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Editorial

The SARS-CoV-2, when first originated in Wuhan, China, little did humanity know that the virus would bring the civilized world to its knees. But now, nearly 6 months after it was discovered, the COVID-19 pandemic has spread to 212 countries claiming nearly 350,000 lives and devastating countless others.

The most powerful human brain, regarded as the wonderful gift of the Almighty seems to be clueless in front of this tiniest microorganism. The humanity, confronted with its preposterous morbidity and mortality is (re)learning both the cost and the necessity of peaceful cohabitation with the nature. The therapeutic and preventive armamentarium that countries have been developing, refining and perfecting has proven wanting in the face of this novel virus. And yet, we persist. Even as we stay in our homes, afraid and suspicious of this invisible enemy, countless healthcare workers have dedicated their lives in combating the disease and protecting those afflicted by it. Many other unsung essential workers also continue to put their lives on the line so that the rest of us can continue to retain some semblance of normalcy. In this, the virus has laid bare a stark paradox of modern life: the people whose work matters the most, often are recognized and rewarded the least.

This edition of the Asian Journal of Medicine and Health Sciences (AJMHS) is therefore dedicated to the selfless and tireless work of those frontline COVID-19 warriors, as a small token of gratitude.

This edition's first review article is extremely timely, with a deep exploration of human behaviour in times of a global crisis like COVID-19. Another article draws a correlation between personality and depression. Not only is this a commonly observed phenomenon among medical students at different stages of their careers, but assumes enormous importance in the middle of the pandemic – as people continue to struggle with mental health conditions and the lack of access to therapeutic services.

The other manuscripts decorating this issue of AJMHS are: a review article focusing on the genetic and environmental aspects of a life threatening disease like Hemophilia and another one depicting the tradition and process of artistic modification and beautification of human body; a section of original articles exemplifying the creative minds of our young student researchers with a touch of refinedness by their supervisors; a brief communication; and few interesting case reports.

I would like to express my deep gratitude to all the authors for contributing their research and the reviewers for spending their valuable time in reviewing the manuscripts despite such trying times. I have my deep appreciation for the associate editor Dr Vignesh for his help in editing and formatting the articles and Mr. Ekhwan Ahmadi for uploading the articles to the website.

This time we have included some objective type questions to create interest among the readers. The questions can be attempted through the link provided at the end of the journal and also by scanning the QR code. The names, affiliations and email IDs of the participants with first 10 correct entries will be published in the next issue of the journal.

I thank AP Dr. FS Malhi for this novel idea.

We hope that as you read this, you and your loved ones are safe and are practicing necessary hygiene and social distancing.

Thank you.

Dr Basanta Kumar Mohanty
Chief Editor, AJMHS

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REVIEW ARTICLE

'SENSE OF COHERENCE' APPROACH TO UNDERSTAND HUMANITY'S RESPONSES TO COVID-19 PANDEMIC AND ADAPTING ROBERTS' CRISIS INTERVENTION MODEL TO COUNSEL PATIENTS.

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Abstract

When facing a crisis like the COVID-19 pandemic, the 'Sense of Coherence' (Antonovsky), which is a composite of Comprehension, Meaningfulness and Manageability, promotes mental wellness and ability to cope with the challenges. Misunderstanding due to false information, and personal beliefs and biases distort the people's perceptions and their coping responses to the pandemic. Medical professionals have an important role and responsibility to foster the sense of coherence among their patients by adapting the 7-step crisis intervention strategy of Roberts and help them cope with the challenges.

Keywords: Sense of Coherence, Coping behavior, COVID-19 pandemic, Crisis-intervention

Introduction

"The meaning of a crisis lies not in the situation but in the interaction between the situation and the ability of the person to successfully cope with it". - WI Thomas (1863-1947)

By all the unprecedented happenings since January 2020, humanity is facing an acute crisis on a global scale due to the corona virus pandemic (CVP) caused by SARS-CoV-2.

Like most crises, the CVP crisis too has five components to it as initially proposed by Roberts[1].

- a hazardous event viz., the emergence of a mutant corona virus SARS- CoV-2.
- a vulnerable state viz., the absence of protective antibodies to combat the virus
- a precipitating factor, which is uncertain and is still being debated
- an active crisis situation, which is based on people's perception of danger; unfortunately in this pandemic, potential danger was not initially recognized by some countries, which has resulted in great hardship and loss of lives
- the resolution of the crisis, which in the case of CVP may take several months more to achieve.

A major crisis nullifies or overwhelms our routine coping mechanisms; it results in feelings of utter helplessness and anguish; it disrupts our equilibrium and engenders functional impairment. Therefore, a stressful life experience compromises our ability to cope or function effectively.

Sense of Coherence (SoC) Perspective of Stressors of a Crisis

Based on his extensive research conducted to study the coping behaviour of the holocaust survivors, Aaron Antonovsky, a medical sociologist proposed that Sense of Coherence (SoC) was the basis of wellness; a strong SoC helped the person to cope better with stressors like crises and diseases. He enunciated that SoC had three components:

i) Comprehensibility, which answered this self-test in an honest manner: "do I truly understand my situation and the reasons for my stress?"
ii) manageability, which answers this self-test: "do I have the resources to cope with it?" and
iii) meaningfulness, which is an unbiased answer to this self-test: "do I feel it is worth my time and effort to manage it – using the resources listed for the preceding query – or should I just be passive and let the crisis pass?"[2]

He proposed that manageability required general resistance resources (GRRs), which were material or non-material in nature and GRR helped in coping with the stressors and challenges in life. He classified GRR into three types:
(i) Adaptability at various levels, viz., biochemical, physical, psychological and socio-cultural levels;
(ii) Deep and meaningful bonding with others, such as family members and friends; and
(iii) Committed and institutionalised supportive links between the person and his/her community.[3]
In addition, Antonovsky stressed on the importance of specific resistance resources (SRRs). He cited numerous examples, which are effective in specific circumstances causing stress and tension, viz., a vaccine for prevention, a specific medication to treat a disease, etc. He indicated that the sense of coherence lead one to focus on active adaptation through the use of GRRs and SRRs to remain well even in a stressful milieu.[2, 3]

I Comprehension

The differences between the cognitive realisation and the emotional reactions of people to a crisis greatly influence their individual comprehension and true understanding of the crisis. In relation to the global crisis of CVP, this is indeed a gut versus brain battle.

