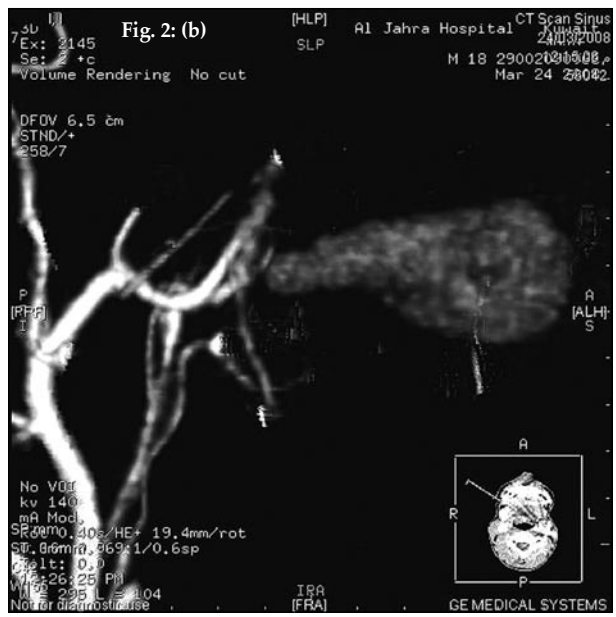


Fig. 2 a, b: CT angiography of the right carotid artery confirming the vascular nature of the tumor; it showed the presence of aneurysm of the IMA

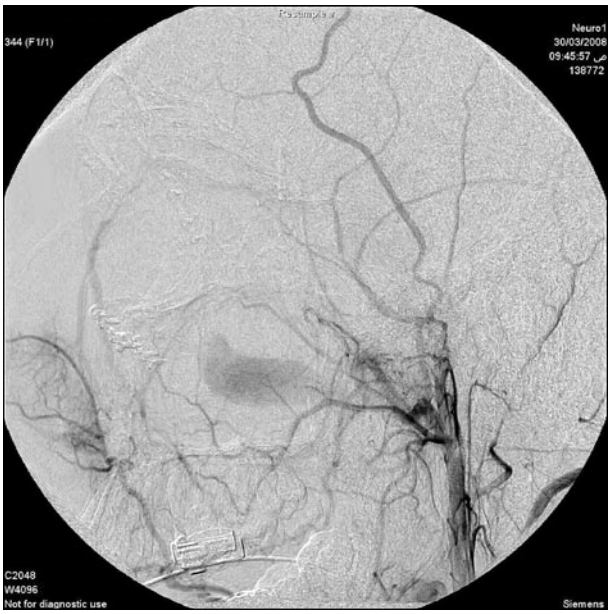


Fig. 3: Diagnostic conventional angiography of the common carotid arteries. It showed a large pseudo-aneurysm of the distal part of the right internal maxillary artery

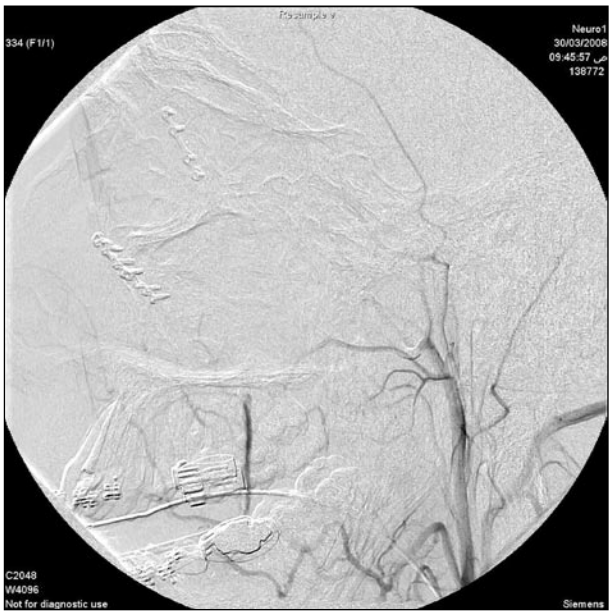


Fig. 4: Post-embolization angiogram showed complete occlusion and disappearance of the pseudo-aneurysm

embolization proves to be less-invasive than surgery[1]. Sokoloff, in 1974 is credited with having performed the first endovascular treatment of epistaxis. Before this, transantral surgical ligation was the definitive treatment[8]. Embolization has proved to be a technically safe procedure with few complications[6].

CONCLUSION

Though rare, PAIMA should be considered in the differential diagnosis of post-traumatic epistaxis. The success of treatment relies heavily on early diagnosis. Carotid angiography with selective endovascular embolization of the IMA is considered as the golden standard of diagnosis and treatment, with fast recovery and no surgical wound. Surgery is no more the first choice of therapy.

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Case Report

Laboratory-Acquired Brucellosis

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ABSTRACT

Laboratory-acquired infections are rarely diagnosed and reported. Brucella species are highly contagious when handled in the laboratory. Therefeore, brucellosis is one of the most common laboratory-acquired bacterial infections. Laboratory workers get infected by either inhalation or by direct contact through the injured skin. We present a case of laboratory-acquired brucellosis (LAB) caused by *Brucella melitensis*. In conclusion, despite the enforcement of infection control measures, including the use of biosafety cabinet in the laboratory, laboratory-acquired brucellosis still maintains its importance because of infected sample handling by the workers.

KEY WORDS: bacterial infection, biosafety, brucellosis

INTRODUCTION

Brucellosis is a zoonosis widely distributed around the world. Although the current incidence of brucellosis in developed countries is low, it occurs sporadically in occupationally exposed groups, including farmers, veterinarians, and laboratory and slaughterhouse workers[1]. Brucellosis is an endemic disease in Turkey. The incidence of this disease in our country is 23 per 100,000 per annum[2]. It is frequent especially in the rural areas of the middle and southeastern regions, and *Brucella melitensis* is the most prevalent strain[1].

Laboratory-acquired infections represent 2% of reported cases of brucellosis[3-5], demonstrating the high risk of acquiring *Brucella* infection in clinical microbiology laboratories where these highly infective bacteria are handled. The attack rate in cases of accidental laboratory exposure ranges from 30 to 100%, depending on the physical location of workers, the quantity of bacteria involved and the source at the moment of the exposure[3,4]. Transmission occurs usually *via* inhalation of bacteria, allowing entry of *Brucella* through the respiratory mucosa[6]. Transmission routes other than aerosol inhalation have been defined, although some of them are speculative[6]. However, laboratory-acquired infections, especially brucellosis, are rarely diagnosed or documented. In this report, we present a case of laboratory-acquired brucellosis (LAB).

CASE HISTORY

A 26-year-old male microbiology laboratory worker presented with a one-week history of weakness, sweats, fever and joint pain in the lower extremities. There was no history of trauma, and he did not reveal any unpasteurized milk or milk products consumption. He had been working on the determination of *Brucella* positive cultures, and was exposed to an accident in the laboratory one month ago. Polystyrene centrifuge tube containing *B. melitensis* strain previously isolated from a patient was accidentally ruptured during transfer of the tube from one room to another. Immediately after the tube rupture, he directly applied 3% phenol solution and paper towels soaked with the same germicide to immediately decontaminate the area, wearing rubber gloves with no mask.

On the day of admission, physical examination revealed that he had back pain and fever (38.5 ºC). The liver was palpable 3 cm below the right costal margin, and the spleen was palpable 2 cm below the left costal margin. Enlargement of lymph nodes

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was not noticed. Complete blood count at admission showed the following values: hemoglobin level of 13.4 g/dl (range, 12.2 - 18.1 g/dl), platelet count 245 x 10^3 /Ul (range, 142 – 424 x 10^3 /Ul) and leucopenia (total leukocyte count: 3660/mm^3; range, 4600-10,200/mm^3). Evaluation of the peripheral blood smear revealed 62% lymphocytes, 30% of neutrophils, and 8% of monocytes. The erythrocyte sedimentation rate and C-reactive protein were 25 mm/h (range, 8 - 15 mm/h) and 12 mg/dl (range, 0 - 8 mg/dl), respectively. He was tested for *brucella* using the Rose Bengal test (Seromed Laboratory Products, Turkey) and serological titer of anti-B. *melitensis* antibodies was evaluated by using a standard tube agglutination test (Seromed Laboratory Products, Turkey). The Rose Bengal test was positive. The *Brucella* serum tube agglutination test was reactive (1/320, cut off value was > 1/160). Two sets of blood samples were obtained for culture. The blood cultures showed bacterial growth (Bactec 9240, Becton Dickinson, USA) following 96 hours of incubation. Bacteria were isolated in 5% sheep blood agar. Grams' stain revealed small Gram-negative coccobacilli. The organism was confirmed to be *B. melitensis* by standard biochemical reactions (production of urease, catalase-positive, oxidase-positive, H_2S and indole negative, the dyes basic fuchsin, thionine, thionine blue are positive) and Sceptor Systems (Becton Dickinson, Maryland, USA). In addition, the routine biochemical test results such as total bilirubin 1.1 mg/dl (range, 0.3 - 1.2 mg/dl), direct bilirubin 0.2 mg/dl (range, < 0.3 mg/dl), alanine aminotransferase 22 U/l (range, 10 - 35 U/l), aspartate aminotransferase 36 U/l (range, 10 - 40 U/l), alkaline phosphatase 112 U/l (range, 53 - 128 U/l), gamma glutamyl transpeptidase 35 U/l (range, 12 - 64 U/l), urea 13 mg/dl (range, 6 - 20 mg/dl) and creatinine 0.9 mg/dl (range, 0.9 - 1.3 mg/dl) were within normal limits. Abdominal ultrasonography revealed enlargement of the liver (160 mm in maximum cranial-caudal extent), and enlarged spleen (162 mm in diameter).

In the light of these findings, we made a diagnosis of LAB and treatment was initiated with a combination of 200 mg of doxycycline plus 600 mg rifampicin every day for six weeks. By the fifth day of the treatment, his fever subsided, and prominent clinical improvement was observed. The patient made a full recovery without any further problem.

DISCUSSION

A large number of laboratory workers are exposed to different occupational health risks. In microbiology laboratory staff, infection is probably the most frequent laboratory-acquired hazard[6]. LAB has been documented and is considered the most important laboratory-acquired bacterial infection[6]. Although in many countries, the incidence of brucellosis has fallen, the existence of sporadic cases in these countries and its permanence as an endemic disease in others, such as the Mediterranean countries including Turkey, mean that brucellosis must still be considered to be a hazard for laboratory workers[7].

The World Health Organization (WHO) classifies brucellosis as a risk group III pathogen, meaning that it poses a high risk to persons but a low risk to the community[6,8]. LAB is not due to occupational accidents in the majority of cases[8], and other possible routes of *Brucella* transmission in the laboratory include direct contact, direct inoculation through needle-stick injuries, sniffing culture plates and contamination of skin and mucous membranes through spills or splashes into eyes, mouth, or nose[6,8,9]. Although a potential source of infection is usually identified, the precise route of disease transmission always has been speculative. Aerosol transmission generated accidentally or during microbiologic techniques from contaminated materials is the most frequently reported cause of disease acquisition in the laboratory[8]. In addition, *Brucella* spp. are highly infectious because the infectious dose by an aerosol is only 10 to 100 organisms[9]. In this report, the patient did not have any suspicious history of unpasteurized milk consumption or animal contact. The absence of this kind of contamination led us to believe that the transmission to our patient was through the laboratory route. He was exposed to an accident in the laboratory and he decontaminated the area, wearing rubber gloves with no mask. Because of this reason, the transmission in our case was probably due to aerosol contamination. In addition, he was unaware of the hazards of aerosol transmission of *Brucella* spp.

In the therapy of adult acute brucellosis, a combination of doxycycline and rifampicin is administered for six weeks according to the recommendations of WHO in 1986[10]. This case also received doxycycline and rifampicin for six weeks, and had a full recovery without any further problem.

It is a fact that the personnel of the microbiology laboratories face some risks. LAB infections are very important in developing countries and in countries with endemic disease, such as Turkey. In our country, biosafety cabinets do not exist in most hospital laboratories. Therefore, using gloves, masks and goggles and also continuous education on biosafety where brucellosis is endemic is very important. To avoid laboratory transmission, taking Center for Disease Control and Prevention (CDC) recommendations into consideration, each laboratory personnel must work cautiously and with responsibility against laboratory risks.Handling of biosafety level 3 microorganisms, such as *Brucella* spp. must be conducted under biosafety

hoods and the plates should be sealed for safety when they are not in use[11].

CONCLUSION

Clinicians should alert the laboratory workers when brucellosis is suspected so that the specimens are handled under the most stringent safety measures, and in order to prevent future infections, close collaboration between clinicians and laboratory staffs is required.

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Case Report

Appendiceal Mucocele: A Case Report and Review of Literature

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ABSTRACT

Appendiceal mucocele is an uncommon disease caused by a progressive dilatation of the ileocecal appendix by a mucus filled lumen. We report the case of a 72-year-old woman who underwent surgery for an appendiceal mucocele. This case highlights the importance of both a correct preoperative diagnosis and a targeted surgical strategy, to reduce the risk of complications like the rupture of the mucocele and consequent pseudomyxoma peritonei (PP).

KEY WORDS: cecal appendix, mucinous cystoadenoma, pseudomyxoma peritonei

INTRODUCTION

Appendiceal mucocele (AM) is a rare pathological condition of the cecal appendix, and may present with non-specific clinical features or be an incidental finding[1]. The purpose of this case report is to clarify the pathologic and clinical characters of AM, as well as analyze the diagnostic pathway and discuss the surgical strategy, inspired by a clinical case example.

CASE REPORT

A 72-year-old woman presented with an 18-month history of recurrent right lower quadrant abdominal pain attacks (mimicking chronic appendicitis). Her past medical and surgical history included cholecystectomy, hemorrhoidectomy and one episode of diverticulitis. She reported a weight loss of about 8 kg over the past four months.

She underwent abdominal ultrasonography (US) that showed a fluid image in the right lower quadrant of the abdomen measuring 4.8 cm x 3.5 cm. A computed tomography (CT) scan of the abdomen and pelvis revealed a 4 cm mass, most likely a mucocele, on the right side of the ascending colon, close to the cecum. Colonoscopy showed an inactivated diverticular disease in the sigmoid and left colon, while cecum was apparently not distorted.

Tumor markers including CEA, Ca125, Ca19.9 were normal.

The patient underwent laparotomy. A cystic dilatation of the appendix with several adhesions to the abdominal wall was found, but there was no colon or ileal tumour. There was neither free fluid in the peritoneal cavity or lymphadenopathy. Appendectomy was performed.

Histopathological analysis showed a mucinous cystoadenoma. Lymph nodes examined were free from the tumour. There was very low potential for local recurrence or pseudomyxoma peritonei (PP). The patient had an uneventful recovery and was discharged on postoperative day 4. She remained asymptomatic in the following 18 months.

DISCUSSION

AM is an infrequent event, recognized as a pathologic entity by Rokitansky in 1842 and formally named by Feren in 1876[1].

The incidence ranges from 0.2 to 0.3% of all appendicular specimens. AM is more frequent in individuals over 50 years of age, and presents a female-to-male ratio of 3-4 to 1[2].

Mucocele consists of a progressive dilatation of the appendiceal lumen due to accumulation of mucous.

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AM may be caused by one of the following four processes: retention cyst (20%), mucosal hyperplasia (20%), mucinous cystadenoma (50%) or mucinous cystadenocarcinoma (10%)[3]. Histologically, simple retention cysts show degenerative epithelial changes due to obstruction and distension of the appendix by a fecolith. Mucosal hyperplasia is similar to a hyperplastic colonic polyp. Mucinous cystadenoma and cystadenocarcinoma are neoplasms: the first is characterized by a tube-glandular or papillar pattern with high production of mucus, while, when glandular and stromal invasion is demonstrated, it is cystadenocarcinoma[4].

The most common symptom of this tumor is pain in the right lower quadrant of the abdomen, despite the fact that up to 50% of patients are asymptomatic and the mucocele is found incidentally at the time of surgery. Other symptoms may be abdominal mass, weight loss, nausea or vomiting or both. Our patient showed a typical presentation in term of age, and lack of clinical features and laboratory abnormalities.

AM was associated with colon adenocarcinoma in 19.5 – 21.4% of cases[5]. Other synchronous neoplasms can be found in gallbladder, breast, kidney, ovary and thyroid[6].

Complications of AM include intussusception, intestinal bleeding, ureteral obstruction and hematuria, but the most dangerous complication is the rupture of the mucocele and consequent PP.

Perforated appendix pours mucoid material into the peritoneal cavity. This material may be acellular or can contain cells with low grade or high grade dysplasia. In all circumstances, this peritoneal dissemination is a potentially lethal condition without treatment[7]. Recent studies about the treatment of PP using cytoreductive surgery and perioperative intraperitoneal chemotherapy has shown encouraging results[8,9].

Generally, mucoceles less than 2 cm are benign, while AM caused by cystadenoma or cystadenocarcinoma is usually larger, about 5 - 6 cm in diameter, with a 20% incidence of perforation[10]. We believe that a correct preoperative diagnosis can be made using combination of US and CT scan. US can confirm the cystic nature of the lesion and reveal acoustic shadowings from the calcifications. In some patients, the US findings of "target lesion" or of "onion skin" may be pathognomonic for mucocele[11].

CT of the abdomen is the gold standard in detecting and evaluating AM, which is characterized by a well encapsulated cystic mass 2 to 20 cm in diameter and curvilinear mural calcific spots seen in more than 50% of cases. Enhancing nodules in the mucocele wall may suggest cystadenocarcinoma[12]. Preoperative diagnosis of mucocele is important to plan the right surgical approach. If the preoperative diagnosis is positive, further exams for synchronous tumors are necessary, especially for elderly patients. In particular, colonoscopy and double contrast barium enema should be performed to exclude possible concomitant colorectal cancers.

The treatment of AM is surgical. Simple appendectomy is curative for non-neoplastic AM. Fundamental is the prevention of dissemination of AM tissue into the peritoneal cavity with subsequent high risk of PP. For this reason, laparotomic appendectomy is preferable than the laparoscopic approach, which should be avoided because of the increased risk of rupture and subsequent spread of mucus, as much as for the risk of seeding of the trocar sites.