The gut feeling is that the CVP would be severe enough to disrupt our normal lives and we may not be able to return to our hitherto way of life for several months. The current reality is that all the experts have predicted a few very challenging months, and perhaps a few years of suffering the adverse sequel to CVP. If one were fully rational, the brain, based on available evidence, would be in agreement with the gut feeling. However, since people are not fully rational beings, some of them may believe that the virus would quickly mutate into a milder strain or that a lifesaving treatment would get discovered overnight.[4]

Balancing Cognition and Emotion in Public Health Campaigns:

i) The public, the target of the campaign, is extremely anxious and yet, often resist rational advice.
ii) The campaign must repeatedly inform the people in an emphatic manner.
iii) The campaign must be proactive and get the people prepared for the subsequent possible actions, such as personal hygiene, social distancing, wearing of protective gear, volunteering to be a convalescent plasma donor, etc.
iv) The campaign leaders must acknowledge the ambivalence of the people, viz., their anxiety and their cognitive resistance, which may make the public initially say the officials are overreacting and later, when the crisis becomes full blown, say the officials showed apathy. The leaders need to acknowledge the public fear and other reactions such as denial, embarrassment, depression, feelings of alienation, etc. so that the people can be at peace with their past behaviour even as they change their mind set.
v) The campaign should be careful in wording the messages. It should not be guilt inducing or intrusive. Such a direct approach can trigger defensive self-doubting denial instead of determination and action. The messages should eschew false optimism and instead foster solidarity, resilience, community-orientedness and adaptability to uncertain days ahead.[4]

II Meaningfulness

Meaningfulness is highly personalised as each individual has a unique set of personal beliefs and values[5]. Every individual perceives all that happens around him/her through these filters.[6]

Recently, a Danish study looked at the individual and personality factors, which correlated with people's willingness in accepting personal restrictions for fighting COVID-19 and their different personality characteristics. In a representative sample of 799 adults, the study found that older age and two personality factors, viz., emotionality and "dark factor" correlated with willingness to accept restrictions. The people found it more meaningful to accept the restrictions if these restrictions were for self-protection rather than to protect others.[7]

Depending on the individual beliefs, people may ascribe the CVP crisis to astrology (malevolent planetary positioning), astronomy (the recent sighting of a comet coming towards the Earth), karma theory (Mother Nature responding to the avaricious exploitation of the natural resources) etc. Their belief system makes them ascribe cause-and-effect relationship to mere coincidental occurrences.

Media cater to such beliefs propagating it further; for example, a recent report stating that Indian Astrologers' predict that CVP will end soon in India and rest of the Globe.[8]

Self-fulfilling prophesy is a related behavioural concept. Merton in 1948 has defined self-fulfilling prophecy as an initially incorrect perception of the situation that evokes behaviours making the incorrect belief appear to be true.[9]

WHO has called the current spread of biased opinions and false information on Coronavirus in various media as an "infodemic". Misleading information is circulating rapidly (virally) on social media. WHO has said that the fight against the "fake news infodemic" would continue as long as the COVID-19 causing virus exists [10].

That the personal belief system distorts the comprehension, meaningfulness and behaviour of the population, is quite evident by the extent of maladaptive coping behaviours discussed in the next section. Therefore, addressing and correcting

personal biases is very important if we want to combat effectively the tsunami of misinformation causing the current infodemic, which is as bad or even worse the real pandemic to the collective human psyche, mental wellbeing and adaptive coping strategies.

III Manageability: Coping with the COVID-19 Viral Pandemic (CVP)

Extrapolating Antonovsky's concept of general resistance resources (GRR) and specific resistance resources (SRR), one could say that the GRR needed to cope with the present CVP crisis would include measures to boost innate immunity, hand hygiene, social distancing, financial support, provision of necessities for living etc. The SRR to cope with the pandemic would be to develop an effective vaccine against COVID-19; develop a reliable rapid diagnostic test; provide various treatment modalities like anti-viral drugs, equipments for respiratory support such as mechanical ventilators, intensive care services etc. The coping ability of an individual depends on the preparation of that individual to meet the threat and his/her motivation to meet the challenge. If preparation is 'taking a horse to water', then motivation is what the horse requires to make the effort to drink it.

Coping abilities of the people vary widely. It could be adaptive or maladaptive in the context of the problem faced. An adaptive strategy aims at resolving the problem, while a maladaptive strategy is often counterproductive.[11]

Some of the strategies in the context of CVP are -

- Anticipatory problem solving: the individual makes a proactive action plan to cover all eventualities and follows it until the end.
- Accepting Responsibility: the individual realises own responsibility in facing up to the challenges and the consequences.
- Confrontation: one meets the crisis head-on and persists with the efforts until achieving the goal.
- Denial: a false belief that nothing has really happened and that people always exaggerate.
- Dependence on social support: these groups of people contact the relief-providers for support.
- Escape or Avoidance: these groups of people believe that they do not have to follow any advice from others and that the crisis will vanish soon.
- Positive reappraisal: these groups of people face the crisis and emerge stronger than they were earlier.
- Self-control: Those, who keep their anxieties and uncertainties to themselves and do not let others, know how bad the crisis has been for them.[11]

It is apparent that denial and avoidance are maladaptive and do not help resolve the CVP crises.

Some of the other coping strategies may be adaptive or maladaptive in the context of the roles and responsibilities of each individual in facing the CVP crisis.[11]

Other coping strategies documented in CVP

Use of unproven remedies as 'cures' – a maladaptive behaviour

Numerous unproven strategies and downright irrational methods, which people are using in various parts of the globe for prevention, diagnosis, treatment of COVID-19 are listed in Wikipedia.[12]

Humour as a coping mechanism

- COVID-19 based cartoons, jokes, memes and videos provide comic relief and distraction from the stark reality unfolding in the pandemic resulting in the populace living in fear and uncertainty.
- Some social psychologists and the artists creating these humorous items opine that the humour and art play an important role in bringing people together, in promoting solidarity and in reducing the anxiety and panic.[13]

According to Christopher Hitchens, laughter makes us feel powerful and humour constitutes a

part of 'the armour-plate of humanity', which shields us from the grim reality of the pandemic. He has opined that in crisis situations, we use humour because if we did not do so, we might only keep crying and feeling depressed and miserable. Robert Provine, a leading expert on laughter, who has done research on how and why people laugh, concluded that laughing together led to social bonding.[14]

Domestic violence as a maladaptive coping behaviour

Globally, there has been an increase in domestic violence and child abuse. Social tensions, which predispose to violent behaviour, seem to arise from reduced access to resources (GRR and SRR), disruption of normal lifestyle, stress of losing job, financial insecurity and being physically isolated from various support systems and relationships.[15]

Coping by the poor without access to food and basic necessities

The CVP crisis and subsequent lockdown in India, done to contain the spread of the virus, has resulted in the poor and marginalised communities without access to food and basic necessities for living. Media have documented them digging in to the city dumps for discarded food items that they could eat and for any other discarded items of value (including face masks and gloves) that they could sell in a flea market.[16, 17]

Meanwhile, thousands of migrant workers, who had lost their jobs in the cities, were stranded without any mode of transport to return home. Perceiving starvation to be a far greater threat than the pandemic, they marched in thousands far and wide in to their native villages. No doubt, several of them might have carried the killer virus to their villages. Time will show its impact in terms of mortality and morbidity in villages, which is lacking in advanced healthcare facilities needed to manage seriously affected individuals.[18]

Panic Buying of Toilet Paper: a maladaptive coping behaviour in the Western nations

Why is toilet paper so much in demand during CVP crisis? Social psychologists opine that there is a psychological reason for stockpiling rolls of toilet paper. Pandemic make people feel vulnerable, uncertain and perhaps create a sense of impending doom. Buying non-perishable items like toilet paper to stock up gives the people some sense of control and preparedness in their lives. They wish to retain their basic dignity in personal hygiene and however irrational it may seem, they feel safer with a stockpile of toilet paper.[19]
Among the media hype that only aggravated panic buying of toilet paper by more people, there were voices of rationality too. The mayor of Houston city tweeted: "Stop panic buying. The world is not coming to an end; but if it does so, the water bottles and toilet paper rolls you have stockpiled will never get used!" [20]

What Medical Professionals can do to help their worried patients?

From clinical and mental health viewpoints, Caplan has listed four stages of human reaction to a crisis.[21]

i) Initial mental tension and agony caused by the hazardous situation,
ii) Intense disruption of daily living by the crisis,
iii) Further rise in tension due to failure of the usual coping mechanisms and
iv) Resolution and relief by successful use of innovative problem-solving methods; alternately, be overwhelmed by the insurmountable crisis leading to mental collapse and depression

The crisis intervention model of Robert is a stepwise blueprint to respond to a crisis like the CVP, which bring in many worried patients for helpful advice. Roberts has enunciated seven stages, which the doctor-patient dyads go through before achieving crisis stabilization, resolution, and mastery.[22]

Adapting Roberts' Seven-Stage Crisis Intervention Model to COVID-19 Pandemic:

Step 1 - Psychosocial & Lethality Assessment: In the context of CVP, explore the resilience and coping abilities of the patient as well as assess his or her vulnerability based on known risk factors for a fatal outcome to COVID-19.

Step 2 - Rapidly Establish Rapport.

Step 3 - Identify Major Problems or Crisis Precipitants: assess the genuine risk for the individual patient based on evidence as against his/her perceived crisis based on personal beliefs and values.

Step 4 - Deal with Feelings & Emotions appropriately.

Step 5 - Generate and Explore Alternatives in a proactive manner for shared decision making.

Step 6 - Implement an Action Plan that the patient can comprehend, find it meaningful and be able to manage; this fosters sense of coherence even in the crisis situation.

Step 7 - Follow-Up: being 'always there for the patient' helps assuage fear and panic. Tele-consultation is a safer way for both the professional and the patient to interact.

Conclusion

The sense of coherence (SoC) seems to be essential for mental wellness and stability during COVID-19 pandemic. To foster SoC, we need to i) promote comprehension of evidence-based scientific information on the pandemic, ii) provide manageable options to cope with the crisis and iii) make it meaningful to the people so that they are motivated to adhere to the crisis management strategies at individual as well as community levels. To help their patients achieve SoC, the medical professionals could adapt the 7-step crisis intervention approach of Robert.

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REVIEW ARTICLE

HETEROGENEITY OF HAEMOPHILIA A GENETIC AND ENVIRONMENTAL FACTORS ON THE DEVELOPMENT OF FACTOR VIII INHIBITORS.