Dhage Ivatury and Sugarbaker suggested a proper pathway for the surgical treatment of AM[13]. When a mucocele is visualized during a laparoscopy, the procedure must be converted to an open midline laparotomy. At this time, laparotomy also helps the surgeon to research more carefully the presence of mucus in other sites of abdominal cavity, especially in right retrohepatic space and deep in the pelvis. Any free fluid in the abdomen must be sent to a cytologic study. Appendectomy should be performed, with assessment of appendiceal lymph nodes and appendiceal stump. If the lymph nodes are positive, the surgeon must perform a right colectomy, but if the margin is positive and the nodes are negative, it is possible to perform a simple cecectomy. If the cytologic study of mucoid fluid is positive for epithelial cells, the patient will be referred to a peritoneal carcinomatosis center for the definitive treatment.

Some authors consider that it is possible to treat AM safely by laparoscopy, avoiding grasper instruments and using an endoBag to pull out the specimen[14], but we think that an open laparotomy is a better option.

If the surface of mucocele remains intact, there will be no risk of progression of disease for the patient[15]. Otherwise, if mucinous cells escape from the mucocele to the peritoneal surface, the clinical course will be different.

CONCLUSION

AM is a rare and potentially lethal disease. A correct preoperative diagnosis is uncommon but possible by appropriate tests. Therapy is surgical and surgeons must know the proper pathway for the right treatment of different degrees of severity of AM.

ACKNOWLEDGEMENT

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Case Report

Schwannoma of the Penis: A Rare Tumor with Rare Presentation

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ABSTRACT

Schwannoma of the penis is extremely rare and arises from Schwann cells. We describe the management of this tumor as well as radiological and histological findings. Surgical excision was done, and patient is pain free six months after surgery with no recurrence.

KEY WORDS: benign tumor, penis, schwann cells

INTRODUCTION

Schwannoma is usually a benign tumor which may occur in any region of the body but is extremely rare in the penis[1]. Pain during intercourse is an unusual presentation. We report a case with such a presentation.

CASE REPORT

A forty-eight year old male patient presented to our hospital with a 25-year history of a penile mass. The patient had noticed an increase in size in the last two years with mild pain during intercourse. He gave no history of trauma, erectile dysfunction, or voiding symptoms. There was no other significant medical history.

Physical examination revealed a 2.5 cm x 1 cm mass at the right dorso-lateral aspect of the base of the penis. The mass was tender, smooth and fixed to the underlying tissues but not to the skin. Superficial inguinal lymph nodes were not palpable. Blood chemistry, urine culture, and urinalysis were normal. An ultrasound of the penis with Doppler was reported as vascular soft tissue mass. MRI revealed a hypo-intense solid mass 2 x 1.2 cm abutting the right aspect of the tunica but not invading it on T1-wieghted image (Fig. 1). T2-wieghted image showed a hyper-intense mass. After contrast administration T1-wieghted image showed the mass to be homogenous with contrast enhancement with no areas of break down within (Fig. 2).

In view of the pain experienced by the patient and uncertainty about the diagnosis, surgical excision was indicated. Under spinal anesthesia, a longitudinal incision was made over the mass. The mass was adherent to the Buck's fascia with a superficial vein going to the mass which was ligated. The mass was closely adherent to the dorsal nerve and was mobilized completely and excised intact. Follow-up at six months showed that the patient was free of pain and there was no recurrence.

Histopathology

Microscopic examination of the tumor revealed proliferation of monomorphic spindle cells ± (hematoxylin and eosin x 200) with predominance of Antoni A areas and presence of Verocay bodies (Fig. 3). Immunohistochemistry showed strong reactivity for S-100 protein (avidin-biotin-peroxidase x 400).

DISCUSSION

Schwannoma is a tumor arising from the Schwann cells. It may occur in any region of the body. However, it is extremely rare on the penis[1]. Among the benign soft tissue tumors of the penis, tumors of vascular origin, including capillary or cavernous hemangioma, epithelioid hemangioma and lymphangioma are the most common, followed by neurofibroma, Schwannoma, leiomyoma, glomus tumor, fibrous histiocytoma and granular cell tumor[2]. Since its first

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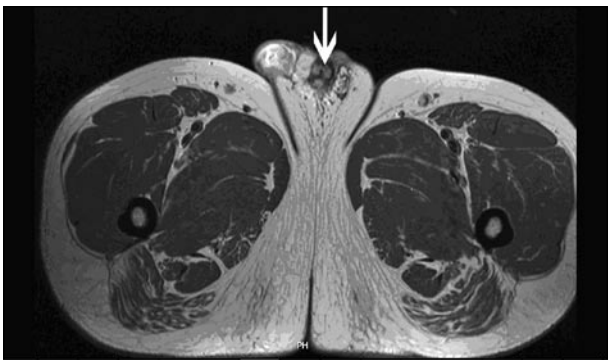

Fig. 1: T1W1: hypo-intense solid mass

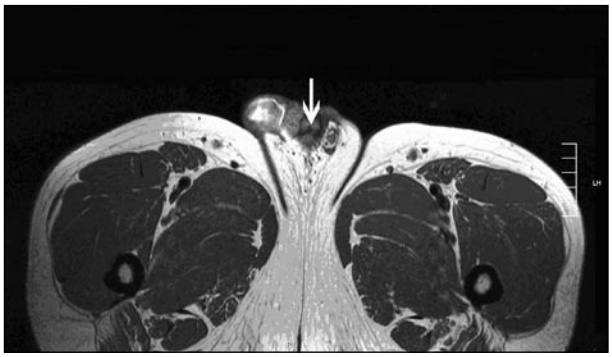

Fig. 2: Post-contrast T1W1: homogenously enhanced mass

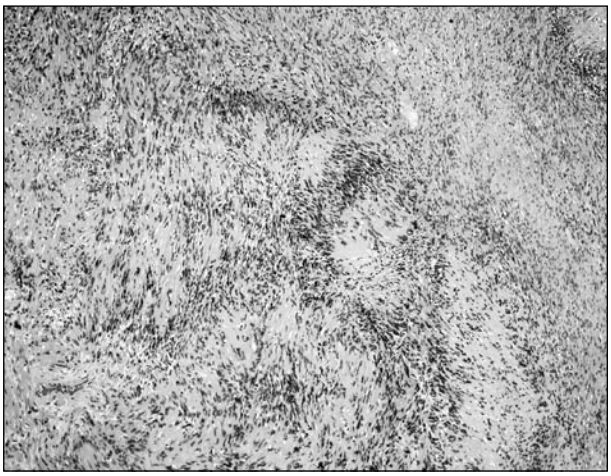

Fig. 3: Antoni A areas with Verocay bodies

description in 1968[3], to the best of our knowledge, only 29 cases including our case have been reported in the literature[4]. Most of penile schwannomas are unifocal. However, Sato *et al* reported five multifocal schwannomas of the penile shaft[5]. Penile schwannomas are usually benign, although malignant variants have been reported[6]. Malignant schwannoma appears to be always associated with Von Reckling Hausen's disease. Three out of four cases reported by Kubotal *et al* were associated with this condition[7-8]. Our patient presented with mild pain during intercourse which is an unusual presentation of a penile schwannoma. Out of 20 cases reported by Berard *et al*, only one patient had pain during intercourse[9]. Out of the 29 cases reported in the literature, our case is considered the second case presenting with pain during intercourse and was the reason for consultation. The histopathologic presence of Antoni A and occasionally B areas, together with Verocay bodies is diagnostic of a schwannoma. Immuno-histochemical staining with vimentin and S-100 protein immunoperoxidase is supportive of the diagnosis[10]. Surgical excision is the treatment of choice for a penile schwannoma. Regular follow-up is recommended because recurrence has been reported[11].

CONCLUSION

Schwannoma arising in the penis is sparingly reported in the literature. It is considered a benign tumor. However, malignant variants have been reported. Pain is an unusual presentation of schwannoma of the penis, but when present, it is usually mild. Treatment is by surgical excision.

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Case Report

Insulin Resistance Causing Post-Transplant Diabetes Late after Successful Kidney-Pancreas Transplant: Insights Relevant to the Pathogenesis of Type 2 Diabetes

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ABSTRACT

New onset diabetes after transplant (NODAT) is common after solid organ transplantation and is associated with factors such as pre-transplant obesity and weight gain.
We report an unusual case of severe insulin resistance (IR) leading to the development of NODAT four years after a technically successful simultaneous combined pancreas-kidney transplant (SPKT) in a patient with long-standing Type 1 Diabetes (T1DM) complicated by end-stage diabetic nephropathy.
Our subject became insulin-independent following his SPKT, but his significant weight gain following a short course of steroids for a biopsy-proven episode of mild pancreatic rejection at one year worsened his IR. His oral glucose tolerance at three years indicated preserved glucose tolerance but showed elevated c-peptide. Homeostasis Model Assessment (HOMA) indicated significant IR and a compensatory increase in beta-cell function. Symptomatic hyperglycemia requiring insulin developed at four years. Repeat metabolic testing confirmed glucose intolerance but demonstrated ongoing c-peptide production, albeit at lower levels. HOMA suggested ongoing IR but a loss of β-cell function. Renal function had been excellent throughout.
This genetically distinct pancreatic allograft maintained normal glucose tolerance in the face of marked insulin resistance for more than three years. Insulin resistance was sufficient to induce a progressive decline in insulin secretion leading to frank, though non-ketotic diabetes.

KEY WORDS: β-cell function, homeostasis model assessment (HOMA), organ transplantation

INTRODUCTION

New onset diabetes after transplant (NODAT) is a common finding after solid organ transplantation[1] which is associated with several adverse outcomes including reduced survival of both recipients and grafts, and increased cardiovascular mortality[1]. Although the use of steroids and other immunosuppressant drugs are important risk factors for NODAT[1], many of the risk factors for NODAT, including obesity, weight gain and pre-existing insulin resistance, are the same as those which predict type 2 diabetes (T2DM)[2].

T2DM is a polygenic disease with a major heritable component. Insulin resistance, most often a consequence of adverse lifestyle factors (obesity, high fat diet, physical inactivity), is widely recognized to play a key role in the pathogenesis of T2DM in genetically predisposed individuals and associations between insulin resistance genes and T2DM have been confirmed by studies taking a candidate gene approach[3,4].

However, recent data suggest that inherited susceptibility to T2DM may result from genetically determined influences on beta cell reserve and islet function since genome wide association studies have identified important genes which appear to be critical for pancreatic development and insulin secretion[4]. Thus although the development of T2DM likely reflects an imbalance between insulin resistance (IR)

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and insulin secretion, the relative importance of these factors in initiating and driving the progression to T2DM remain unclear.

We present the case of a young man, with a very strong family history of T2DM, who underwent successful kidney-pancreas transplant for diabetic nephropathy due to Type 1 diabetes (T1DM) and who had serial metabolic monitoring. Post-transplant, he developed significant and sustained IR which led to a progressive decline in insulin secretion and the development of hyperglycemia five years post-transplant in a genetically distinct pancreas and in the absence of evidence of rejection.

CASE REPORT

A 35-year-old man of East Indian descent, non-smoker, with T1DM since the age of four years complicated by proliferative retinopathy, peripheral neuropathy and end-stage diabetic nephropathy, initially became insulin independent after receiving a pre-emptive, deceased donor, simultaneous pancreas-kidney transplant (SPKT) in the year 2000.

He experienced a mild episode of biopsy-confirmed acute rejection of the pancreas graft at one year post-transplant, which was effectively managed with three doses of intravenous methylprednisolone and a course of oral prednisone. There was no further evidence of acute rejection of either organ. Maintenance immunosuppression was with tacrolimus and mycophenylatemofetil (2 g per day). Other medications included daily doses of aspirin 81 mg, fosinopril 20 mg, folic acid 2 mg, felodipine 15 mg, a multivitamin (Replavite) tablet and vitamin D 800 units.

Clinical and metabolic parameters are presented in Tables 1 and 2. HOMA scores were calculated from fasting glucose and C-peptide levels using the HOMA-2 calculator (v2.2 Diabetes Trials Unit, University of Oxford, www.dtu.ox.ac.uk/homa). By three years, there had been very significant weight gain since transplant (19 kg gain: BMI 32.7 kg/m^2 Vs 24.5 kg/m^2). The weight gain was predominantly abdominal as indicated by the waist:hip ratio. Renal graft function and tacrolimus levels had been stable.

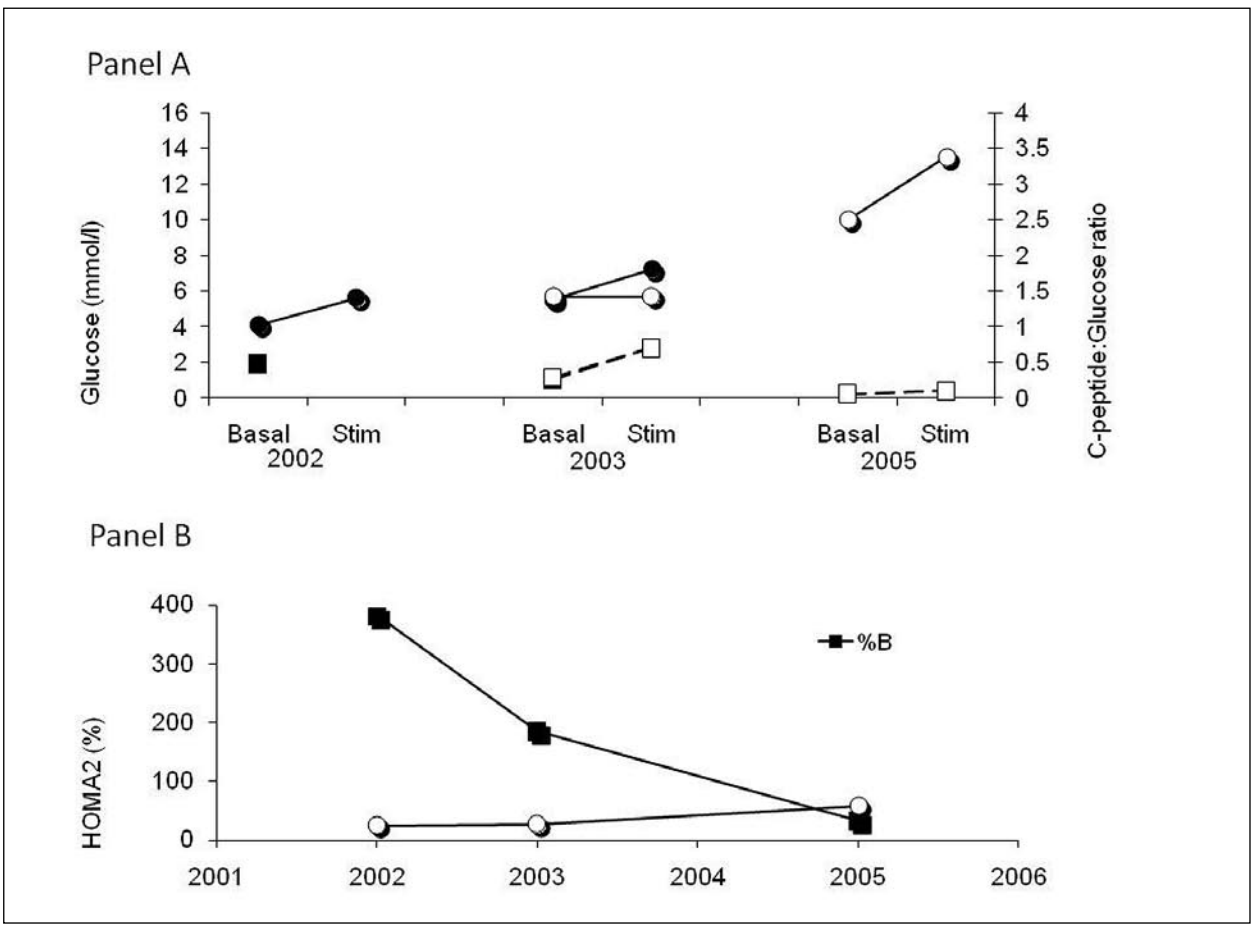

Fig 1: Panel A illustrates the HOMA-B (solid squares) and HOMA-S (open circles) values calculated from fasting glucose and c-peptide values at different time points. Values are expressed as %age, with 100% representing a normal response. stim = stimulated
Panel B illustrates the basal and stimulated glucose values (solid markers) and c-peptide:glucose ratios (open markers) in response to a standard 75g OGTT (squares) or a mixed meal tolerance test (circles).

At two years post-transplant, the HOMA scores indicated marked insulin resistance (HOMA-S = 25%: 100% indicating normal insulin sensitivity) and evidence of compensatory hyperinsulinemia (HOMA-B = 382.2%: 100% indicating normal beta cell function). The pancreatic graft was compensating effectively since glucose tolerance (to a standard 75 g oral glucose tolerance test (OGTT)) was normal as was the HbA1c.

Table 1: Clinical and metabolic parameters before and after simultaneous kidney-pancreas transplant

	Pre-Tx	Post-Tx		
		+2 years	+3 years	+5 years
Weight (kg)	65	—	84	81.3
BMI (kg/m²)	24.5	—	32.7	30.6
Waist:Hip ratio	—	—		1.78
Insulin dose (u/kg/day)	1.5	0	0	0.5
Fasting glucose (mmol/l)	7.9	4.1	5.7	10
HbA1c (%)	6.8	5.8	5.7	7.2
Creatinine (μmol/l)	—	80	88	90
Tacrolimus (μg/l)	n/a	10.2	6.4	7.6
HOMA %B	—	382.2	185.8	33.4
HOMA %S	—	25	26.2	57.7
HOMA IR	—	4	3.8	1.7

At three years post-transplant, graft function and glycemic control were maintained by compensatory hyperinsulinemia in the face of ongoing IR (Table 1). During the OGTT, the 2-hour glucose was slightly higher than the preceding year, although it was still in the non-diabetic range (7.2 mmol/l). A mixed-meal tolerance test (MMTT: using 360 ml of Ensure, providing 391 kcal with 8.5 g fat, 44 g carbohydrate, and 17 g protein, with sampling at 0 and 90 minutes) confirmed a robust c-peptide response, although, as would be expected given the lower glucose content, the stimulated glucose level was lower than after OGTT. Nevertheless, both OGTT and MMTT provided similar estimates of graft function since c-peptide:glucose ratios were almost identical in both the basal and stimulated conditions (Table 2, Fig. 1).

Four years post-transplant, the subject was found to have biochemical evidence of hyperglycemia (random glucose 17.1 mmol/l, HbA1c 9.7%) despite ongoing c-peptide production (0.91 nmol/l: [reference range 0.3-1.3]) and a tacrolimus level which was neither excessively high, nor too low (5.3 μg/l). Despite counseling regarding lifestyle intervention, his hyperglycemia progressed (HbA1c rising to 10.4%), prompting the initiation of aspart insulin with meals and NPH insulin at bed-time (0.5 units/kg) along with metformin 1 g bid as an insulin sensitizing agent.

At five years post-transplant, the subject continued on insulin and HbA1c improved. HOMA indicated a marked decrease in insulin secretion, despite ongoing insulin resistance and blood glucose levels were high before and after MMTT. C-peptide:glucose ratios were markedly lower than two years previously with a very modest increase with stimulation (Table 2, Fig. 1).

At present, the patient is stabilized on insulin and metformin and remains c-peptide positive with reasonable glycemic control. The kidney graft continues to function well with serum creatinine levels between 76 and 103 μmol/l. Blood pressure control is excellent (120/70 mmHg), and his lipid profile is controlled on atorvastatin (LDL cholesterol was 1.68 mmol/l and total cholesterol / HDL ratio was < 3.5).

DISCUSSION

The pathogenesis of NODAT and T2DM are similar and is due to insufficient insulin secretion for the body's prevailing insulin requirements, largely because of insulin resistance. After a period of compensatory hyperinsulinemia, beta cell function declines leading to hyperglycemia[5,6]. The cause of this beta cell failure is multifactorial and factors including genetics, age, insulin resistance, glucotoxicity and lipotoxicity are implicated[6].

This case demonstrates that insulin resistance *per se* is sufficient to induce a slow, but relentless and progressive decline in beta cell function / mass,

Table 2: HOMA and dynamic testing parameters after simultaneous kidney-pancreas transplant

	+2 years		+3 years		+5 years	
Metabolic Tests	Basal	Stimulated	Basal	Stimulated	Basal	Stimulated
OGTT						
Glucose (mmol/l)	4.1	5.6	5.5	7.2	-	-
C-Peptide (nmol/l)	1.95	-	1.42	5.05	-	-
C-Peptide:Glucose ratio	0.48	-	0.26	0.7	-	-
MMTT						
Glucose (mmol/l)	-	-	5.7	5.7	10	13.5
C-Peptide (nmol/l)	-	-	1.67	3.98	0.63	1.29
C-Peptide:Glucose ratio	-	-	0.29	0.7	0.06	0.1

similar to that observed in T2DM. There is clear evidence of significant insulin resistance developing post-transplant with effective compensation by the transplanted pancreas followed by a progressive decline in beta cell function, leading to frank diabetes due to a significant reduction in beta-cell function (indicated by reduced HOMA-B and c-peptide:glucose ratio).

Ongoing c-peptide production and the absence of ketosis rule out recurrent T1DM. Rejection seems unlikely as a cause for NODAT since excellent renal function continued. Although a role for mild or sub-clinical chronic pancreatic graft rejection cannot be completely excluded, the graft's ability to maintain significant hyperinsulinemia beyond three years suggests that "metabolic exhaustion" may be a more significant factor.

Ethnicity and family history of T2DM are important risk factors for NODAT. Since the pancreas graft is genetically distinct, the contribution of these heritable factors must be *via* a role in the development of insulin resistance[7] rather than *via* genetically determined beta-cell reserve.

"Recurrent diabetes" following pancreas-alone transplantation has been reported in up to one fifth of recipients and is associated with higher pre-transplant insulin dose, BMI and acute rejection episodes[8]. However in the setting of SPKT, increased risk of pancreatic graft loss is only seen in subjects with episodes of acute rejection of both pancreas and renal grafts[9]. It is difficult to establish direct evidence of chronic rejection due to a lack of non-invasive diagnostic markers[10].

Immunosuppressant drugs are key, potentially modifiable, risk factors for NODAT[11]. The diabetogenic effects of corticosteroids are well recognized and are predominantly due to inducing insulin resistance, both directly and *via* their effects to promote weight gain and obesity. Tacrolimus, and other calcineurin inhibitors (CNI), predominantly reduce insulin secretion, and have little effect on insulin sensitivity[12]. The combination of CNI with sirolimus is particularly toxic for islets[13]. Mycophenylate appears to be metabolically neutral and associated with a low risk for NODAT[14].

It would seem that the development of T2DM following technically successful SPKT for T1DM is very rare since only two similar cases have been reported[15,16]. Our case provides sequential metabolic evaluations providing unique insights into the time course of IR, compensatory hyperinsulinemia and metabolic decompensation with hyperglycemia. Most other studies examining outcomes following SPKT use registry data and have not systematically evaluated metabolic function and the prevalence of NODAT is probably underestimated.

This unique case documenting the metabolic abnormalities preceding the onset of NODAT following SPKT in a T1DM patient suggests that IR *per se* may be sufficient to result in a progressive decline in beta cell function as is typically seen in T2DM. It suggests a key role for insulin resistance and highlights the interaction of familial and ethnic factors with lifestyle factors such as weight gain.

CONCLUSION

In clinical practice patients undergoing SPKT, particularly those with risk factors for T2DM, should be counseled to avoid excessive weight gain in the post-operative period and should be monitored regularly for the development of NODAT. Close attention to control of cardiovascular risk factors is important, particularly in those who develop glucose intolerance. The choice of immunosuppressant drugs will need to balance risks of rejection with adverse metabolic effects.

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Declaration of competing interests: None

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Letter to the Editor

Counseling and Educating Diabetic Patients about HbA1C Laboratory Test

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Health care providers should not assume their diabetic patients understand the HbA1C test because most patients do not know their most recent HbA1C values or the meaning of those values. It is better to have immediate feedback of HbA1C results during the clinical encounter, because this gives the opportunity for enhanced clinical decisions, intensification of treatment regimens, and better subsequent glycemic control[1-3]. Lowering HbA1C to below 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes[4-6]. Glycated hemoglobin has been recommended only for the determination of glucose control among persons who have already received the diagnosis of diabetes. New clinical practice recommendations from the American Diabetes Association advocate the use of glycated hemoglobin in the diagnosis of diabetes, largely on the basis of the established association between glycated hemoglobin and micro vascular disease[7,8]. Finally, it is better and worthwhile for practicing physicians to educate and counsel diabetic patients and give immediate feedback of HbA1C results during clinical consultation.

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Letter to the Editor

No Association between Statin Use and Pancreatic Cancer Risk in Taiwan

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In order to investigate the effects of statin use on pancreatic cancer risk in Taiwan, we designed a case-control study by analyzing the database of Taiwan National Health Insurance program from 2000 to 2010. There were 823 cases with newly diagnosed pancreatic cancer (based on ICD-9 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, and 157.90), who were aged 20 years or older on the date of diagnosing pancreatic cancer (484 men and 339 women, mean age 67.8 years and standard deviation 12.7 years). In addition, 3292 controls without pancreatic cancer were matched for sex, age and index date (1936 men and 1356 women, mean age 67.3 years and standard deviation 12.8 years). The details of the insurance program can be addressed in a number of published studies[1-3]. The association between statin use and pancreatic cancer risk in the presence of co-morbidities was analyzed.

The demographic characteristics and co-morbidities were compared between pancreatic cancer cases and controls. The cases were more likely to have pancreatitis (15.1% Vs 1.67%, Chi-square test for $p < 0.0001$), diabetes mellitus (29.4% Vs 19.8%, Chi-square test for $p < 0.0001$), gallstones (19.1% Vs 8.2%, Chi-square test for $p < 0.0001$), hepatitis C infection (3.4% Vs 2.22%, Chi-square test for $p < 0.05$), alcoholism (2.31% Vs 0.73%, Chi-square test for $p < 0.0001$), and ever use of non-statin lipid-lowering drugs (15.0% Vs 11.8%, Chi-square test for $p < 0.05$). In addition, 146 subjects had used statins among pancreatic cancer cases (17.7%) and 572 subjects had ever used statins among controls (17.4%) (Chi-square test for $p = 0.81$). The duration of statin use was not statistically different between pancreatic cancer cases and controls (mean ± SD, 20.8 ± 35.6 Vs 21.2 ± 31.4 months, t-test for $p = 0.92$). After adjustment for confounding factors, multivariate logistic regression showed that the adjusted odds ratio (OR) of pancreatic cancer was 0.81 for the statin use group (95% confidence interval (CI) = 0.65-1.03), with reference to statin non-use group. Pancreatitis (OR = 8.81, 95% CI = 6.29-12.3), diabetes mellitus (OR = 1.65, 95% CI =1.37-2.00), gallstones (OR = 2.07, 95% CI = 1.64-2.60), and alcoholism (OR = 2.60, 95% CI = 1.32-5.10), were independent co-morbidities significantly associated with pancreatic cancer.

To date, uncertainty exists as regards the association between statin use and pancreatic cancer risk in the literature[4-6]. In one case-control study in the US, using statins for more than six months could reduce risk of pancreatic cancer by 67% (95% CI = 0.26-0.41)[4]. However, in one cohort study in Finland and one case-control study in the UK, statin use was not associated with the risk of pancreatic cancer (incidence rate ratio = 0.99, 95% CI = 0.95-1.02, and odds ratio = 0.93, 95% CI = 0.76-1.14, respectively)[5,6]. Our study also clearly indicates no association between statin use and pancreatic cancer risk. Because there are conflicting results between the above mentioned observational studies, further well-designed prospective investigation is warranted to comprehensively understand the overall effects of statin use on the risk of pancreatic cancer.

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This brief report is succinct and cogent in discussing the association between statin use and pancreatic cancer risk. Furthermore, it also provides a different context from Taiwan which adds to the cultural variations that can be accounted for. We conclude that no association is detected between statin use and pancreatic cancer risk.

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Declaration: The first two authors equally contributed to this study

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Letter to the Editor

Alcoholism Correlates with Increased Risk of Parkinson's Disease in Taiwan: A Population-based Cohort Study

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INTRODUCTION

So far, there are conflicting results about the association between alcohol consumption and Parkinson's disease. In Ragonese *et al*'s case-control study in Italy, alcohol consumption was found to be inversely related to Parkinson's disease (odds ratio = 0.61, 95% confidence interval (CI) = 0.39 - 0.97)[1]. In Hernán *et al*'s study, beer drinkers have a 30% lower incidence of Parkinson's disease than non-beer drinkers (95% CI = 0.5 - 0.9)[2]. However, another study has shown no association between alcohol consumption and Parkinson's disease[3]. As far as public health is concerned, if more epidemiological information can be illustrated between alcoholism and Parkinson's disease, preventive strategy may be adopted by early targeted intervention of alcoholism. To clarify the impact of alcohol consumption, we conducted this population-based cohort study to explore the relationship between alcoholism and Parkinson's disease in Taiwan.

We used data retrieved from claims information of the National Health Insurance program, implemented in Taiwan from March 1995. This insurance program has covered more than 99% of all national population. The details of insurance program can be found in previous studies[4-6].

The criteria of diseases were defined according to International Classification of Diseases (ICD) 9th Revision. This follow-up design would investigate whether individuals with alcoholism (according to International Classification of Diseases 9th Revision-Clinical Modification, ICD-9 codes 303, 305.00, 305.03, V11.3, V79.1 and V61.41) were at an increased risk of Parkinson's disease (ICD-9 codes 332). The index date was defined as the date of diagnosing alcoholism.

If Parkinson's disease was diagnosed before the date at which cases and controls were identified, these people were excluded from this study. The exposure group consisted of 2244 patients aged 20 years or older with newly diagnosed alcoholism and the non-exposed group consisted of 8976 people without alcoholism (exposed group: non-exposed group = 1:4). Both groups were matched for age and index date from 2000 - 2007. Among 11,220 eligible study subjects, there were 6171 (55%) males and 5049 (45%) females.

The follow-up results showed a higher incidence of Parkinson's disease in the alcoholism group than in the non-alcoholism group (20.7 Vs 11.9 per 10,000 person-years, $p < 0.0001$). After adjustment for confounding factors, multivariate analysis demonstrated that patients with alcoholism were 2.25 times more likely to develop Parkinson's disease than non-alcoholic subjects (hazard ratio = 2.25, 95% confidence interval = 1.31 - 3.86).

The evidence has shown that ethanol reduces dopamine turnover in the *substantia nigra* and caudate nucleus in rats and further interferes with dopaminergic transmission, which may be involved in the behavioral effects of ethanol[7,8]. To date, some case reports have illustrated that alcoholism can induce or aggravate Parkinsonism[9,10]. Although

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the pathogenesis underlying alcoholism-associated Parkinsonism remains unclear, the above case reports indicate that alcohol may impair central dopaminergic mechanism in humans[9,10].

We conclude that alcoholism correlates with increased risk of Parkinson's disease. The mechanism remains to be explored through future research.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Application of Three Uniplex Polymerase Chain Reaction Assays for the Detection of Atypical Bacteria in Asthmatic Patients in Kuwait

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Background: Respiratory infections are known to exacerbate wheezing in many asthmatic patients. We aimed to use molecular methods for the fast detection of *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila* in respiratory specimens from asthmatic patients in Kuwait.
Methods: We used uniplex PCR assays to detect the three atypical bacteria in clinical specimens from 235 asthmatic and non-asthmatic patients in Kuwait. A regression analysis was used to identify the risk factors related to the bacterial type. Group comparisons for similarity were conducted and correlation coefficients were calculated using SPSS statistical software.
Results: The detection limits using uniplex PCR for *C. pneumoniae, L. pneumophila* and *M. pneumoniae* were approximately 1pg, 2.4fg and 12pg of DNA, respectively. *M. pneumoniae* PCR positivity was more common in asthmatic patients (15%) than in non-asthmatic subjects (9%) ($P < 0.05$). A marked difference was observed between patients with acute asthma exacerbation (11%) and patients with chronic (stable) asthma (7%) among Kuwaiti patients; these percentages were 16% for non-Kuwaiti acute asthma patients and 14% for non-Kuwaiti chronic asthma patients ($P < 0.201$). There was a weak positive correlation between asthma severity and PCR positivity for *M. pneumoniae*. The PCR results for *C. pneumoniae* and *L. pneumoniae* were found to be statistically insignificant.
Conclusions: The results of this study suggest that infection with *M. pneumoniae* may be related to the exacerbation of asthma symptoms and could possibly be a factor that induces wheezing.

Different Norovirus Genotypes in Patients with Gastroenteritis in Kuwait

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Norovirus is a leading cause of acute gastroenteritis worldwide. The importance of this virus infection in Kuwait is not known. Eight out of 100 stool samples (8.0%) from children up to 5 years of age with gastroenteritis studied during 2006 - 2007 from one hospital, and 6 out of 70 stool samples (8.5%) from similar children studied from another hospital during 2010-2011 were positive for norovirus by RT-PCR. Out of these 170 samples studied from both hospitals, 10 samples were positive for norovirus when tested by ELISA. Phylogenetic tree analysis of norovirus strains showed that 50% of the norovirus strains belonged to genotype GII.4, and the predominant strain was GII.4 2006b. Other detected genotypes were GII.12, GII.b, GII.3, GII.8, and GII.7. This study highlights the importance of screening for norovirus infection in acute gastroenteritis and having a reporting system to understand better the epidemiology of norovirus infection in Kuwait.

Phthalates in Indoor Dust in Kuwait: Implications for Non-Dietary Human Exposure

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Phthalates are semivolatile organic compounds with a ubiquitous environmental distribution. Their presence in indoor environments is linked to their use in a variety of consumer products such as children's toys, cosmetics, food packaging, flexible PVC flooring among others. The goal of this study was to investigate the occurrence and concentration of phthalates in dust from homes in Kuwait and to assess non-dietary human exposure to these phthalates. Dust samples were randomly collected from 21 homes and analyzed for eight phthalates. The concentrations of total phthalates were log normally distributed and ranged from 470 to 7800 μg/g. Five phthalates [Di(2-ethylhexyl) phthalate (DEHP), Di-n-octyl phthalate (DnOP), Di-n-butyl phthalate (DBP), Benzyl butyl phthalate (BzBP), and Dicyclohexyl phthalate (DcHP)] were routinely detected. The major phthalate compound was DEHP at a geometric mean concentration of 1704 μg/g (median, 2256 μg/g) accounting for 92% of the total phthalates measured. Using the measured concentrations and estimates of dust ingestion rates for children and adults, estimated human non-dietary exposure based on median phthalate concentrations ranged from 938 ng/kg-bd/day for adults to 13362 ng/kg-bd/day for toddlers. The difference in exposure estimates between children and adults in this study supports previous reports that children are at greater risk from pollutants that accumulate indoors.

Genotypic Diversity of Polyomaviruses Circulating among Kidney Transplant Recipients in Kuwait

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BK virus (BKV) and JC virus (JCV) are human polyomaviruses that cause asymptomatic latent infections. Under immunosuppression, BKV-associated nephropathy has been documented in Kuwait and elsewhere. Even though different BKV and JCV genotypes with distinct geographical distribution have been described, the genotype of polyomavirus detected in Kuwait is still unknown. The aim of this study was to determine the genotypes of BKV and JCV detected in renal transplant recipients. The detection of polyomavirus DNA was carried out in serum and urine samples of 200 post-transplant recipients during a 1-year follow-up period. Fifty-one (25.5%) post-transplant recipients were tested positive for polyomavirus DNA by semi-nested PCR. JCV DNA could be detected in 29 (57%) patients, and BKV DNA in 22 (43%) patients. In two renal transplant recipients, both BKV and JCV were detected. According to the Bayesian phylogenetic analysis of polyomavirus VP1 sequences, the majority of detected BKV sequences were most closely related to genotypes I and IV, whereas the majority of JCV sequences were most closely related to genotype 3. Polyomavirus VP1 sequences showed strong stability for up to 12 months in most patients; however, in one patient, an amino acid substitution in the BKV VP1 protein was identified over time. The results suggest a close relationship of BKV sequences with the Asian and European strains, and of JCV sequences with the African strains. Long follow-up studies are needed to investigate the association of polyomavirus polymorphism or genotypic shift with the development of nephropathy.