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Abstract

Haemophilia A (HA) is a rare disease by definition, as it affects 1 in 5,000 male livebirths, but it is the commonest among inherited bleeding disorders. There are 1,295 HA cases registered in hospitals under Ministry of Health (MOH) for Factor VIII (FVIII) replacement therapy and 83 (6.4%) are identified to have FVIII allo-antibodies or inhibitors, which is an under-reported figure as studies have shown that 30% of HA develop inhibitors. With the recent adoption of prophylactic FVIII replacement therapy, this treatment modality will greatly improve the quality of life for HA. Unfortunately, 30% of HA develop inhibitors and this causes management of HA with inhibitors very challenging with progressive arthropathy, disability and increase in treatment costs. There have been many studies on mechanisms of inhibitor development, but the pathogenesis is not being fully elucidated. Risk factors to inhibitor development are grouped into genetic or non-modifiable and environmental risk factors. FVIII gene mutation has been consistently identified to be the most important risk factor. This review paper discusses on the genetics and environmental risk factors on inhibitor development in HA, towards better understanding in predicting which HA have the highest risk and lowest risk of inhibitor development and strategized appropriate treatment modality.

Keywords: Haemophilia A, Factor VIII inhibitors, Genetic risk factors, Environmental risk factors.

Prevalence of Haemophilia A

Haemophilia A (HA) is an X-linked recessive disorder, affecting only the boys and manifested as spontaneous musculoskeletal bleeds due to absence or dysfunctional FVIII coagulation protein. Mean prevalence of HA in Malaysia has increased from 5.6 per 100,000 males in 1998 to 6.6 per 100,000 males in 2006, with a mean of 5.9 ± 0.4 per 100,000 males[1]. There are 1,295 HAs registered with Ministry of Health (MOH) in 2017 with 83 (6.4%) of them are having FVIII inhibitors[2]. HA occurs 1 in 5,000-10,000 live male births around the globe and there is no ethnic predilection. Prevalence of HA in high income countries is 12.8 ± 6.0 per 100,000 males and the rest of the world is 6.6 ± 4.8 per 100,000 males. Discrepancy between these 2 categories of countries are due to under reporting of HAs, for example, the number of HAs registered with Haemophilia Federation of India is only about 10% of the expected cases, and similarly in Malaysia and South Africa, the numbers of HA reported are < 50% of the expected cases[3]. Canadian Haemophilia Registry has 3006 HA registered in 2018[4], with 381 HA are in the age group of 65 years and above. A review by Pratap et al, 2019[5] identified that the challenges faced by HA in Canada are of under-diagnosing of HA, ageing community of HA and inhibitor development.

There has been a great improvement in the treatment of HA in Malaysia, the latest being the use of prophylactic treatment with FVIII concentrates as recommended by MOH in 2018. With this treatment strategy, the cost to purchase FVIII concentrates will be increased due to the increase in volume purchased by MOH but there will be reduction in healthcare costs as this will be offset by the resultant reduction in major bleeding episodes, reduction in corrective surgeries for damaged joints and overall improvement in quality of life for children and adults with HA. The economic costs from reduction in absenteeism from work and school will, in totality, save costs to the nation. Nevertheless, there is still a big problem with HA on FVIII replacement therapy, where 20%-35% of severe HAs develop inhibitors[6]. Development of inhibitors is understandably caused from allo-immunization to exogenous FVIII since there is no circulating endogenous FVIII protein. This is not seen in all severe HAs. Inhibitors are also seen in 3-13% of mild and moderate severity HAs[7] where there is endogenous low level production of FVIII. Pathogenesis of inhibitor development is still not well understood. Presence of inhibitor in HA will cause neutralization of the administered FVIII concentrates. This leads to increase in cost of treatment by more than 3 fold as higher doses of FVIII is needed to overcome the antibodies for effective haemostasis.

Factor VIII biology and genetics

Absence of FVIII results in impaired thrombin generation and produces less stable fibrin clots. Severity of bleeding depends on FVIII levels measured by clotting activity in the plasma. Most severe has <1% FVIII activity or equivalent to <0.01 IU of clotting activity per 1 ml of plasma. Moderate has 1-5% of FVIII activity while mild HA has 5-40% of FVIII activity. Severe haemophilia manifested as spontaneous bleeding into muscles and joints, while moderate and mild HA, bleeding is triggered by injury or trauma that leads to prolonged bleeding with poor wound healing. Treatment is by replacement therapy with FVIII concentrates.

FVIII is produced mainly by the liver sinusoidal endothelial cells. The sites of FVIII synthesis was detected using complementary DNA (cDNA) probe which hybridized to messenger RNA (mRNA) of FVIII in tissues and it was discovered that not only most of FVIII mRNA is produced in the liver sinusoidal cells, but there exists expression of FVIII mRNA in isolated hepatocytes, lymph nodes and kidney cells, but not in white blood cells or cultured endothelial cells[8].