Laparoscopic Varicocelectomy in Infertile Men: Does Age Matter?

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Introduction: Varicocele affects up to 15% of men in the general population. In couples with subfertility, the prevalence of varicocele in male partners was about 12%. In certain countries like the Middle East and Arabian Gulf, it is not rare to find people in their 5th or 6th decades or even older, who are seeking infertility clinics wishing to achieve paternity.
Objectives: What are the results of laparoscopic varicocelectomy in relatively older infertile men (>40 years) in comparison with young infertile men (<40 years)?
Methods: It is a prospective observational study done in Farwaniya Hospital, Kuwait. Patients (83 cases) were categorized into two age groups: group I (55 patients) with age ranging from 25 to 40 years, and group II (28 patients) with age >40 years (range 41 - 53 years). Cases with clinically detectable varicocele only were included (grade II and III). Cases who underwent varicocelectomy for pain were excluded from the study as well as cases with previous abdominal surgeries. Cases with subclinical and mild varicocele (grade I) were also excluded from the study. The intra- and postoperative parameters as well as the improvement in semen quality were compared in both groups. Patients were seen after 3 and 6 months as outpatients. Cases were followed up for a mean period of 1 year (range from 6 to 22 months).
Results: The intraoperative and postoperative parameters as well as the improvement in semen quality were compared in both groups. There was colonic adhesion to the posterior peritoneum covering internal spermatic veins in 3 cases in group I (3.6%) and in 5 cases in group II (17.8%). This required more dissection to retract the colon and to expose the internal spermatic veins. The mean operative duration for laparoscopic varicocelectomy was significantly longer in group II (75 vs. 45 min in group I). After 3 months, 26 cases (47.2%) of group I and 11 cases (39.2%) of group II had improvement in semen quality. After 6 months, there was improvement in semen quality in 32 cases (58.2%) in group I and in 15 cases in group II (53.5%).
Conclusions: Laparoscopic varicocelectomy in relatively old men is sometimes more difficult technically with relatively longer operative duration. However, it can achieve improvement in semen quality comparable to relatively younger patients. Further randomized controlled trials are needed to draw a more relevant conclusion about the impact of age in the outcome of laparoscopic varicocelectomy.

The Postantifungal Effect of Nystatin and Its Impact on Adhesion Attributes of Oral Candida Dubliniensis Isolates

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Mycoses 2013 Jun 17; doi: 10.1111/myc.12102

The postantifungal effect (PAFE) has an impact on candidal pathogenicity. However, there is no information on either the PAFE or its impact on adhesion traits of oral Candida dubliniensis isolates. Oral candidosis can be treated topically with nystatin. Adhesion to buccal epithelial cells (BEC), germ tube (GT) formation and relative cell surface hydrophobicity (CSH) are all colonisation attributes of candidal pathogenicity. Hence, the main objective of this study was to investigate the in vitro PAFE on 20 C. dubliniensis isolates following exposure to nystatin. In addition, the impact of nystatin-induced PAFE on adhesion to BEC, GT formation and relative CSH of C. dubliniensis isolates were also evaluated. After determining the minimum inhibitory concentration (MIC) of nystatin, C. dubliniensis isolates were exposed to sublethal

concentrations of nystatin for 1 h. Following this exposure, the drug was removed and PAFE, adhesion to BEC, GT formation and relative CSH were determined by a previously described turbidometric method, adhesion assay, germ tube induction assay and biphasic aqueous-hydrocarbon assay respectively. MIC (μg/ml) of C. dubliniensis isolates to nystatin ranged from 0.09 to 0.78. The nystatin-induced mean PAFE (hours) on C. dubliniensis isolates was 2.17. Compared with the controls, exposure to nystatin suppressed the ability of C. dubliniensis isolates to adhere BEC, GT formation and relative CSH by a mean percentage reduction of 74.45% ($P < 0.0001$), 95.92% ($P < 0.0001$) and 34.81 ($P < 0.05$) respectively. Hence, brief exposure of C. dubliniensis isolates to nystatin would continue to wield an antifungal effect by suppressing growth as well as its adhesion attributes.

Oral Immunization with Cholera Toxin Provides Protection against Campylobacter Jejuni in an Adult Mouse Intestinal Colonization Model

Albert MJ, Mustafa AS, Islam A, Haridas S
Department of Microbiology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait. E-mail: john@hsc.edu.kw

MBio 2013 May 7; 4(3):e00246-13. doi: 10.1128/mBio.00246-13

Immunity to Campylobacter jejuni, a major diarrheal pathogen, is largely Penner serotype specific. For broad protection, a vaccine should be based on a common antigen(s) present in all strains. In our previous study (M. J. Albert, S. Haridas, D. Steer, G. S. Dhaunsi, A. I. Smith, and B. Adler, Infect. Immun. 75:3070-3073, 2007), we demonstrated that antibody to cholera toxin (CT) cross-reacted with the major outer membrane proteins (MOMPs) of all Campylobacter jejuni strains tested. In the current study, we investigated whether immunization with CT protects against intestinal colonization by C. jejuni in an adult mouse model and whether the nontoxic subunit of CT (CT-B) is the portion mediating cross-reaction. Mice were orally immunized with CT and later challenged with C. jejuni strains (48, 75, and 111) of different serotypes. Control animals were immunized with phosphate-buffered saline. Fecal shedding of challenge organisms was studied daily for 9 days. Serum and fecal antibody responses were studied by enzyme-linked immunosorbent assay (ELISA) and immunoblotting. The cross-reactivity of rabbit CT-B antibody to MOMP was studied by immunoblotting. The reactivity of 21 overlapping 30-mer oligopeptides (based on MOMP's sequence) against rabbit CT antibody was tested by ELISA. Test animals produced antibodies to CT and MMP in serum and feces and showed resistance to colonization, the vaccine efficacies being 49% (for strain 48), 37% (for strain 75), and 34% (for strain 111) ($P, \leq 0.05$ to ≤ 0.001). One peptide corresponding to a variable region of MOMP showed significant reactivity. CT-B antibody cross-reacted with MOMP. Since CT-B is a component of oral cholera vaccines, it might be possible to control C. jejuni diarrhea with these vaccines.

Importance: Campylobacter jejuni is a major cause of diarrhea worldwide. Patients who recover from C. jejuni diarrhea develop immunity to the infecting serotype and remain susceptible to infection with other serotypes. A vaccine based on a common protective antigen(s) present in all C. jejuni serotypes is expected to provide broad protection. In our previous study, we showed that antibody to cholera toxin (CT) reacted with the major outer membrane proteins (MOMPs) from different strains of C. jejuni. We assumed that the B subunit of the toxin (CT-B), which is nontoxic and a component of licensed oral cholera vaccines, might be the component that cross-reacts with MOMP. In the current study, we showed that orally immunizing mice with CT protected them against colonization upon challenge with different serotypes of C. jejuni. We also showed that CT-B is the component mediating cross-reaction. Therefore, it might be possible to use cholera vaccines to prevent C. jejuni diarrhea. This could result in significant savings in vaccine development and treatment of the disease.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013; 45 (3): 259 - 270

Anticoagulation Management in Primary Care
Sep 16 - 18, 2013
United Kingdom / Birmingham
Contact: Amy Partleton, Centre for Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

Benign **Abdominal Surgery** - Open And Laparoscopic
Sep 16 - 17, 2013
United Kingdom / London
Contact: Royal College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6200
Email: events@rcog.org.uk

Neuroradiology Post Graduate Course - **Head & Neck Radiology**
Sep 16 - 20, 2013
United States / Massachusetts / Cambridge
Contact: Department of Continuing Education, Harvard Medical School
Phone: 617-384-8600; Fax: 617-384-8686
Email: hms-cme@hms.harvard.edu

2013 **Childhood Infections**
Sep 17, 2013
United Kingdom / London
Contact: MA Healthcare Limited
Phone: 011-44-20-7501-6762; Fax: 011-44-20-7978-8319
Email: conferences@markallengroup.com

2013 **Neuroradiology** Review
Sep 18 - 23, 2013
United States / California / Long Beach
Contact: Johns Hopkins University School of Medicine
Phone: 410-502-9634

5th Annual NAPA Course: Advancements in **Shoulder & Hip Arthroscopy**
Sep 18 - 20, 2013
United States / California / Napa
Contact: Paige Ballus, The Napa Course Coordinator
Phone: 336-287-9895; Fax: 336-776-0318
Email: pballus@triad.rr.com

6th Annual World **Molecular Imaging** Congress (WMIC)
Sep 18 - 21, 2013
Georgia / Savannah
Contact: WMIC Office
Phone: 310-215-9730; Fax: 310-215-9731
Email: wmis@wmis.org

ACI **Lung Cancer** Symposium
Sep 18 - 20, 2013
United States / Florida / Tampa
Contact: Chrystyna Pospolyta , Moffitt Cancer Center
Phone: 813-745-4918
Email: Chrystyna.Pospolyta@Moffitt.org

Cancer Vaccines
Sep 18 - 19, 2013
United Kingdom / London
Contact: Fateja Begum, SMi Group Ltd
Phone: 011-44-20-7827-6184
Email: fbegum@smi-online.co.uk

Advanced **Head & Neck** MR Imaging
Sep 19 - 21, 2013
Poland / Krakow
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

Advanced **MR Imaging** of the Chest
Sep 19 - 21, 2013
Spain / Valencia
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

Simultaneous **Multi-Slice/Multiband Imaging**
Sep 19 - 21, 2013
Germany / Essen
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

2013 International Congress for **Joint Reconstruction (ICJR)**: 5th Annual Modern Trends in Joint Replacement
Sep 19 - 21, 2013
United States / California / Indian Wells Orthopedics
Contact: Sylke Anderson, Meeting Administrator , ICJR
Phone: 760-942-7859; Fax: 760-942-1140
Email: sanderson@icjr.net

2013 Quebec CME Program: Update in **Obstetrics and Gynaecology**
Sept 19 – 21, 2013
Canada / Quebec
Contact: Society of Obstetricians and Gynaecologists of Canada
Phone: 800-561-2416 or 613-730-4192
Fax: 613-730-4314

2013 **Reproductive** Health
Sep 19 - 21, 2013
United States / Colorado / Denver
Contact: Association of Reproductive Health Professionals
Phone: 202-466-3825
Email: conferences@arhp.org

5th Florence-Utah Symposium on **Genetics of Male Infertility**
Sep 19 - 21, 2013
Italy / Florence
Contact: Organizing Secretariat, AIM Group International
Phone: 011-39-5-523-3881; Fax: 011-39-55-248-0246

Focused **Thoracic and Vascular Ultrasound**
Sep 19 - 20, 2013
United States / Illinois / Wheeling
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

Breast Reconstruction with Anatomical Implants Course
Sep 19, 2013
United Kingdom / Newcastle
Contact: Professional Education Department, Ethicon
Email: profed@its.jnj.com

ESGAR **Liver Imaging** Workshop 2013
Sep 19 - 20, 2013
Sweden / Stockholm
Contact: European Society of Gastrointestinal & Abdominal Radiology
Phone: 011-43-1-535-8927; Fax: 011-43-1-535-7037
Email: office@esgar.org

Focused **Thoracic and Vascular Ultrasound**
Sep 19 - 20, 2013
United States / Illinois
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

Human Cadaveric **Transurethral Resection and Ureteroscopy** Course
Sep 19 - 20, 2013
United Kingdom / Dundee
Contact: Mr Gordon Hogg , Course Co-ordinator/ Facilitator , Cuschieri Skills Centre
Phone: 011-44-13-8238-3400; Fax: 011-44-13-8264-6042
Email: g.hogg@dundee.ac.uk

Intensive **Breast Ultrasound**: A Histopathologically-Based Approach to Diagnosis & Screening Breast Ultrasound
Sep 19 - 22, 2013
United States / Texas / Dallas
Contact: iiCME, Inc.
Phone: 205-467-0290; Fax: 205-467-0195
Email: iicmemail@gmail.com

One Day Essentials | **Musculoskeletal**
Sep 19, 2013
United Kingdom / London
Contact: RCGP London, Royal College of General Practitioners Conferences Ltd
Phone: 011-44-20-3188-7658
Email: rcgpconf@rcgp.org.uk

Side Effects: Adherence, Tolerability and Insight in **Psychiatric Treatment**
Sep 19 - 22, 2013
United States / North Carolina / Asheville
Contact: Katy Dorman, Membership Coordinator & Meeting Planner , NC Psychiatric Association
Phone: 919-859-3370; Fax: 919-851-0044
Email: kdorman@ncpsychiatry.org

Simultaneous **Multi-Slice/Multiband Imaging**
Sep 19 - 21, 2013
Germany / Essen
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: office@esmrmb.org

State of the Art: **Kidney & Pancreas Transplantation**
Sep 19, 2013
United States / Michigan / Detroit
Contact: Stacy Brand, Office of Continuous Professional Development, University of Michigan Health System
Phone: 734-615-0832
Email: slipson@umich.edu

Virtual **Colonoscopy** Workshop
Sep 19 - 21, 2013
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

12th Annual Update in **Nephrology and Kidney Transplantation**
Sep 20 - 21, 2013
United States / Minnesota / Minneapolis
Contact: Sheila Fick, Education Specialist, Mayo Clinic
Phone: 507-284-0536; Fax: 507-266-7403
Email: cvcme@mayo.edu

14th Annual Interventional **Neuroradiology** Symposium
Sep 20 - 21, 2013
Canada / Ontario / Toronto
Contact: Continuing Education & Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info@cepd.utoronto.ca

17th World Congress of International Society for the Study of **Trophoblastic Diseases (ISSTD)**
Sep 20 - 23, 2013
United States / Illinois
Contact: Society of Gynecologic Oncology
Fax: 312-235-4059
Email: meetings@sgo.org

2013 Fetal and Women's **Imaging**
Sep 20 - 22, 2013
United States / Washington
Contact: World Class CME
Phone: 980-819-5095; Fax: 980-819-5099
Email: office@worldclasscme.com

2013 International **"Stress and Behavior"** PTSD Symposium
Sep 20 - 21, 2013
Armenia / Yerevan
Contact: NA Nutsa, Conference Secretary, International Stress and Behavior Society
Phone: 011-240-899-9571
Email: isbs.congress@gmail.com

21st World Congress of **Neurology**
Sep 21 - 26, 2013
Austria / Vienna
Contact: Rene Chait, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: wcn@kenes.com

Critical Care **Echocardiography**
Sep 21 - 22, 2013
United States / Illinois
Contact: American College of Chest Physicians
Phone: 847-498-1400; Fax: 847-498-5460

GASTRO 2013: Asian Pacific Digestive Week 2013 | World Congress of **Gastroenterology**
Sep 21 - 24, 2013
China / Shanghai
Contact: Congress Central Secretariat, The Meeting Lab
Phone: 011-65-6346-4402; Fax: 011-65-6346-4403
Email: congress_international@gastro2013.org

15th International **Celiac Disease** Symposium
Sep 22 - 25, 2013
United States / Illinois / Chicago
Contact: VISTA Medical Meetings and Events
Phone: 312-803-6840; Fax: 312-577-0959

Liver Biopsy in the Assessment of Medical Liver Disease
Sep 23, 2013
United Kingdom / London
Contact: Royal College of Pathologists
Phone: 011-44-20-7451-6700
Email: info@rcpath.org

Lung Transplantation - Minimally Invasive Surgery
Sep 23 - 24, 2013
France / Elancourt
Contact: ESTS Secretariat , European Society of Thoracic Surgeons
Fax: 011-44-13-9243-0671
Email: sue@ests.org.uk

Cell Culture Asia Congress 2013
Sept 24 - 25, 2013
Singapore / Singapore
Contact: Kathryn Randall , Events and Marketing Assistant , Oxford Global
Email: k.randall@oxfordglobal.co.uk

Damage Control **Orthopaedic Trauma Surgery** (DCOTS)
Sep 24 - 25, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2013 Mucosal Vaccines, Adjuvants & Delivery
Sep 25 - 27, 2013
Denmark / Copenhagen
Contact: Caroline Sumner, Conference Manager , Meetings Management
Phone: 011-44-14-8342-7770; Fax: 011-44-14-8342-8516
Email: csumner@meetingsmgmt.u-net.com

Musculoskeletal Medicine
Sep 25, 2013
United Kingdom / Manchester
Contact: BMJ Masterclasses
Phone: 011-44-20-7387-4410; Fax: 011-44-20-7383-6974

2013 **Viral Hepatitis** Congress
Sep 26 - 28, 2013
Germany / Frankfurt
Contact: Sophie Lea, Senior Account Director, KP360
Phone: 011-44-16-2566-4392
Email: hep@kp360group.com

Cardiology, Diabetes and CKD
Sep 26, 2013
United Kingdom / Manchester Cardiology, Endocrinology, General Medicine
Contact: BMJ Masterclasses
Phone: 011-44-20-7387-4410; Fax: 011-44-20-7383-6974

6th International Conference on **Autoimmunity:** Mechanisms & Novel Treatments
Sep 27 to Oct 3, 2013
Greece / Corfu
Contact: Aegean Conferences, Inc.
Phone: 610-527-7630; Fax: 610-527-7631

Practical Approach to **Electromyography and Neuromuscular Disorders**
Sep 27 – 29, 2013
United States / Massachusetts / Boston
Contact: Continuing Medical Education , Boston University School of Medicine
Phone: 617-638-4605; Fax: 617-638-4905
Email: cme@bu.edu

3rd Abu Dhabi Advanced **Rheumatology** Review Course
Sep 28 - 30, 2013
United Arab Emirates / Abu Dhabi
Contact: Charline Richard, K.I.T. Group GmbH
Phone: 011-49-30-2460-3286
Email: crichard@kit-group.org

9th International Symposium on **Melanoma** & Other Cutaneous Malignancies
Sep 28, 2013
United States / Florida / Tampa
Contact: Chrystyna Pospolyta, Moffitt Cancer Center
Phone: 813-745-4918
Email: Chrystyna.Pospolyta@Moffitt.org