Located at Xq28 chromosome[9], the Factor VIII gene spans about 180kb with 26 exons and 25 introns. The exons ranges from the smallest exon 5 with 69 base pairs (bp) to the biggest 3.106

kilobase pairs (kb) of exon 14, while the biggest introns, intron 22 (*IVS22)*, are 32.4 kb[9]. Exon 14 encodes the central B domain. All 26 exons produce 9kb of mature mRNA which is only from 5% of the whole gene and it also produces 2 additional mRNA which is expressed ubiquitously. In *IVS22*, there is a CpG island that promotes 2 additional coding genes *F8A* and *F8B*[10]. *F8A* is transcribed backwards from intronic sequence within *IVS22*. *F8A* has 2 additional repeat sequences placed nearer to *Xq* telomere (telomeric to *F8).* These 2 sites of *F8A* repeats are frequently involved in intra-chromosomal homologous recombination, resulting in recurrent inversion of *IVS22* (inv*IVS22*)[11]. Naylor et al, has defined the repeated region as 9.5 kb and termed as *inth22h-1*(intron 22 homologous region) and the other 2 copies, called *int22h-2* and *int22h-3,* are 300 kb and 400 kb, respectively, and situated 5' end or towards telomere of the *F8* gene (Figure 1C). Using chemical mismatch analysis, these 3 sites involved in inv *IVS 22* are matched 99.9%, hence inv *IVS 22* is one of the commonest *F8* mutations seen in HAs and severe HAs[12].

The exons 1-26 translate into 2,332 amino acids, forming a dimeric protein, consisting of light chain and heavy chain. The heavy chain domain structure A1-a1-A2-a2-B and the light chain with a3-A3-C1-C2. Sulfated tyrosines residues at a2 and a3 domain are the sites that act as co-factor of FVIII with von Willebrand factor (vWf). vWF protect and carried FVIII in the circulation. FVIII is activated by proteolysis at cleavage sites by thrombin and activated FX on C-terminal sites of arginine residues 372, 740 and 1689[12]. Upon activation FVIII leaves vWF to enter the tenase complex for thrombin generation in the coagulation pathway. Participation of FVIII in the tenase complex increases the efficiency of thrombin formation by 200,000-fold. This explain why severe FVIII deficiency profoundly reduces thrombin generation leading to spontaneous and prolonged bleeding.

Immunological response genes and development of inhibitors:

A systematic review on epidemiology of inhibitors in HAs revealed that inhibitors develop early in treatment to FVIII with an average of 10 to 15 days of exposure[13]. After 50-75 exposure days, the cumulative incidence of inhibitors reaches a plateau and beyond 75 days, incidences are not frequent[13]. There exist differences among epidemiology studies of HA inhibitor, especially in cohort studies as data captured are more of prevalence of HAs with inhibitors rather than true incidence rate.

Studies have been done to understand the pathophysiology of inhibitors development. Alloantibodies to FVIII are a mixed subclass of inhibitory immunoglobulin G (IgG) with IgG4 being the main contributor. Antigen presenting cells (APCs) such as dendritic cells (DC) internalized exogenous FVIII, cleaved into peptides, and presents via major histocompatibility / human leucocyte antigen complex class II (MHC/HLA Class II) to CD4+ T cell. Dasgupta et al (2007), has demonstrated that endocytosis of FVIII by human monocyte-derived DC is through the macrophage mannose receptor (MMR/CD206) that recognizes mannose-ending glycans on both heavy and light chains of FVIII[14]. The fragmented peptides of FVIII is presented via HLA Class II to CD4+T cells. The same study also shows that vWf prevents binding of FVIII to MMR/CD206 and blocked by dose-dependent manner the endocytosis of FVIII. This may explain why there is reduced inhibitors seen in HA patients treated with plasma derived FVIII (pdFVIII) concentrates which contain mixture of vWf[15]. Upon recognition of FVIII epitopes, T cells can undergo either one of these two transformations i.e. either to develop tolerance to FVIII or to help B-cell transform into plasma cells to produce antibodies against the epitopes recognised by the T cells.

A study by Hay CR et al (1997), on polymorphisms of HLA Class II genes in HA patients with and without inhibitors and has shown that risk of inhibitors is seen in 3 single-nucleotide polymorphisms (SNPs) HLA Class II which are HLADRB*1501, DQB1*0602 and

DQA1*0102, especially DQA1*0102 (OR 2.7; 1.2-5.9)[16]. Frequency of 3SNPs was reported to be high in patients with inhibitor and inv *IVS22* (OR 3.1; 1.0-10.1) for DQA1*0102[16]. However, this finding is not seen in a similar study by Oldenburg J et al (1997), on patients with inv *IVS22*[17].

In 2009, Pavlova et al performed another study on 260 severe HAs and correlate risk of inhibitors with HLA Class II and immune-regulatory genes. Their results revealed there were higher frequency of inhibitors occurrence in severe HAs with HLA Class II - DRB1*15 and DQB1*0602 alleles as well as of the haplotype DRB1*15/DQB1*0602[18]. Analysis on polymorphisms of the immune-regulatory genes showed alleles -308A in TNF-α, and -1082G allele in the IL-10 have a higher risk of developing inhibitors[18].

A recent study by David S et al (2019), on 447 Indian HAs patients, showed a prevalence of 19.5% inhibitors in this group, and results revealed there was a significant higher risk of inhibitor among HAs that have HLA DRB1*13 positive (RR=2.04; 95% CI 1.06-3.911; p=0.033)[19]. There is also a trend in decreased risk of inhibitor in HAs with HLA DRB1*07 and this achieved significance among high titre inhibitor positive (RR =0.24; 95% CI 0.055-1.05; p=0.047). Of the 14 polymorphisms of immuno-regulatory genes studied, it is found that there is a decreased risk of inhibitor noted with heterozygous IL4-590 C/T allele (residue 2243250) (RR = 0.22;95% CI 0.108-0.442: P-0.000)[17]. IL-4 plays a major role in differentiation of antigen-stimulated naïve T cells and immunoglobulin class switching of IgE and IgG4.

FVIII gene mutations and development of inhibitors:

Up to now there are ~ 2179 mutations of FVIII identified to cause haemophilia A and listed in databases Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php), European Association for Haemophilia and Allied Disorders (EAHAD) FVIII gene variant database, previously called HAMSTeR (the Haemophilia A Mutation, Structures, Test and Resource (website; www.factorviii-db.org), CDC Haemophilia Mutation Project-CHAMP for FVIII mutations, and Hemobase: Haemophilia A mutation registry.

Mutations of FVIII gene are divided into 2 main groups, null mutations where no FVIII protein is being produced and the second group where dysfunctional FVIII protein is being produced. The null mutation consists of large single or multi-domain deletions, nonsense mutations, and inv*IVS22* and more than 30% of HAs in this group has develop inhibitors[19]. The second group consists of small deletions, missense and splice site mutations and less than 10% of HAs with these mutations develop inhibitors[20]. Oldenburg J et al (2002), evaluated more genetic data based on type, size and location of FVIII mutations, and include all severity of HAs and concluded that large deletions affecting more than 1 domain have a high risk of (~88%) developing inhibitors than a single domain deletion (~25%) [21]. 40% of HAs with nonsense mutations in the light chain developed inhibitors while 17% of HAs with nonsense mutations in the heavy chain developed inhibitors. Inv *IVS22* and inv *IVS1*demonstrated an intermediate inhibitor prevalence of 21% and 17%, respectively. Mutations of the poly-(A) tail, either a small deletions or insertions were associated with only 3% inhibitor risk while mutations located outside the poly-(A) region has 21% of HA developed inhibitors. Splice site mutations contributed to 17% prevalence in inhibitor where this mutation produced a corrupted mRNA which formed a different FVIII protein to the FVIII concentrates being used as treatment. Missense mutations in the light chain leads to structural and functional changes and this differences carried a higher risk (10%) of developing inhibitors than those in the heavy chain (3%) [12]. It can be generalised that any light chain mutations have a higher risk of developing inhibitors than any heavy chain mutations[21].

In Malaysia, Zahari M et al (2018), from National Blood Centre, Kuala Lumpur performed a study on 100 unrelated HAs, which consisted of 83 (83%) with severe HA, 9 (9%) moderate and 8 (8%) mild HA[22]. This is the first study in Malaysia to comprehensively analyse FVIII gene mutations in 100 HA patients, and the data may

not be representative with other centres in Malaysia. In UK, Green et al, 2008 reported there were 42.7% of severe HA, 16.3% moderate and 41.0% mild HA after they screened 842 families with HA[23]. Hence, the 83% of severe HA in Zahari M et al study was probably due to the fact that, severe HAs were the most frequently seen seeking treatment in hospitals. In this study, there are 14 (14%) HAs with inhibitors. Within the severe HA, 44 (53%) has inv *IVS22*, and 3 (3.6%) have inv *IVS1*[22]. Zahari M et al has also identified 22 novel mutations, including one involving intron 22 with 2 donor splice sites mutation. Of the 44 patients with inv *IVS22*, 5 (11.4%) have inhibitors, and among 3 patients with large deletions, 2 (66.6%) has inhibitors[22]. There should be more studies on HA to include HLA Class II polymorphisms, immune-regulatory genes with FVIII mutations and correlate with risk of inhibitor development. 6.4% of HA with inhibitors in Malaysia[2] is probably under-reporting and should be substantiated further in collaboration with other centres treating haemophilia.

A study by the Italian AICE (Italian Association of Haemophilia Centres) study group on genetics of haemophilia A has analysed 1,296 unrelated HAs and identified *F8* mutations in only 89% of these HAs[24]. They characterised 380 mutations including inv *IVS22* and inv *IVS1*. Inv *IVS22* was found in 52% of patients with severe HA, while inversion *IVS1* was present in 2% of them. Null mutations which includes inv *IVS22*, inv *IVS1*, large deletions, insertions and nonsense mutations are seen in 80% of severe HA, 15% of moderate HAs, and < 1% in mild HAs. About 1/4th of point mutations identified are seen in the coding region of exon 14. After excluding inv *IVS22* and *IVS1*, most of the mutations leading to null phenotype allele are seen in exon 14 which comprises of small deletions (53%), small insertions (74%) and nonsense mutations (33%)[24]. Gouw SC et al, 2012 performed a meta-analysis of 5,383 severe HA and estimated the relative risk of inhibitor development using inv *IVS22* as the reference. Inhibitor risk with large deletions and nonsense mutations was higher than inv *IVS22* (pooled OR= 3.6, 95% CI, 2.3-5.7, and OR = 1.4, 95% CI, 1.1-1.8, respectively[25]. Inhibitor risk with inv *IVS1* and splice-site mutations are equal with inv *IVS22* (pooled OR = 0.9; 9 5%CI, 0.6-1.5 and OR = 1.0; 95% CI, 0.6-1.5), and the risk in small deletions/insertions and missense mutations was lower (pooled OR = 0.5; 95% CI, 0.4-0.6 and OR = 0.3; 95%CI, 0.2-0.4, respectively) [25].

Inv *IVS22* is a null mutation but it poses as an intermediate risk to inhibitor development. It is hypothesized that there are 2 separate FVIII protein which includes exons 1-22 and exons 23-26, expressed intracellularly (refer to Figure 1D). Hence, inv *IVS 22* has endogenous FVIII protein which is non-functional but may provide some degree of tolerance toward exogenous FVIII concentrates used as replacement therapy and this lead to a reduced risk of inhibitor development[25]. Similar hypothesis may explain why risk inhibitor in mutations involving light chain is higher than heavy chain mutations in both missense and nonsense mutations. It is the expression of second mRNA, *F8B* which runs from within the CpG island in *IVS22* through exon 26 at the end of the F8 gene[10]. that is expressed intracellularly that may give the partial tolerance to exogenous FVIII. Any mutations outside *F8B* gene, will have partial tolerance, hence reduced likelihood of developing inhibitor while mutations that also involve *F8B* gene will have increased risk of developing inhibitor[26].