Cancer Medicine and Hematology
Sep 29 - Oct 4, 2013
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

Infectious Diseases in Pregnant Women, Fetuses and Newborns
Sep 29 - Oct 3, 2013
Italy / Bertinoro
Contact: Roberta Partisani, Administrative Secretariat, CEUB Bertinoro
Phone: 011-39-54-344-6500; Fax: 011-39-54-344-6557

3rd World **Parkinson Congress**
Oct 1 - 4, 2013
Canada / Quebec / Montreal
Contact: Catherine Vallé, Congress Secretariat , JPdL International
Phone: 514-287-9898 ext. 300; Fax: 514-287-1248
Email: secretariat@worldparkinsoncongress.org

Advanced Techniques in **Benign Oesophago Gastric Surgery**
Oct 3 - 4, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, IMACS Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: najma.amir@nhs.net

Intermediate **Cognitive Therapy** Course
Oct 3 - 5, 2013
Canada / Ontario / Toronto
Contact: Janey Haggart, Centre for Addiction and Mental Health, Toronto
Phone: 416-535-8501 ext. 6021, Fax: 416-595-6617
Email: janey_haggart@camh.net

UAE **Cancer** Congress 2013
Oct 3 - 5, 2013
United Arab Emirates / Dubai Radiology / Imaging
Contact: Eyad Zerba, MR, MCI Dubai Office
Phone: 011-971-4-311-6300; Fax: 011-971-4-311-6301
Email: Uaecancercongress@Mci-Group.Com

Musculoskeletal MRI LI
Oct 4 - 18, 2013
Latvia / Riga
Contact: Walter Rijsselaere, Department Of Radiology, Uz Brussel
Phone: 011-32-2-477-5322; Fax: 011-32-2-477-5622
Email: Walter.Rijsselaere@Uzbrussel.Be

23rd World Congress on Ultrasound in **Obstetrics & Gynecology**
Oct 6 - 9, 2013
Australia / Sydney
Contact: Congress Secretariat, International Society Of Ultrasound In Obstetrics & Gynecology
Phone: 011-44-20-7471-9955; Fax: 011-44-20-7471-9959
Email: Congress@Isuog.Org

2nd International Summit on **Toxicology**
Oct 7 - 9, 2013
Nevada / Las Vegas
Contact: Mr. Lincy, Toxicology-2013, Omics Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: Toxicology2013@Omicsgroup.Com

Advancing **IV Therapy**
Oct 9, 2013
United Kingdom / London
Contact: Kerry Tarrant, Programme Director, Healthcare Conferences UK
Phone: 011-44-19-3242-9933; Fax: 011-44-19-3288-0402
Email: Kerry@Healthcareconferencesuk.Co.UK

Infectious Diseases
Oct 9, 2013
Canada / Ontario
Contact: Continuing Professional Development, Faculty of Health Sciences, Queen's University
Phone: 613-533-2540; Fax: 613-533-6642
Email: Cpd.Che@Queensu.Ca

Skin Cancer Course
Oct 9, 2013
United Kingdom / Manchester
Contact: British Association Of Plastic, Reconstructive And Aesthetic Surgeons
Phone: 011-44-20-7831-5161; Fax: 011-44-20-7831-4041

2013 Global **Breast Cancer** Conference
Oct 10 - 12, 2013
South Korea / Seoul
Contact: Jay Hwang, Secretariat For Gbcc2013, Intercom
Phone: 011-82-2-501-7065; Fax: 011-82-2-3452-7292
Email: Gbcc@Intercom.Co.Kr

Diabetic Limb Salvage 2013
Oct 10 - 12, 2013
United States /District of Columbia / Washington
Contact: International Conference Management
Phone: 337-235-6606; Fax: 337-235-7300
Email: Info@Dlsconference.Com

1st Annual World Congress of **Geriatrics and Gerontology** 2013 (WCGG-2013)
Oct 12 - 15, 2013
China / Dalian
Contact: Julia Wang, Bit Congress Inc.
Phone: 011-86-411-8457-5669 Ext. 873; Fax: 011-86-411-8457-5669 Ext. 873
Email: Julia@Wcgg-Bit.Com

8th World Congress of **Immunopathology, Respiratory Allergy & Asthma**
Oct 12 - 15, 2013
United Arab Emirates / Dubai
Contact: World Immunopathology Organization
Phone: 011-7-495-735-1414; Fax: 011-7-495-735-1414
Email: Info@Wipocis.Org

Acute Cardiac Care 2013
Oct 12 - 14, 2013
Spain / Madrid
Contact: European Society of Cardiology
Phone: 011-33-4-9294-7600; Fax: 011-33-4-9294-8622

Diffusion: What it means and how to measure it
Oct 12 - 14, 2013
Croatia / Split
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: Office@Esmrmb.Org

Sclerotherapy
Oct 12 - 13, 2013
United States / Nevada / Las Vegas
Contact: Julie Woods, Registration and Product Coordinator , National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: Julie@Npinstitute.Com

10th International Congress on **Coronary Heart Disease**
Oct 13 -16, 2013
Italy / Florence
Contact: Tammy Lessick , Apm , Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: Iccad@Kenes.Com

RCGP Certificate in the Detection, Diagnosis & Management of **Hepatitis B & C** in Primary Care Part 1
Oct 15, 2013
United Kingdom / Birmingham
Contact: Lynette Houghton, Royal College of General Practitioners Conferences Ltd
Email: Lynette.Houghton@Nhs.Net

Diabetes and Endocrinology
Oct 16, 2013
United Kingdom / London
Contact: BMJ Masterclasses
Phone: 011-44-20-7387-4410; Fax: 011-44-20-7383-6974

Transplant **Immunosuppression**
Oct 16 -19, 2013
United States / Minnesota / Minneapolis
Contact: Jolene Bell Makowesky, Education Coordinator, Office of Continuing Medical Education, University of Minnesota
Phone: 612-626-1712; Fax: 612-626-7766
Email: Jolenem@Umn.Edu

3rd **Pediatric Allergy & Asthma** Meeting
Oct 17 -19, 2013
Greece / Athens
Contact: European Academy of Allergy & Clinical Immunology Hq
Phone: 011-41-44-205-5533; Fax: 011-41-44-205-5539
Email: Events@Eaaci.Org

8th International Congress On **Vascular Dementia** & 1st Cognitive Impairment European Meeting
Oct 17 - 20, 2013
Greece / Athens
Contact: Ronit Eisenbach, Apm, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: Icvd@Kenes.Com

Advanced Neuro Imaging: **Diffusion, Perfusion, Spectroscopy**
Oct 17 - 19, 2013
Croatia / Split
Contact: European Society For Magnetic Resonance In Medicine & Biology
Email: Office@Esmrmb.Org

Anatomy & Surgical Exposures In Orthopaedics Course
Oct 17 - 18, 2013
United Kingdom / Oswestry
Contact: Institute Of Orthopaedics, The Robert Jones And Agnes Hunt Orthopaedic Hospital NHS Foundation Trust
Phone: 011-44-16-9140-4661

Skin & Wound Management Course & NAWC Certification Exam
Oct 21 - 25, 2013
United States / Texas / Dallas
Contact: Wound Care Education Institute
Phone: 877-462-9234

Sports Injuries of the Ankle and Foot
Oct 22 - 23, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

2013 Australasian **Sexual Health** Conference
Oct 23 - 25, 2013
Australia / Darwin
Contact: Conference Secretariat, Ashm
Phone: 011-61-2-8204-0770
Email: Info@Shconference.Com.Au

3rd International Congress on **Dual Disorders**
Oct 23 - 26, 2013
Spain / Barcelona
Contact: Natalia Ribas, PM, Tilesa Kenes Spain
Phone: 011-34-91-361-2600; Fax: 011-34-91-355-9208
Email: Secretariat@Cipd2013.Com

Congress Of **Rheumatology**
Oct 23 - 25, 2013
Ukraine / Kiev
Contact: Kristina Zadorina, Nbscience
Phone: 011-380-6-3233-2770; Fax: 011-380-6-3277-6465
Email: Uk@Nbscience.Com

Laparoscopic Suturing Course
Oct 23, 2013
United Kingdom / Dundee
Contact: Mr Gordon Hogg, Course Co-Ordinator/ Facilitator, Cuschieri Skills Centre
Phone: 011-44-13-8238-3400; Fax: 011-44-13-8264-6042
Email: G.Hogg@Dundee.Ac.Uk

2013 **Diabetes** Asia
Oct 24 - 27, 2013
Malaysia / Kuala Lumpur
Contact: Secretariat, National Diabetes Institute
Phone: 011-60-3-7876-1676; Fax: 011-60-3-7876-1679
Email: Enquiry@Nadidiabetes.Com.My

5th Egyptian Annual **Dialysis** Conference
Oct 24 - 26, 2013
Egypt / Cairo
Contact: Mohamed Gomaa, Pure Spot Congress & Event Organizer
Phone: 011-20-2-2672-1944
Email: Info@Egypure.Org

Advanced **MR Imaging** of the Abdomen
Oct 24 - 26, 2013
Belgium / Bruges
Contact: European Society for Magnetic Resonance in Medicine & Biology
Email: Office@Esmrmb.Org

International Conference on **HIV/Aids, STDs, & STIs**
Oct 24 - 25, 2013
United States / Florida / Orlando
Contact: Omics Group, International Conference on Hiv/Aids, Stds, & Stis, Omics Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: Std-Aids2013@Omicsgroup.Com

Lymphoma & Myeloma 2013: An International Congress on Hematologic Malignancies
Oct 24 - 26, 2013
United States / New York
Contact: Imedex, Customer Service, Imedex
Phone: 770-751-7332; Fax: 770-751-7334
Email: Meetings@Imedex.Com

4th Asia Pacific-Singapore **Otology Neurotology & Skull Base** Congress
Oct 25 - 27, 2013
Singapore / Singapore
Contact: Tan Ee Sia, Events360
Phone: 011-65-6618-2235; Fax: 011-65-6886-9536
Email: Register@Events360.Com.Sg

Cardio/Pulmonary Medicine for Primary Care
Oct 25 - 27, 2013
United States / New York
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 / 303-798-9682; Fax: 303-798-5731
Email: Info@Mer.Org

29th Turkish **Cardiology** Congress With International Participation
Oct 26 - 29, 2013
Turkey / Antalya
Contact: Pinar Ceyhun, Meeting Planner, Genx Congress
Phone: 011-90-55-5804-0020; Fax: 011-90-21-6310-0600
Email: Sadik.Yilmaz@Genx.Com.Tr

13th Congress of **Medical Biology** and Genetics
Oct 27 - 30, 2013
Turkey / Aydin
Contact: Medical Biology & Genetics Society, Conplus
Phone: 011-90-216-541-0054; Fax: 011-90-216-541-0108
Email: Sekreterya@Tbgk2013.Org

15th World Conference on **Lung Cancer**
Oct 27 - 30, 2013
Australia / Sydney
Contact: Conference Secretariat, International Conference Services Ltd.
Phone: 604-681-2153; Fax: 604-681-1049
Email: Wclc2013@Icsevents.Com

Laparoscopic Cholecystectomy
Oct 28, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, Imacs Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: Najma.Amir@Nhs.Net

Skin & Wound Management Course & Nawc Certification Exam
Oct 28 - Nov 1, 2013
United States / Connecticut / Hartford
Contact: Wound Care Education Institute
Phone: 877-462-9234

Laser **Ureteric Stone** Removal
Oct 31, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, Imacs Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: Najma.Amir@Nhs.Net

Esor Asklepios Course on **Cardiovascular Imaging For Radiologists** From The Middle East
Nov 1 - 2, 2013
Lebanon / Beirut
Contact: European School of Radiology
Phone: 011-43-1-533-4064
Fax: 011-43-1-533-4064 Ext. 447
Email: Communications@Myesr.Org

Laparoscopic Complex **Hernia Surgical Techniques Symposium**
Nov 1, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, Imacs Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: Najma.Amir@Nhs.Net

5th International **Cancer Control** Congress
Nov 3 - 6, 2013
Peru / Lima
Contact: Conference Secretariat, International Conference Services Ltd.
Phone: 604-681-2153; Fax: 604-681-1049
Email: Iccc2013@Icsevents.Com

Comprehensive Review Of **Musculoskeletal MRI**
Nov 3 - 6, 2013
United States / Hawaii
Contact: Debbie Griffin, Department Of Radiology, Duke University School Of Medicine
Email: Deborah.Griffin@Duke.Edu

15th World Congress of **Psycho-Oncology and Psychosocial Academy**
Nov 4 - 8, 2013
Netherlands / Rotterdam
Contact: International Psycho-Oncology Society
Phone: 434-293-5350; Fax: 434-977-1856
Email: Info@Ipos-Society.Org

2013 **Meningitis & Septicaemia** in Children and Adults
Nov 5th To 6, 2013
United Kingdom / London
Contact: Gillian Currie, Research Officer, Meningitis Research Foundation
Phone: 011-44-14-5428-1811
Email: Gillianc@Meningitis.Org

International **Dementia** Conference
Nov 5 - 6, 2013
United States / Arizona
Contact: Kathleen Nightingale, Co-Founder And CFO , Dementia Therapy Specialists
Phone: 480-688-3924
Email: Kathy@Dementiatherapyspecialists.Com

Laparoscopic **Biliary Surgery**
Nov 5 - 6, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, Imacs Manager, International Minimal Access Centre For Surgery
Phone: 011-44-16-2222-3058
Email: Najma.Amir@Nhs.Net

Advanced **Laparoscopic Renal Resection** Course Using Thiel's Cadavers
Nov 6 - 7, 2013
United Kingdom / Dundee
Contact: Mr Gordon Hogg, Course Co-Ordinator/ Facilitator, Cuschieri Skills Centre
Phone: 011-44-13-8238-3400; Fax: 011-44-13-8264-6042
Email: G.Hogg@Dundee.Ac.Uk

Dermatology & Ophthalmology
Nov 6, 2013
United Kingdom / London
Contact: BMJ Masterclasses
Phone: 011-44-20-7387-4410; Fax: 011-44-20-7383-6974

Fetus & Newborn: State-Of-The-Art Care
Nov 6 - 9, 2013
United States / District of Columbia / Washington
Contact: Contemporary Forums
Phone: 800-377-7707

Gynaecological Cancers
Nov 6, 2013
United Kingdom / London
Contact: Education And Conference Centre, Royal Marsden
Phone: 011-44-20-7808-2921 Or 2924
Email: Conferencecentre@Rmh.Nhs.Uk

Science and Practice of **Head & Neck Pathology**
Nov 6, 2013
United Kingdom / London
Contact:, Royal College Of Pathologists
Phone: 011-44-20-7451-6700
Email: Info@Rcpath.Org

Selected Topics In **Internal Medicine**
Nov 6 - 9, 2013
United States / Florida
Contact: American Academy of Family Physicians
Phone: 800-274-2237 / 913-906-6000; Fax: 913-906-6075

4th Emirates **Cardiac** Society Congress / 1st **Pediatric Cardiology** Meeting
Nov 7 - 9, 2013
United Arab Emirates / Dubai
Contact: Hilda Angel, Project Coordinator, Mci Middle East Llc
Phone: 011-97-1-4311-6300; Fax: 011-97-1-4311-6301
Email: Ecsc@Mci-Group.Com

Advanced Breast & Female Pelvis **MR Imaging**
Nov 7 - 9, 2013
Spain / Barcelona
Contact: European Society For Magnetic Resonance In Medicine & Biology
Email: Office@Esmrmb.Org

Advanced MR Imaging of The **Musculoskeletal** System
Nov 7 - 9, 2013
Norway / Bergen
Contact: European Society For Magnetic Resonance In Medicine & Biology
Email: Office@Esmrmb.Org

RCGP Certificate in the Detection, Diagnosis & Management of **Hepatitis B & C** in Primary Care Part 1
Nov 7, 2013
United Kingdom / London
Contact: Marianne Thompson, Rcgp London, Royal College of General Practitioners Conferences Ltd
Phone: 011-44-20-3188-7658
Email: Hepbandc@Rcgp.Org.Uk

9th National **Sexual Health** in the Surgery Conference
Nov 8, 2013
United Kingdom / London
Contact: Jackie Smith, North West England Faculty, Royal College of General Practitioners
Phone: 011-44-19-2564-6318 / 6310
Email: Jsmith@Rcgp.Org.Uk

Laser & Aesthetic Skin Therapy: What's the Truth?
Nov 8 - 10, 2013
United States / Massachusetts / Boston
Contact: Jennifer Agri, Meeting Manager, Harvard Medical School - Department of Continuing Education
Phone: 617-384-8600; Fax: 617-384-8686
Email: Info@Agrimeetings.Com

Pediatric Anesthesia Conference
Nov 8 - 10, 2013
Canada / Ontario / Toronto
Contact: Michelle Wan, Hospital For Sick Children
Phone: 416-813-7654 Ext. 28120; Fax: 416-813-6924
Email: Li.Conferences@Sickkids.Ca

Ophthalmic Block Hands-On Workshop
Nov 9 - 10, 2013
United States / Florida / Orlando
Contact: Northwest Anesthesia Seminars, Inc.
Phone: 509-547-7065; Fax: 509-547-1265
Email: Info@Nwas.Com

Three Day Course on Obstetric **Anaesthesia and Analgesia**
Nov 11 - 13, 2013
United Kingdom / London
Contact: Obstetric Anaesthetists' Association
Phone: 011-44-20-7631-8883; Fax: 011-44-20-7631-4352

2013 **Trauma** in Critical Care Course
Nov 13 - 14, 2013
United States / Colorado
Contact: Evelyn Smith, Denver Health & Hospital Authority
Phone: 303-602-2703
Email: Evelyn.Smith@Dhha.Org

3rd International Meeting On New Drugs In **Breast Cancer**
Nov 14 - 15, 2013
Italy / Rome
Contact: Aim International
Phone: 011-39-06-330-531; Fax: 011-39-06-3305-3249

4th International **Diabetic Foot** Conference
Nov 14 - 15, 2013
United Arab Emirates / Dubai
Contact: Eyad Zerba, Project Executive, Mci Middle East
Phone: 011-971-4-311-6300; Fax: 011-971-4-311-6301
Email: Idfc@Mci-Group.Com