Environmental risk factors:

Inhibitor development has also been studied with clinical parameters which includes age of HA when the first treatment was started with FVIII concentrates, intensity of treatment and type of FVIII concentrates used either pdFVIII concentrates and recombinant FVIII products (rFVIII). Lorenzo et al (2001) reported that infusing FVIII concentrates before 6 months of age is associated with higher risk of inhibitor formation[27].

Intensity of treatment with continuous infusion and large doses given has been reported to induce inhibitor formation[28]. Gouw SC et al (2013) reported the findings under the Research of Determinants of Inhibitor development (RODIN) Study Group that high-dose intensive FVIII

treatment used to control haemostasis in surgery was associated with increased risk for inhibitor development[28]. The same study also revealed that, between prophylactic treatment and on-demand treatment, there is a decreased risk of inhibitor development in patients given prophylactic FVIII concentrates. This a surprising finding because the study also discovered that within the first 20 exposure days, patients receiving prophylaxis had exactly the same inhibitor risks as the patients treated on demand[28]. Hence, there is no clear conclusion which patients will benefit from the protective effect of prophylactic treatment on inhibitor development.

Rosendaal et al (2017) reported that in previously untreated haemophilia A patients (PUPs), those randomised to pdFVIII concentrates have shown no development of inhibitors in PUPs with low risk FVIII mutations, whereas high risk of FVIII mutations PUPs had a cumulative incidence of 31%[29]. The risk was similar among low risk FVIII mutations and high risk FVIII mutations PUPs when they were treated with rFVIII (43% and 47%, respectively). This implied that there was a 43% risk increment for patients with low risk FVIII mutations when they were exposed to treatment with rFVIII. Number needed to harm with rFVIII, was 6.3 for patients with high risk FVIII mutation and only 2.3 for patients with low risk FVIII mutations. This study illustrated the need to stratify patients based on their genetic mutations to allocate appropriate FVIII products for their replacement therapy[29].

PdFVIII concentrates contains vWf and transforming growth factor beta (TGF-β) [28]. vWF bind to FVIII and protects it from proteolysis and stabilizes in circulations. As pdFVIII products are manufactured from plasma of numerous donors, heterogeneity in FVIII protein sequence and other minor plasma proteins exposed to HA patient, may have an immunomodulatory effect or a role in reducing the immune response relative to rFVIII concentrates[30]. Presence of TGF-β reduces the inflammatory response and stimulation to recognise the exogenous FVIII as foreign antigen. Recombinant FVIII has second generation full length rFVIII products utilising albumin and sucrose as a stabilizer, whereas the third generation does not have these stabilizers. Studies has not proven any of these stabilizers to influence immune response[30].

Conclusion:

Studies on mutations of FVIII, family history of inhibitors among family members afflicted with HA, MHC class II and polymorphism in immune-regulatory genes were undertaken to identify risk factors for development of inhibitors. Some studies were not able to replicate results shown by others but mutations of FVIII gene has been a consistent finding as a strong risk factor to develop inhibitor.

The mutations that lead to absence of circulating FVIII and including absence of endogenous intracellular expression of FVIII protein has the highest rate of inhibitor development > 80%. Inv *IVS22* is a null mutation that has no circulating FVIII glycoprotein but if the disrupted exon 1-22 and exon 23-26 able to produce 2 fragmented FVIII glycoproteins, this may induce partial tolerance to exogenous FVIII and reduce the development of inhibitors. Profiling the genetic risks also involve profiling the polymorphisms exhibit by HLA Class II genes and immuno-regulatory gene variants. Although results on these 2 genetic risks studies are not conclusive, it is probably the polymorphisms are dependent on ethnicity or races of the population being studied and some of the studies are actually underpowered due to rarity of the disease.

On the environmental risks, inhibitors are seen in HAs who is exposed at earlier age and with high dose exposure of the first treatment. On products used for replacement therapy rFVIII product has a higher risk that pdFVIII in development of inhibitors. Most of these studies are using second generation rFVIII product. There are better rFVIII designed product with third generation FVIII without albumin, B domain deleted rFVIII product and extended half-life FVIII product in the market. There is a need to design a more robust study on risk factors that incorporates genetic risks namely, FVIII gene mutations, polymorphisms in HLA Class III, immuno-regulatory gene polymorphisms and, although it is not being discussed in this paper, FVIII gene

haplotype polymorphisms together with the environmental risk factors. Using this data, predictive algorithm can be constructed and a personalised treatment strategy can be planned to a newly diagnosed HA patient to reduce the probability of developing inhibitors. New bypassing agents that do not require FVIII exposure can be given to reduce early exposure for exogenous FVIII concentrates in large deletion mutations.

From this review, it is highly recommended that Malaysia needs a national HA database registry that incorporate genetics, laboratory and clinical data so that a predictive strategy can be used to decide on how best to treat our HAs in order to reduce their incidence of developing inhibitors. Any HA child diagnosed with large deletion, inv *IVS22* and inv *IVS1* should not be given large doses of FVIII concentrates in their first exposure. Bypassing agents may be a better choice for these HAs.

Studies on FVIII inhibitors has been carried out for 3 decades and a lot has been discovered but not totally conclusive. There remain a lot more to be discovered and understood, and inhibitor development need to be solved in order for an effective treatment strategy that actually reduces the healthcare costs of treating haemophilia A.