6th Clinical Trials Conference on **Alzheimer's Disease**
Nov 14 - 16, 2013
United States
Contact: Clinical Trials On Alzheimer's Disease
Email: Ctad@Ant-Congres.Com

Clinical Endocrinology for Primary Care
Nov 15 - 17, 2013
United States / Florida / Orlando
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 Or 303-798-9682; Fax: 303-798-5731
Email: Info@Mer.Org

Clinical Vaccinology Course
Nov 15 - 17, 2013
United States / Massachusetts / Cambridge
Contact: National Foundation for Infectious Diseases
Phone: 301-656-0003
Fax: 301-907-0878

Medical Record Keeping
Nov 15, 2013
Canada / Ontario / Toronto
Contact: Cathy Middleton, Event Coordinator, University Of Toronto
Phone: 888-512-8173 / 416-978-2719
Email: Info@Cepdtoronto.Ca

Multiple Sclerosis: Integrating Scientific Progress into Patient Management
Nov 15 - 16, 2013
Chile / Santiago
Contact: Sara Guglielmini, Congress Coordinator, Meridiano Congress International
Phone: 011-39-6-8859-5211; Fax: 011-39-6-8859-5234
Email: S.Guglielmini@Meridiano.It

Contraceptive and Perineal Procedures
Nov 16 - 17, 2013
United States / Georgia
Contact: Julie Woods, Registration And Product Coordinator, National Procedures Institute
Phone: 800-674-2631; Fax: 512-329-0442
Email: Julie@Npinstitute.Com

How to Manage: **Paediatric Oncology**
Nov 16, 2013
United Kingdom / London Pediatrics
Contact: Events Team, Royal College oOf Paediatrics and Child Health
Phone: 011-44-20-7092-6104
Email: Events@Rcpch.Ac.Uk

5th Pan Arab **Human Genetics** Conference
Nov 17 - 19, 2013
United Arab Emirates / Dubai Genetics
Contact: Shilpa Alakkal, Event Co-Ordinator, Meeting Minds Experts
Email: Shilpa@Meetingmindsdubai.Com

Multidisciplinary Treatment of **CNS (Brain) Tumors**
Nov 17 - 19, 2013
Belgium / Brussels
Contact: European Society for Radiotherapy & Oncology
Phone: 011-32-2-775-9340; Fax: 011-32-2-779-5494
Email: Education@Estro.Org

Child and Adolescent Psychiatry
Nov 20, 2013
Canada / Ontario
Contact: Continuing Professional Development, Faculty of Health Sciences, Queen's University
Phone: 613-533-2540; Fax: 613-533-6642
Email: Cpd.Che@Queensu.Ca

Laparoscopic Hysterectomy
Nov 20, 2013
United Kingdom / Maidstone
Contact: Dr Najma Amir, Imacs Manager, International Minimal Access Centre for Surgery
Phone: 011-44-16-2222-3058
Email: Najma.Amir@Nhs.Net

10th World Congress on **Urological Research**
Nov 21 - 24, 2013
United States / Tennessee
Contact: Society for Basic Urologic Research
Phone: 410-689-3950; Fax: 410-689-3825
Email: Info@Sbur.Org

2nd World Congress on Controversies, Debates & Consensus in **Bone, Muscle & Joint** Diseases
Nov 21 - 24, 2013
Belgium / Brussels
Contact: Bmjd Secretariat, Congressmed
Phone: 011-972-73-706-6950; Fax: 011-972-3-725-6266
Email: Bmjd@Congressmed.Com

5th International Conference on Fixed Combination in the Treatment of **Hypertension, Dyslipidemia & Diabetes Mellitus**
Nov 21 - 24, 2013
Thailand / Bangkok
Contact: Noa Beer-Raveh, Conference Secretariat, Paragon Conventions
Phone: 011-41-22-533-0948
Email: Fixed2013@Fixedcombination.Com

Advances in the Diagnosis and Treatment of **Lung Cancer**
Nov 21, 2013
United Kingdom / London
Contact: Education and Conference Centre, Royal Marsden
Phone: 011-44-20-7808-2921 Or 2924
Email: Conferencecentre@Rmh.Nhs.Uk

IMCAS India 2013: International Master Course on **Aging Skin**
Nov 23 - 24, 2013
India / Goa
Contact: IMCAS
Phone: 011-33-1-4073-8282; Fax: 011-33-1-4070-9240
Email: Contact@Imcas.Com

Refresher Day - **Otolaryngology- Head and Neck Surgery**
Nov 27, 2013
Canada / Ontario
Contact: Angelika Edwards Continuing Professional Development, Schulich School of Medicine and Dentistry
Phone: 519-685-8500 Ext. 55807
Email: Angelika.Edwards@Lhsc.On.Ca

Oral Cancer: What You Need to Know but were Afraid to Ask
Nov 30, 2013
Canada / Ontario
Contact: Linda Bruce, Continuing Professional Development , Schulich School of Medicine and Dentistry
Phone: 519-661-2111 Ext. 81577
Email: Cpd@Schulich.Uwo.Ca

Echocardiography: Hands-on Cardiac Ultrasound Imaging and Doppler
Dec 2 - 7, 2013
United States / Texas
Contact: Keith Mauney & Associates Ultrasound Training
Phone: 800-845-3484 Or 972-353-3200
Fax: 817-577-4250

Operative Skills in **Orthopaedic Surgery**
Dec 2 - 4, 2013
United Kingdom / Sheffield
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

10th Malaysia **Genetics Congress** (Mgc10)
Dec 3 - 5, 2013
Malaysia / Kuala Lumpur
Contact: Ms Marcus Chew, Genetics Society Of Malaysia
Phone: 011-603-2162-0566; Fax: 011-603-2161-6560
Email: Mgc2013@Console.Com.My

11th International Congress of **Dermatology**
Dec 4 - 7, 2013
India / New Delhi
Contact: All India Institute of Medical Sciences
Phone: 011-91-11- 2659-3217 / 2659-4224; Fax: 011-91-11-2658-8663

2013 Excellence in **Paedatrics**
Dec 4 - 7, 2013
Qatar / Doha
Contact: Excellence in Paediatrics
Email: Eip@2eic.Com

Bit 5th International **Congress of Cardiology**-2013
Dec 4 - 5, 2013
Italy / Rome
Contact: Ruby, Bit's 5th International Congress of Cardiology-2013 , Bit
Phone: 011-86-411-847-9960 Ext. 9898; Fax: 011-86-411-8479-9609 Ext. 836

2013 **Menopause-Andropause-Antiaging** Congress
Dec 5 - 7, 2013
Austria / Vienna
Contact: Romy Reiser, Kuoni Destination Management Austria Gmbh
Phone: 011-43-1-319-7690 Ext. 29; Fax: 011-43-1-319-1180
Email: Menopause@At.Kuoni.Com

Paediatric Radiation Oncology
Dec 5 - 7, 2013
Belgium / Brussels
Contact: European Society For Radiotherapy & Oncology
Phone: 011-32-2-775-9340; Fax: 011-32-2-779-5494
Email: Education@Estro.Org

2013 **Brain and Behavior**
Dec 6 - 7, 2013
United States / Louisiana / New Orleans
Contact: Center for Continuing Education, Tulane University Health Sciences Center
Phone: 504-988-5466; Fax: 504-988-1779
Email: Cme@Tulane.Edu

Reconstructive Techniques in **Urology**
Dec 6, 2013
United Kingdom / London
Contact: Royal College of Surgeons Of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

15th Emirates **Ophthalmology** Congress
Dec 12 - 14, 2013
United Arab Emirates / Dubai
Contact: Eoc 2013, Pco, Mci Middle East
Phone: 011-97-1-4311-6300; Fax: 011-97-1-4311-6301
Email: Eoc@Mci-Group.Com

2013 Advances in **Inflammatory Bowel Disease**
Dec 12 - 14, 2013
United States / Florida / Hollywood
Contact: Imedex
Phone: 770-751-7332; Fax: 770-751-7334

4th Asia-Pacific **Osteoporosis** Meeting
Dec 12 - 15, 2013
China / Hong Kong
Contact:MeetingSecretariat,InternationalOsteoporosis Foundation
Phone: 011-41-22-994-0100
Fax: 011-41-22-994-0101
Email: Hongkong2013@Iofbonehealth.Org

Musculoskeletal Ultrasound
Dec 13 - 15, 2013
Belgium / Brussels
Contact: Hitachi Medical Systems Europe Holding Ag
Fax: 011-41-41-748-6332
Email: Courseregistration@Hitachi-Medical-Systems.Com

World Allergy Organization (WAO) Symposium on **Immunotherapy & Biologics**
Dec 13 - 14, 2013
United States / Illinois / Chicago
Contact: Wao Secretariat, Wao
Phone: 414-276-1791; Fax: 414-276-3349
Email: Symposium@Worldallergy.Org

3rd Workshop on **HCV Therapy** Advances
Dec 14 - 15, 2013
Italy / Rome
Contact: Organizing Secretariat, Virology Education
Phone: 011-31-30-230-7140
Fax: 011-31-30-230-7148
Email: Info@Virology-Education.Com

2nd International Training Course on **Renal Transplantation**
Dec 22 - 25, 2013
Egypt / Mansoura
Contact: Urology & Nephrology Center, Mansoura University
Phone: 011-20-50-226-2222
Fax: 011-20-50-226-3717
Email: Ahmed.Shokeir@Hotmail.Com

Rheumatology and Musculoskeletal Medicine for Primary Care
Dec 29 - 31, 2013
United States / Florida / Orlando
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 / 303-798-9682; Fax: 303-798-5731
Email: Info@Mer.Org

Operative Skills in **Urology:** Modules 1 and 2
Jan 7 - 8, 2014
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

43rd **Critical Care** Congress
Jan 9 - 13, 2014
United States / California / San Francisco
Contact: Society of Critical Care Medicine
Phone: 847-827-6869
Fax: 847-827-6886
Email: Info@Sccm.Org

Intermediate **Cardiac Surgery**
Jan 14 - 15, 2014
United Kingdom / Edinburgh
Contact: H. Anderson, Royal College of Surgeons of Edinburgh
Phone: 011-44-13-1668-9239
Email: H. Anderson@Rcsed.Ac.Uk

Pan Arab **Rheumatology** 2014
Jan 14 - 17, 2014
United Arab Emirates / Dubai
Contact: Parc 2014, Pco, Mci Middle East
Phone: 011-971-40-311-6300; Fax: 011-971-40-311-6301
Email: Parc2014@Mci-Group.Com

16th International Conference on Dialysis Advances iIn **Chronic Kidney Disease**
Jan 22 - 24, 2014
United States / Nevada / Las Vegas
Contact: Ingrid Adelsberge, Renal Research Institute
Phone: 646-672-4059; Fax: 646-672-4174
Email: Iadelsberger@Rriny.Com

2014 **Arthroscopic** Surgery
Jan 22 - 25, 2014
United States / Utah / Snowbird
Contact: Sue Duncan, Program Manager, Orthopedic Surgery Seminars, Inc.
Phone: 801-587-5457; Fax: 801-587-7149

2014 Progress and Controversies In **Gynecologic Oncology** Conference
Jan 24 - 25, 2014
Spain / Barcelona
Contact: Prime Oncology
Email: Gyncongress2014@Primeoncology.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
Phone: 011-41-27-771-8585; Fax: 011-41-27-771-8586
Email: Icf@Ms-Event.Ch

2014 Society for **Cardiovascular Magnetic Resonance** (SCMR) Scientific Sessions
Jan 16 - 19, 2014
United States / Louisiana / New Orleans
Contact: SCMR
Phone: 856-423-8955; Fax: 856-423-3420
Email: hq@scmr.org

6th Annual Winter **Hip & Knee** Course
Jan 16 - 19, 2014
United States / Colorado / Vail
Contact: International Congress for Joint Reconstruction
Phone: 760-942-7859
Email: info@icjr.net

Clinical Endocrinology for Primary Care
Jan 24 – 26, 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

2014 **Melanoma**
Jan 25 - 26, 2014
United States / California / San Diego
Contact: Scripps Conference Services
Phone: 858-652-5400
Email: med.edu@scrippshealth.org

Internal Medicine for Primary Care: Endo/Pulm/Ent/Id
Jan 26 - 30, 2014
Hawaii / Maui
Contact: Medical Education Resources, Inc.
Phone: 800-421-3756 or 303-798-9682; Fax: 303-798-5731
Email: info@mer.org

WHO-Facts Sheet

1. The Top 10 Causes of Death
2. Buruli Ulcer (Mycobacterium ulcerans infection)
3. Foodborne Trematode Infections
4. Immunization Coverage
5. Yellow Fever
6. Poliomyelitis

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013, 45 (3): 271 - 282

1. THE TOP 10 CAUSES OF DEATH

The 10 leading causes of death in the world, 2000 and 2011

Ischaemic heart disease, stroke, lower respiratory infections, chronic obstructive lung disease, diarrhoea and HIV/AIDS have remained the top major killers during the past decade.

Tuberculosis is no longer among the 10 leading causes of death, but is still among the top 15, killing one million people in 2011.

Chronic diseases cause increasing numbers of deaths worldwide. Lung cancers (along with trachea and bronchus cancers) caused 1.5 million (2.7%) deaths in 2011, up from 1.2 million (2.2%) deaths in 2000. Similarly, diabetes caused 1.4 million (2.6%) deaths in 2011, up from 1.0 million (1.9%) deaths in 2000.

Road traffic accidents claimed nearly 3500 lives each day in 2011 – about 700 more than in the year 2000 – making it among the top 10 leading causes in 2011. Prematurity claimed 200,000 fewer infant lives in 2011 than in 2000, but remains among the 10 leading causes of death.

Low income

Causes of death	Deaths (in Millions)	% of deaths (within income group)
Lower respiratory infections	0.8	10.4
HIV/AIDS	0.6	7.4
Diarrhoeal diseases	0.6	7.3
Stroke	0.5	5.9
Ischaemic heart disease	0.4	5.0
Preterm birth complications	0.3	4.5
Malaria	0.3	4.1
Tuberculosis	0.3	3.4
Protein-energy malnutrition	0.3	3.4
Birth asphyxia and birth trauma	0.2	3.2

Lower-middle income

Causes of death	Deaths (in Millions)	% of deaths (within income group)
Ischaemic heart disease	2.3	11.7
Stroke	1.9	9.4
Lower respiratory infections	1.5	7.5
Chronic obstructive pulmonary disease	1.3	6.4
Diarrhoeal diseases	1.2	5.9
Preterm birth complications	0.7	3.4
HIV/AIDS	0.6	3.0
Tuberculosis	0.6	2.8
Diabetes mellitus	0.5	2.6
Road injury	0.5	2.4

Upper-middle income

Causes of death	Deaths (in Millions)	% of deaths (within income group)
Stroke	3.2	17.9
Ischaemic heart disease	3.0	17.1
Chronic obstructive pulmonary disease	1.1	6.5
Trachea, bronchus, lung cancers	0.7	4.0
Lower respiratory infections	0.6	3.1
Road injury	0.5	3.1
Diabetes mellitus	0.5	2.9
Liver cancer	0.5	2.6
Hypertensive heart disease	0.5	2.6
Stomach cancer	0.5	2.6

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

High income

Causes of death	Deaths (in Millions)	% of deaths (within income group)
Ischaemic heart disease	1.3	14.1
Stroke	0.8	8.2
Trachea, bronchus, lung cancers	0.6	6.0
Alzheimer disease and other dementia	0.5	5.7
Chronic obstructive pulmonary disease	0.3	3.8
Lower respiratory infections	0.3	3.8
Colon and rectum cancers	0.3	3.2
Diabetes mellitus	0.2	2.5
Hypertensive heart disease	0.2	2.4
Breast cancer	0.2	1.9

Worldwide

Causes of death	Deaths (in Millions)	% of deaths (within income group)
Ischaemic heart disease	7.0	12.9
Stroke	6.2	11.4
Lower respiratory infections	3.2	5.9
Chronic obstructive pulmonary disease	3.0	5.4
Diarrhoeal diseases	1.9	3.5
HIV/AIDS	1.6	2.9
Trachea, bronchus, lung cancers	1.5	2.7
Diabetes mellitus	1.4	2.6
Road injury	1.3	2.3
Preterm birth complications	1.2	2.2

Major causes of death

Q: How many people die every year?

In 2011, an estimated 55 million people died worldwide.

Q: What kills more people: infectious diseases or noncommunicable diseases?

Noncommunicable diseases were responsible for two-thirds of all deaths globally in 2011, up from 60% in 2000. The four main NCDs are cardiovascular diseases, cancers, diabetes and chronic lung diseases. Communicable, maternal, perinatal and nutrition conditions collectively were responsible for a quarter of global deaths, and injuries caused 9% of all deaths.

Q: Are cardiovascular diseases the number one cause of death throughout the world?

Yes, cardiovascular diseases killed nearly 17 million people in 2011, that is three in every 10 deaths. Of these, 7 million people died of ischaemic heart disease and 6.2 million from stroke.

Q: Do most NCD deaths occur in high-income countries?

In terms of number of deaths, 26 million (nearly 80%) of the 36 million of global NCD deaths in 2011 occurred in low- and middle-income countries. In terms of proportion of deaths that are due to NCDs, high-income countries have the highest proportion – 87% of all deaths were caused by NCDs – followed by upper-middle income countries (81%). The proportions are lower in low-income countries (36%) and lower-middle income countries (56%).

Q: WHO often says that smoking is a top cause of death. Where does tobacco use affect these causes of death?

Tobacco use is a major cause of many of the world's top killer diseases – including cardiovascular disease, chronic obstructive lung disease and lung cancer. In total, tobacco use is responsible for the death of about one in 10 adults worldwide. Smoking is often the hidden cause of the disease recorded as responsible for death.

Q: What are the main differences between rich and poor countries with respect to causes of death?

In high-income countries, seven in every 10 deaths are among people aged 70 years and older. People predominantly die of chronic diseases: cardiovascular diseases, cancers, dementia, chronic obstructive lung disease or diabetes. Lower respiratory infections remain the only leading infectious cause of death. Only one in every 100 deaths are among children under 15 years.

In low-income countries, nearly four in every 10 deaths are among children under 15 years, and only two in every 10 deaths are among people aged 70 years and older. People predominantly die of infectious diseases: lower respiratory infections, HIV/AIDS, diarrhoeal diseases, malaria and tuberculosis collectively account for almost one third of all deaths in these countries. Complications of childbirth due to prematurity, and birth asphyxia and birth trauma are among the leading causes of death, claiming the lives of many newborns and infants.

Q: How has the situation changed in the past decade?

Ischaemic heart disease, stroke, lower respiratory infections, chronic obstructive lung disease, diarrhoea and HIV/AIDS have remained the top major killers during the past decade.

Noncommunicable diseases (NCDs) were responsible for two-thirds (36 million) of all deaths globally in 2011, up from 60% (31 million) in 2000. Cardiovascular diseases alone killed nearly two million more people in 2011 than in the year 2000.

Tuberculosis, while no longer among the 10 leading causes of death in 2011, was still among the 15 causes, killing one million people in 2011. Maternal

deaths have dropped from 420,000 in the year 2000 to 280,000 in 2011, but are still unacceptably high: nearly 800 women die due to complications of pregnancy and childbirth every day.

Injuries continue to kill 5 million people each year. Road traffic accidents claimed nearly 3500 lives each day in 2011 – about 700 more than in the year 2000 – making it among the top 10 leading causes in 2011.

Top 10 causes of deaths

Causes of death	World	Low-income Countries	Lower-middle-income countries	Upper-middle-income countries	High-income countries
Ischaemic heart disease	129	7	43	55	24
Stroke	114	8	34	58	14
Lower respiratory infections	59	15	28	10	6
Chronic obstructive pulmonary disease	54	4	23	21	6
Diarrhoeal diseases	35	10	22	2	1
HIV/AIDS	29	10	11	7	0
Trachea, bronchus, lung cancers	27	1	3	13	10
Diabetes mellitus	26	3	9	9	4
Road injury	23	3	9	10	2
Prematurity	22	6	12	2	0

Q: How many young children die each year, and why?

In 2011, 6.9 million children died before reaching their fifth birthday; almost all (99%) of these deaths occurred in low- and middle-income countries. The major killers of children aged less than five years were pneumonia, prematurity, birth asphyxia and birth trauma, and diarrhoeal diseases. Malaria was still a major killer in sub-Saharan Africa, causing about 14% of under-five deaths in the region.

About 43% of deaths in children younger than five years in 2011 occurred within 28 days of birth – the neonatal period. The most important cause of death was prematurity, which was responsible for one-third of all deaths during this period.

Deaths across the globe: an overview

Imagine a diverse international group of 1000 individuals representative of the women, men and children from all over the globe who died in 2011.

Of those 1000 people:

- 141 would have come from low-income countries, 368 from lower-middle-income countries, 322 from upper-middle-income countries and 169 from high-income countries.
- 153 would have been children under 15 years of age, 412 adults aged 15-69 years old and 435 adults aged 70 years and older.

What would be the top 10 causes of their deaths?

More than half (517) of these 1000 deaths would have been caused by the following 10 conditions:

Why do we need to know the reasons people die?

Measuring how many people die each year and why they died is one of the most important means – along with gauging how diseases and injuries are affecting people – for assessing the effectiveness of a country's health system. Cause-of-death statistics help health authorities determine their focus for public health actions. A country where deaths from heart disease and diabetes rapidly rise over a period of a few years, for example, has a strong interest in starting a vigorous programe to encourage lifestyles to help prevent these illnesses. Similarly, if a country recognizes that many children are dying of malaria, but only a small portion of the health budget is dedicated to providing effective treatment, it can increase spending in this area.

High-income countries have systems in place for collecting information on causes of death in the population. Many low- and middle-income countries do not have such systems, and the numbers of deaths from specific causes have to be estimated from incomplete data. Improvements in producing high quality cause-of-death data are crucial for improving health and reducing preventable deaths in these countries.

2. BURULI ULCER (*MYCOBACTERIUM ULCERANS* INFECTION)

KEY FACTS

- Buruli ulcer is a chronic debilitating skin and soft tissue infection that can lead to permanent disfigurement and disability.
- It is caused by the *Mycobacterium ulcerans* bacterium.
- At least 33 countries with tropical, subtropical and temperate climates have reported Buruli ulcer.
- Between 5000 – 6000 cases are reported annually from 15 of the 33 countries.
- Most cases occur in rural communities in sub-Saharan Africa.
- Nearly half of people affected in Africa are children under 15.
- 80% of cases detected early can be cured with a combination of antibiotics.

- Buruli ulcer is a neglected tropical disease. It is caused by infection with *Mycobacterium ulcerans*, an organism which belongs to the family of bacteria that causes tuberculosis and leprosy.
- Infection leads to destruction of skin and soft tissue with large ulcers usually on the legs or arms. Patients who are not treated early suffer long-term functional disability like restricted joint movement and noticeable cosmetic problems. Early diagnosis and treatment are vital in preventing such disabilities.

Scope of the problem

Buruli ulcer has been reported in 33 countries in Africa, the Americas, and the Western Pacific. The majority of cases occur in tropical and subtropical regions, although, cases have been reported in Australia, China, and Japan.

Most cases are from West Africa notably Benin, Côte d'Ivoire and Ghana. Côte d'Ivoire is the most affected country reporting over 2500 cases per year. Globally, between 5000 – 6000 cases are reported every year from 15 of the 33 countries but considerable under-reporting exists within countries.

Clinical and epidemiological characteristics of cases

The clinical and epidemiological aspects of cases vary (according to geographic area) from different countries and settings. Differences largely depend on the demographical characteristics of the population, level of endemicity and awareness about the disease, extent of active detection efforts, and accessibility to treatment.

In Africa, the majority of patients are children compared to Australia and Japan where most patients are adults (Table I). The sex distribution in Africa and Australia is the same but it appears that more females are affected in Japan (Table II). In general, most lesions occur on exposed parts of the body, particularly the limbs (Table III). The lesions are more frequent on the lower limbs in Africa and Australia compared to Japan.

Table I: Age distribution in years

Countries	<15 years	Mean	Median	Range
Africa	48%	24	15	0.5 – 90
Australia	10%	50	62	1 – 96
Japan	19%	41	48	2 – 81

Table II: Sex distribution

Countries	Males	Females
Africa	52%	48%
Australia	55%	45%
Japan	34%	66%

Table III: Location of lesions

Countries	Upper limb	Lower limb	Other parts of the body
Africa	25%	63%	11%
Australia	31%	64%	5%
Japan	50%	38%	13%

Causative organism

M. ulcerans needs a temperature between 29 – 33 °C (M. tuberculosis grows at 37 °C) and a low (2.5%) oxygen concentration to grow. The organism produces a destructive toxin – mycolactone – which causes tissue damage and inhibits the immune response.

Transmission

The disease is usually found in communities near rivers, swamps and wetlands. Human-linked environmental changes such as deforestation, construction of dams and irrigation systems, sand mining, surface mining of minerals, and agriculture have been linked to the occurrence or exacerbation of the disease.

The exact mode of transmission of *M. ulcerans* is still unknown. However, it appears that different modes of transmission occur in different geographic areas and epidemiological settings. There may be some role for living agents as reservoirs and as vectors of *M. ulcerans*, in particular aquatic insects, adult mosquitoes or other biting arthropods.

In south-eastern Australia for example, there is growing evidence that mosquitoes may be involved in the transmission cycle. Recently, Australian scientists discovered high levels of *M. ulcerans* DNA in the faeces of common ringtail and common brushtail possums collected in endemic areas. However, studies done in Africa on small mammals in endemic areas did not find any *M. ulcerans*.

Buruli ulcer in wild and domestic animals

In Victoria, Australia, Buruli ulcer also occurs in native wildlife and domestic animals. Laboratory-confirmed cases have been diagnosed in koalas, common ringtail possums, a common brushtail possum, a mountain brushtail possum, a long-footed potoroo, horses, dogs, alpacas and a cat.

Signs and symptoms

Buruli ulcer often starts as a painless, swelling (nodule). It can initially also present as a large painless area of induration (plaque) or a diffuse painless swelling of the legs, arms or face (oedema). Local immunosuppressive properties of the mycolactone toxin enable the disease to progress with no pain and fever. Without treatment or sometimes even during antibiotics treatment, the nodule, plaque or oedema

will ulcerate within four weeks with the classical, undermined borders. Occasionally, bone is affected causing gross deformities.

Clinical forms and categories

There are two ways of recording and classifying the disease. The first way is the clinical form of disease: non-ulcerative (nodule, plaque and oedema) versus ulcerative. The second way is based on the size of the lesion. Category I lesions are < 5 cm in diameter; Category II lesions are between 5 - 15 cm and Category III lesions are above 15 cm.

The second classification was introduced following the implementation of antibiotic treatment in 2004 to provide a better appreciation of early detection efforts and how lesions would respond to antibiotic treatment.

Diagnosis

There is no diagnostic test that can be used in the field. Research is in progress to develop one.

Four standard laboratory methods can be used to confirm Buruli ulcer. IS2404 polymerase chain reaction (PCR) is the main method for confirmation because it has the highest sensitivity and results can be available within 48 hours.

WHO recommends that at least 50% of cases reported should be confirmed by PCR. Due to logistical and operational difficulties, results of laboratory confirmation by PCR are not immediately available. However, in experienced hands, clinical diagnosis may be sufficient to make decisions about treatment. A WHO network comprising 16 laboratories in 13 endemic and non-endemic institutions support national control programmes to implement this recommendation.

Depending on the patient's age, location of lesions, pain, and geographic area, other conditions should be excluded from the diagnosis. These include tropical phagedenic ulcers, chronic lower leg ulcers due to arterial and venous insufficiency (often in the older and elderly populations), diabetic ulcer; cutaneous leishmaniasis, extensive yaws. Early nodular lesions are occasionally confused with boils, lipomas, ganglions, lymph node tuberculosis, onchocerciasis nodules or other subcutaneous infections such as fungal infection. In Australia, papular lesions may initially be confused with an insect bite. Cellulitis may look like oedema caused by *M. ulcerans* infection but in the case of cellulitis, the lesions are painful and the patient is ill and febrile.

Treatment

Current treatments for Buruli ulcer are:

1. Antibiotics kill *M. ulcerans bacilli*, stop further production of mycolactone, arrest the progression of the disease, and promote healing. The following combinations of antibiotics for eight weeks may be used to treat the disease:

- Rifampicin (10 mg/kg once daily) and streptomycin (15 mg/kg once daily) (standard treatment and effectiveness proven by a randomised controlled trial); or
- Rifampicin (10 mg/kg once daily) and clarithromycin (7.5 mg/kg twice daily) has been used but effectiveness not proven by a randomized trial. Since streptomycin is contraindicated in pregnancy, the combination of rifampicin and clarithromycin is also considered the safer option for this group of patients.
- Rifampicin (10 mg/kg once daily) and moxifloxacin (400 mg once daily) in adults has also been used, though effectiveness not proven by randomized trial.

2. Complementary treatment such as wound care, surgery (mainly debridement and skin grafting) and interventions to minimize or prevent disabilities are necessary depending on the stage of the disease.

If cases are detected early (Category I), more than 80% of people will heal without the need for hospitalization, surgery and without any disability.

Recurrence of Buruli ulcer after antibiotic treatment is less than 2% compared to 16–30% for surgical treatment alone. In cases where surgery is needed, the extent of surgical removal is reduced after antibiotic treatment.

The average cost of drugs for the 2-month treatment of a patient is 45 Euros or US$ 60.

Paradoxical reaction

Paradoxical reactions have been recently recognized during or after antibiotic treatment when there is new inflammatory disease (presenting as a nodule, plaque or oedema) leading to extension of the existing ulcer, increased local induration or a new lesion on a different part of the body, usually, with pus formation and pain. Sometimes, these are also seen in parts of the body where there was no evidence of disease prior to antibiotic treatment; this may be a result of subclinical infection. These seem to be triggered by mycobacterial antigens and immunostimulators released from clinically unrecognized bacterial foci.

Buruli ulcer and HIV

Until now, coinfection of HIV and Buruli ulcer has not been adequately investigated. However, currently available data on frequency of coinfection suggests this is an area of increasing concern. A study conducted from 2002 – 2003 found that HIV prevalence among patients with Buruli ulcer was higher (2.6%, 11/426) than among controls (0.3%, 2/613). HIV weakens the immune system, making Buruli ulcer progress more aggressive and possibly affects the response to

antibiotic treatment. Co-infected patients are often adults (>15 years old) who present with multifocal lesions and osteomyelitis.

Although further studies are required to improve our understanding of this issue, the management of Buruli ulcer/HIV co-infection may follow the guidelines for managing TB/HIV co-infection.

- HIV counselling and testing should be offered for all patients presenting with BU.
- Buruli ulcer/HIV co-infected patients should be screened for tuberculosis.
- For TB, Buruli ulcer/HIV co-infected patients may receive early antiretroviral treatment to ensure a better response to treatment.

Prevention

There is no vaccine for primary prevention of Buruli ulcer. Bacille Calmette-Guérin (BCG) vaccination appears to offer some short-term protection from the disease.

Secondary prevention is based on early detection of cases.

Control

The objective of Buruli ulcer control is to minimize the suffering, disabilities and socioeconomic burden.

The strategy is based on early detection and antibiotic treatment. The following activities are essential for implementing this strategy:

- information, education and communication at the community level to enhance early reporting;
- training of health workers and village volunteers;
- laboratory confirmation of cases;
- standardized recording and reporting system and mapping;
- strengthening of health facilities;
- monitoring and evaluation of control activities.

WHO has developed technical and information materials to support the implementation of these activities.

Research priorities

Based on the need to improve control measures in the field, there are three main priorities for BU research:

- improvements in antibiotic treatment
- development of simple diagnostic tests
- deciphering the mode of transmission.

Basic and applied research is necessary to achieve these priorities.

6. FOODBORNE TREMATODE INFECTIONS

KEY FACTS

- At least 56 million people suffer from one or more foodborne trematode infections.
- People become infected through the consumption of raw fish, crustaceans or vegetables that harbour the parasite larvae.
- Foodborne trematode infections are most prevalent in South-East Asia and South America.
- Foodborne trematode infections result in severe liver and lung morbidity.
- Safe and effective medicines are available to prevent and treat foodborne trematode infections.

Foodborne trematode infections affect more than 56 million people throughout the world. They are caused by trematode worms ("flukes"), of which the most common species affecting people are *Clonorchis, Opisthorchis, Fasciola* and *Paragonimus*.

People become infected through the consumption of raw or poorly cooked fish, crustaceans and vegetables that harbour the minute larval stages of the parasites (see table 1).

Transmission

Foodborne trematode infections are zoonoses, i.e. they are naturally transmissible from vertebrate animals to people and vice versa. They have complex life-cycles that usually involve two intermediate hosts. The first intermediate host in all cases is a freshwater snail, while the second host differs: in clonorchiasis and opisthorchiasis it is a freshwater fish, while in paragonimiasis it is a crustacean. The final host is always a mammal. People become infected when they ingest the second intermediate host that is infected with larval forms of the parasite. Fascioliasis does not require a second intermediate host and people become infected when the larvae are ingested together with the aquatic vegetables to which they are attached (see Table 1 for details).

Table 1: Epidemiological characteristics of foodborne trematode infections

Disease	Infectious agent	Acquired through consumption of	Natural final hosts of the infection
Clonorchiasis	*Clonorchis sinensis*	Fish	Dogs and other fish-eating carnivores
Opisthorchiasis	*Opisthorchis viverrini*	Fish	Cats and other fish-eating carnivores
Fascioliasis	*Fasciola hepatica, F. gigantica*	Aquatic vegetables	Sheep, cattle and other herbivores
Paragonimiasis	*Paragonimus spp.*	Crustaceans (crabs and crayfish)	Cats, dogs and other crustacean-eating carnivores

Epidemiology

In 2005, more than 56 million people were infected with foodborne trematodes and over 7 000 people died.

Cases of foodborne trematode infections have been reported from over 70 countries worldwide; however South-East Asia and South America are the most affected areas. In these regions, foodborne trematode infections represent a significant public health problem.

Within countries, transmission is often restricted to limited areas and reflects behavioural and ecological patterns, such as people's food habits, methods of food production and preparation, and the distribution of the intermediate hosts. Information on the epidemiological status of foodborne trematode infections in Africa is largely missing.

The economic impact of foodborne trematode infections is significant, and is mainly linked to the expanding aquaculture industry.

Symptoms

The public health burden attributable to foodborne trematode infections is predominantly due to morbidity rather than mortality.

Early and light infections often pass unnoticed, as they are asymptomatic or only scarcely symptomatic. Conversely, if the worm load is high, general malaise is common and severe pain can occur, especially in the abdominal region, and most frequently in the case of fascioliasis.

Chronic infections are invariably associated with severe morbidity. Symptoms are mainly organ-specific and reflect the final location of the adult worms in the body.

Clonorchiasis and opisthorchiasis: the adult worms lodge in the smaller bile ducts of the liver, causing inflammation and fibrosis of the adjacent tissues and eventually cholangiocarcinoma, a severe and fatal form of bile cancer. Both *C. sinensis* and *O. viverrini*, but not *O. felineus*, are classified as carcinogenic agents.

Table 2: Recommended treatments and strategies

Disease	Recommended drug and dosage	Recommended strategy
Clonorchiasis and opisthorchiasis	**Praziquantel** • 40 mg/kg in single administration, or • 25 mg/kg three times daily for 2–3 consecutive days	**Preventive chemotherapy** • In districts where the prevalence of infection is ≥ 20%, treat all residents every 12 months • In districts where the prevalence of infection is < 20%, treat all residences every 24 months, or treat only those individuals reporting the habit of eating raw fish, every 12 months
Fascioliasis	**Triclabendazole** • 10 mg/kg in single administration	**Individual case-management** • Treat all confirmed cases • In endemic areas: treat all suspect cases **Preventive chemotherapy** • In sub-districts, villages or communities where cases of fascioliasis appear to be clustered: treat all school-age children (5–14 years) or all residents, every 12 months
Paragonimiasis	**Triclabendazole** • 2 x 10 mg/kg in the same day (individual case-management), or • 20 mg/kg in single administration (preventive chemotherapy), or **Praziquantel** • 25 mg/kg three times daily for three days (individual case-management)	**Individual case-management** • Treat all confirmed cases • In endemic areas: treat all suspect cases **Preventive chemotherapy** • In sub-districts, villages or communities where cases of paragonimiasis appear to be clustered: treat all residents every 12 months

Fascioliasis: the adult worms lodge in the larger bile ducts and the gall bladder, where they cause inflammation, fibrosis, blockage, colic pain and jaundice. Liver fibrosis and anaemia are also frequent.

Paragonimiasis: the final location of the worms is the lung tissue. They cause symptoms that can be confounded with tuberculosis: chronic cough with blood-stained sputum, chest pain, dyspnoea (shortness of breath) and fever. Migration of the worms is possible: cerebral locations are the most severe.

Prevention and control

Control of foodborne trematode infections aims at reducing the risk of infection and at controlling associated morbidity.

Veterinary public health measures and food safety practices, are recommended to reduce the risk of infection, while, to control morbidity, WHO recommends preventive chemotherapy and improved access to treatment using safe and effective anthelminthic medicines (drugs that expel the worms).

Preventive chemotherapy involves a population-based approach whereby everyone in a given region or area is given medicines, irrespective of their infection status. Individual case-management involves the treatment of people with confirmed or suspected infection (see Table 2).

WHO response

WHO's work on foodborne trematode infections is part of an integrated approach to the control of neglected tropical diseases, and includes:

- development of strategic directions and recommendations
- support for mapping in endemic countries
- support for pilot interventions and control programmes in endemic countries
- support for monitoring and evaluation of implemented activities
- documentation of the burden of foodborne trematode infections and the impact of implemented interventions.

4. IMMUNIZATION COVERAGE

Overview

Immunization averts an estimated 2 - 3 million deaths every year from diphtheria, tetanus, pertussis (whooping cough), and measles. Global vaccination coverage - the proportion of the world's children who receive recommended vaccines - has remained steady for the past few years. For example, the percentage of infants fully vaccinated against diphtheria-tetanus-pertussis (DTP3) was 83% in 2011, 84% in 2010 and 83% in 2009.

During 2011, about 107 million infants worldwide got three doses of DTP3 vaccine, protecting them against infectious diseases that can cause serious illness and disability or be fatal. By 2011, 130 countries had reached at least 90% coverage of DTP3.

KEY FACTS

- Immunization prevents illness, disability and death from vaccine-preventable diseases including diphtheria, measles, pertussis, pneumonia, polio, rotavirus diarrhoea, rubella and tetanus.
- Global vaccination coverage is holding steady
- Immunization currently averts an estimated 2 to 3 million deaths every year
- But, an estimated 22 million infants worldwide are still missing out on basic vaccines
- Current levels of access to recommended vaccines

Haemophilus influenzae type b (Hib) causes meningitis and pneumonia. Hib vaccine was introduced in 177 countries by the end of 2011. Global coverage with three doses of Hib vaccine is estimated at 43%.

Hepatitis B is a viral infection that attacks the liver. Hepatitis B vaccine for infants had been introduced nationwide in 180 countries by the end of 2011. Global hepatitis B vaccine coverage is estimated at 75%.

Human papillomavirus — the most common viral infection of the reproductive tract — can cause cervical cancer, and other types of cancer and genital warts in both men and women. Human papillomavirus vaccine was introduced in 43 countries by the end of 2011.

Measles is a highly contagious disease caused by a virus, which usually results in a high fever and rash, and can lead to blindness, encephalitis or death. By the end of 2011, 84% of children had received one dose of measles vaccine by their second birthday, and 141 countries had included a second dose as part of routine immunization.

Meningitis A is an infection that can cause severe brain damage and is often deadly. By the end of 2012—two years after its introduction—the MenAfriVac vaccine, developed by WHO and PATH, was available in 10 of the 26 African countries affected by the disease. Mumps is a highly contagious virus that causes painful swelling at the side of the face under the ears (the parotid glands), fever, headache and muscle aches. It can lead to viral meningitis. Mumps vaccine had been introduced nationwide in 120 countries by the end of 2011.

Pneumococcal diseases include pneumonia, meningitis and febrile bacteraemia, as well as otitis media, sinusitis and bronchitis. Pneumococcal vaccine had been introduced in 72 countries by the end of 2011.

Polio is a highly infectious viral disease that can cause irreversible paralysis. In 2011, 84% of infants around the world received three doses of polio vaccine. Only three countries - Afghanistan, Nigeria and Pakistan - remain polio-endemic.

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world. Rotavirus vaccine was introduced in 31 countries by the end of 2011.

Rubella is a viral disease which is usually mild in children, but infection during early pregnancy may cause fetal death or congenital rubella syndrome, which can lead to defects of the brain, heart, eyes and ears. Rubella vaccine was introduced nationwide in 130 countries by the end of 2011.

Tetanus is caused by a bacterium which grows in the absence of oxygen, e.g., in dirty wounds or in the umbilical cord if it is not kept clean. It produces a toxin which can cause serious complications or death. The vaccine to prevent maternal and neonatal tetanus had been introduced in over 100 countries by the end of 2011. Vaccination coverage with at least two doses was estimated at 70%, and an estimated 82% of newborns were protected through immunization. Maternal and neonatal tetanus persist as public health problems in 36 countries, mainly in Africa and Asia.

Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. As of 2011, yellow fever vaccine had been introduced in routine infant immunization programmes in 36 of the 48 countries and territories at risk for yellow fever in Africa and the Americas.

Key challenges

Despite improvements in global vaccine coverage during the past decade, there continue to be regional and local disparities resulting from:

- limited resources;
- competing health priorities;
- poor management of health systems; and
- inadequate monitoring and supervision

In 2011, an estimated 22 million infants worldwide were not reached with routine immunization services. About half of them live in three countries: India, Indonesia and Nigeria.

Priority needs to be given to strengthening routine vaccination globally, especially in the countries that are home to the highest number of unvaccinated children. Particular efforts are needed to reach the underserved, especially those in remote areas, in deprived urban settings, in fragile states and strife-torn regions.

World Immunization Week

The last week of April each year is marked by WHO and partners as World Immunization Week. In 2013, more than 180 countries, territories and areas are expected to mark the week with activities including vaccination campaigns, training workshops, round-table discussions and public information campaigns. The theme of World Immunization Week is "Protect your world – get vaccinated". It aims to raise public awareness of how immunization saves lives, encouraging people everywhere to vaccinate themselves and their children against deadly diseases.

5. YELLOW FEVER

KEY FACTS

- Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. The "yellow" in the name refers to the jaundice that affects some patients.
- Up to 50% of severely affected persons without treatment will die from yellow fever.
- There are an estimated 200,000 cases of yellow fever, causing 30,000 deaths, worldwide each year.
- The virus is endemic in tropical areas of Africa and Latin America, with a combined population of over 900 million people.
- The number of yellow fever cases has increased over the past two decades due to declining population immunity to infection, deforestation, urbanization, population movements and climate change.
- There is no specific treatment for yellow fever. Treatment is symptomatic, aimed at reducing the symptoms for the comfort of the patient.
- Vaccination is the most important preventive measure against yellow fever. The vaccine is safe, affordable and highly effective, and a single dose of yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease and a booster dose of yellow fever vaccine is not needed. The vaccine provides effective immunity within 30 days for 99% of persons vaccinated.

Signs and symptoms

Once contracted, the virus incubates in the body for 3 - 6 days, followed by infection that can occur in one or two phases. The first, "acute", phase usually causes fever, muscle pain with prominent backache, headache, shivers, loss of appetite, and nausea or vomiting. Most patients improve and their symptoms disappear after 3 - 4 days.

However, 15% of patients enter a second, more toxic phase within 24 hours of the initial remission. High fever returns and several body systems are affected. The patient rapidly develops jaundice and complains of abdominal pain with vomiting. Bleeding

can occur from the mouth, nose, eyes or stomach. Once this happens, blood appears in the vomit and faeces. Kidney function deteriorates. Half of the patients who enter the toxic phase die within 10 to 14 days, the rest recover without significant organ damage.

Yellow fever is difficult to diagnose, especially during the early stages. It can be confused with severe malaria, dengue hemorrhagic fever, leptospirosis, viral hepatitis (especially the fulminating forms of hepatitis B and D), other hemorrhagic fevers (Bolivian, Argentine, Venezuelan hemorrhagic fevers and others flavivirus as West Nile, Zika virus etc) and other diseases, as well as poisoning. Blood tests can detect yellow fever antibodies produced in response to the infection. Several other techniques are used to identify the virus in blood specimens or liver tissue collected after death. These tests require highly trained laboratory staff and specialized equipment and materials.

Populations at risk

Forty-four endemic countries in Africa and Latin America, with a combined population of over 900 million, are at risk. In Africa, an estimated 508 million people live in 31 countries at risk. The remaining population at risk are in 13 countries in Latin America, with Bolivia, Brazil, Colombia, Ecuador and Peru at greatest risk.

There are an estimated 200,000 cases of yellow fever (causing 30,000 deaths) worldwide each year. Small numbers of imported cases occur in countries free of yellow fever. Although the disease has never been reported in Asia, the region is at risk because the conditions required for transmission are present there. In the past centuries (XVII to XIX), outbreaks of yellow fever were reported in North America (New York, Philadelphia, Charleston, New Orleans, etc) and Europe (Ireland, England, France, Italy, Spain and Portugal).

Transmission

The yellow fever virus is an arbovirus of the flavivirus genus, and the mosquito is the primary vector. It carries the virus from one host to another, primarily between monkeys, from monkeys to humans, and from person to person.

Several different species of the Aedes and Haemogogus mosquitoes transmit the virus. The mosquitoes either breed around houses (domestic), in the jungle (wild) or in both habitats (semi-domestic). There are three types of transmission cycles.

- Sylvatic (or jungle) yellow fever: In tropical rainforests, yellow fever occurs in monkeys that are infected by wild mosquitoes. The infected monkeys then pass the virus to other mosquitoes that feed on them. The infected mosquitoes bite humans entering the forest, resulting in occasional cases of yellow fever. The majority of infections occur in young men working in the forest (e.g., for logging).
- Intermediate yellow fever: In humid or semi-humid parts of Africa, small-scale epidemics occur. Semi-domestic mosquitoes (that breed in the wild and around households) infect both monkeys and humans. Increased contact between people and infected mosquitoes leads to transmission. Many separate villages in an area can suffer cases simultaneously. This is the most common type of outbreak in Africa. An outbreak can become a more severe epidemic if the infection is carried into an area populated with both domestic mosquitoes and unvaccinated people.
- Urban yellow fever: Large epidemics occur when infected people introduce the virus into densely populated areas with a high number of non-immune people and Aedes mosquitoes. Infected mosquitoes transmit the virus from person to person.

Treatment

There is no specific treatment for yellow fever, only supportive care to treat dehydration, respiratory failure and fever. Associated bacterial infections can be treated with antibiotics. Supportive care may improve outcomes for seriously ill patients, but it is rarely available in poorer areas.

Prevention

1. Vaccination: Vaccination is the single most important measure for preventing yellow fever. In high risk areas where vaccination coverage is low, prompt recognition and control of outbreaks through immunization is critical to prevent epidemics. To prevent outbreaks throughout affected regions, vaccination coverage must reach at least 60% to 80% of a population at risk. Few endemic countries that recently benefited from a preventive mass vaccination campaign in Africa currently have this level of coverage.

Preventive vaccination can be offered through routine infant immunization and one-time mass campaigns to increase vaccination coverage in countries at risk, as well as for travelers to yellow fever endemic area. WHO strongly recommends routine yellow fever vaccination for children in areas at risk for the disease.

The yellow fever vaccine is safe and affordable, providing effective immunity against yellow fever within 7 - 10 days for 95% of those vaccinated. A single dose of yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease and a booster dose of yellow fever vaccine is not needed. Serious side effects are extremely rare. Serious adverse events have been reported rarely

following immunization in a few endemic areas and among vaccinated travelers (*e.g.,* in Brazil, Australia, the United States, Peru and Togo). Scientists are investigating the causes.

In regard to the use of yellow fever vaccine in people over 60 years of age, it is noted that while the risk of yellow fever vaccine-associated viscerotropic disease in persons ≥60 years of age is higher than in younger ages, the overall risk remains low. Vaccination should be administrated after careful risk-benefit assessment, comparing the risk of acquiring yellow fever disease versus the risk of a potential serious adverse event following immunization for persons ≥60 years of age who have not been previously vaccinated and for whom the vaccine is recommended.

The risk of death from yellow fever disease is far greater than the risks related to the vaccine. People who should not be recommended to be vaccinated include:

- children aged less than 9 months (or between 6 - 9 months during an epidemic, where the risk of disease is higher than an adverse event of the vaccine);
- pregnant women – except during a yellow fever outbreak when the risk of infection is high;
- people with severe allergies to egg protein; and
- people with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or in the presence of a thymus disorder.

Travelers, particularly those arriving to Asia from Africa or Latin America must have a certificate of yellow fever vaccination. If there are medical grounds for not getting vaccinated, International Health Regulations state that this must be certified by the appropriate authorities.

2. Mosquito control: In some situations, mosquito control is vital until vaccination takes effect. The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites and applying insecticides to water where they develop in their earliest stages. Application of spray insecticides to kill adult mosquitoes during urban epidemics, combined with emergency vaccination campaigns, can reduce or halt yellow fever transmission, "buying time" for vaccinated populations to build immunity.

Historically, mosquito control campaigns successfully eliminated Aedes aegypti, the urban yellow fever vector, from most mainland countries of Central and South America. However, this mosquito species has re-colonized urban areas in the region and poses a renewed risk of urban yellow fever.

Mosquito control programmes targeting wild mosquitoes in forested areas are not practical for preventing jungle (or sylvatic) yellow fever transmission.

3. Epidemic preparedness and response: Prompt detection of yellow fever and rapid response through emergency vaccination campaigns are essential for controlling outbreaks. However, underreporting is a concern – the true number of cases is estimated to be 10 to 250 times what is now being reported.

WHO recommends that every at-risk country have at least one national laboratory where basic yellow fever blood tests can be performed. One laboratory confirmed case of yellow fever in an unvaccinated population could be considered an outbreak, and a confirmed case in any context must be fully investigated, particularly in any area where most of the population has been vaccinated. Investigation teams must assess and respond to the outbreak with both emergency measures and longer-term immunization plans.

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6. POLIOMYELITIS

Introduction

Polio is a highly infectious disease caused by a virus. It invades the nervous system, and can cause total paralysis in a matter of hours. The virus enters the body through the mouth and multiplies in the intestine.

KEY FACTS

- Polio (poliomyelitis) mainly affects children under five years of age.
- One in 200 infections leads to irreversible paralysis. Among those paralyzed, 5% to 10% die when their breathing muscles become immobilized.
- Polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases then, to 650 reported cases in 2011. The reduction is the result of the global effort to eradicate the disease.
- In 2012, only three countries (Afghanistan, Nigeria and Pakistan) remain polio-endemic, down from more than 125 in 1988.
- As long as a single child remains infected, children in all countries are at risk of contracting polio. Failure to eradicate polio from these last remaining strongholds could result in as many as 200,000 new cases every year, within 10 years, all over the world.
- In most countries, the global effort has expanded capacities to tackle other infectious diseases by building effective surveillance and immunization systems.

Symptoms

Initial symptoms are fever, fatigue, headache, vomiting, and stiffness in the neck and pain in the limbs. One in 200 infections leads to irreversible paralysis (usually in the legs). Among those paralyzed, 5% to 10% die when their breathing muscles become immobilized.

People most at risk: Polio mainly affects children under five years of age.

Prevention

There is no cure for polio, it can only be prevented. Polio vaccine, given multiple times, can protect a child for life.

Global caseload

Polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases in more than 125 endemic countries then, to 650 reported cases in 2011. In 2012, only parts of three countries in the world remain endemic for the disease - the smallest geographic area in history – and case numbers of wild poliovirus type 3 are down to lowest-ever levels.

The Global Polio Eradication Initiativ

In 1988, the forty-first World Health Assembly adopted a resolution for the worldwide eradication of polio, which marked the launch of the Global Polio Eradication Initiative (GPEI). Overall, since the GPEI was launched, the number of cases has fallen by over 99%. In 2012, only three countries in the world remain polio-endemic: Nigeria, Pakistan and Afghanistan.

Of the three types of wild poliovirus (type 1, type 2 and type 3), type 2 wild poliovirus transmission has been successfully stopped (since 1999).

More than 10 million people are today walking, who would otherwise have been paralyzed. An estimated more than 1.5 million childhood deaths have been prevented, through the systematic administration of Vitamin A during polio immunization activities.

Opportunity and risks: an emergency approach

The strategies for polio eradication work when they are fully implemented. This is clearly demonstrated by India's success in stopping polio in January 2011, in arguably the most technically-challenging place. However, failure to implement strategic approaches leads to ongoing transmission of the virus. Endemic transmission is continuing in Nigeria, Pakistan and Afghanistan. Failure to stop polio in these last remaining areas could result in as many as 200,000 new cases every year, within 10 years, all over the world.

Recognizing both the epidemiological opportunity and the significant risks of potential failure, the World Health Assembly in May 2012 adopted a resolution declaring the completion of polio eradication a programmatic emergency for global public health.

Subsequently, the three remaining endemic countries launched national polio emergency action plans, overseen in each case by the respective head of state, and the partner agencies of the GPEI also moved their operations to an emergency footing, working under the auspices of the Global Emergency Action Plan 2012 - 2013.

As of mid-2012, the impact of the emergency approaches is being seen, with the lowest number of reported cases in fewer districts of fewer countries than at any previous time.Full financing and implementation of the Global Emergency Action Plan 2012-2013 can realistically and rapidly achieve a lasting polio-free world. But achieving success is a global responsibility, and is now a question of political and societal will.

The benefits of a polio-free world will be shared equally by all countries and peoples everywhere.

Future benefits of polio eradication

Once polio is eradicated, the world can celebrate the delivery of a major global public good that will benefit all people equally, no matter where they live. Economic modeling has found that the eradication of polio in the next five years would save at least US$ 40 – 50 billion, mostly in low-income countries.