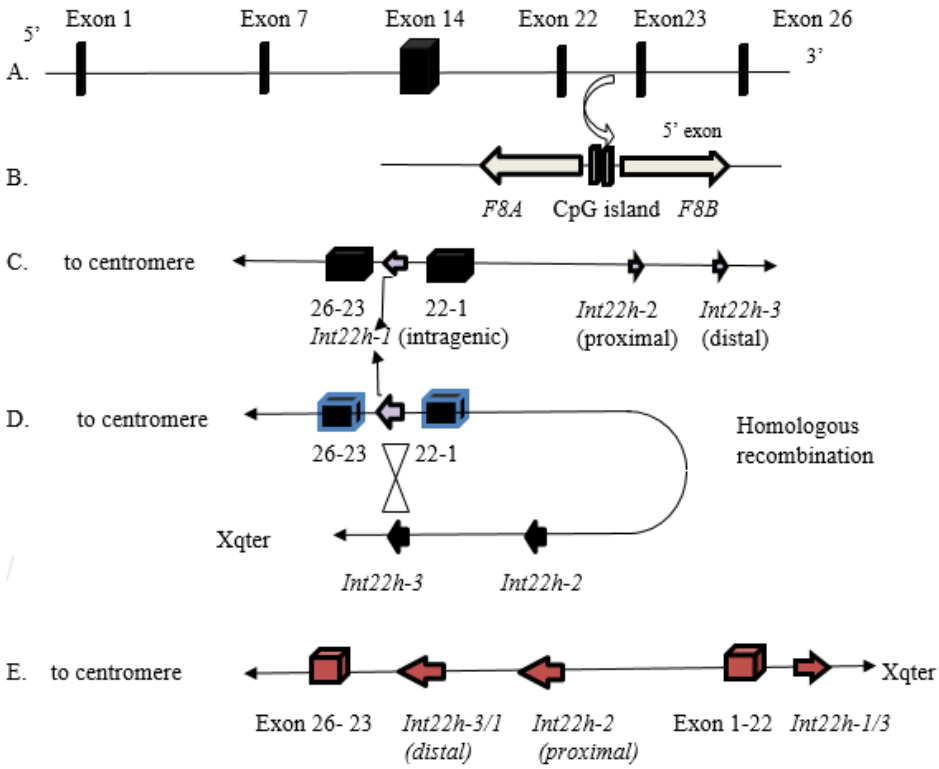

Figure 1: A. Organization of human Factor VIII with 26 exons span over184kb DNA. B. FVIII gene with 3 ORF (open reading frame) and transcribe 3 FVIII mRNA - 9kb FVIII transcript, F8A with backwards transcription and F8B with 5'exon taken from intron 22 and spliced to join the exons 23 o 26[11,12]. C: Location of the Int22h homologues. D. In homologous recombination of chromosome X, the intragenic inth22h homologue will align with either the distal inth22h-3 or the proximal inth22h-2 and produce a disrupted FVIII gene in E with Exons 1-22 are displaced towards the telomere[11,12]. This result in non-continuity from exon 1-22 to exon 26-23 of FVIII gene and mRNA transcription is disrupted leading to absence of FVIII protein in circulation [10,12].

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REVIEW ARTICLE

BODY SCULPTING (AKA AESTHETIC SURGERY) - AN OVERVIEW.

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Abstract

"Beauty is in the eyes of the beholder" Plato – Greek Philosopher (427–347 BCE)

"Love of beauty is taste; Creation of beauty is an Art" – Ralph Waldo Emerson (1803–1882)

From time immemorial people want to appear more beautiful and attractive. This has two objectives, viz. to attract the opposite sex and second to boost their self-esteem amongst the same sex. This article reviews customs used by people of ancient civilization to beautify themselves along with the modern techniques like Rhinoplasty, Mammoplasty, liposuction, etc., to make oneself more beautiful and attractive.

History

Cleopatra was considered to have a perfect nose and the 17th-century philosopher Pascal famously wrote, “Cleopatra's nose, had it been shorter, the whole face of the world would have been changed”. The same is also said about “Helen of Troy” whose beautiful face launched a thousand ships. Her legs were most beautiful legs ever described and mouth, the cutest.

People have always been concerned about their outer appearance since the beginning of civilization. Egyptians used a mixture of water & natron (a form of baking soda) to form a cream. They also used rosemary oil & almond oil. Greek women used olive oil & honey. Ancient Indians used sandalwood paste with turmeric. In fact, Indians were the first to use face masks (made of sandalwood & rosewater) to treat acne[1].

Cosmetic surgery procedures have been in existence for long. The types of plastic surgery and augmentation procedures we see today were already used by surgeons even back in the 18th century AD[2]. The first recorded documents on rhinoplasty was by an ancient Indian surgeon Sushruta[2], way back in 6th century BCE. In 16th century AD an Italian surgeon Gasparo Tagliacozzi[2] described his technique of rhinoplasty using skin flap from the patient’s arm. He is also credited with writing the first complete textbook on Plastic surgery[3].

Timeline of Cosmetic Surgery:

1895 – First breast augmentation (using patient’s lipoma)
1899 – First breast implant (using beeswax and vegetable oil)
1923 – First modern rhinoplasty performed
1924 – First formal training in Plastic surgery established by Dr.John Davis in USA
1931 – First face-lift performed
1937 – American Board of Plastic Surgeons formed
1962 – First silicone breast implant introduced by Dr Thomas Cronin
1970 – 1979 – Advances in craniofacial surgery helps cosmetic facial surgeries
1974 – 1978 – Liposuction introduced first by Italian Gynaecologists Arpad and Georgio Fischer and later improved by French surgeons Yves-Gerard Illouz and Pierre Fournier
1985 – American Academy of Cosmetic Surgery founded[2]

Figure 1. Sushrutha

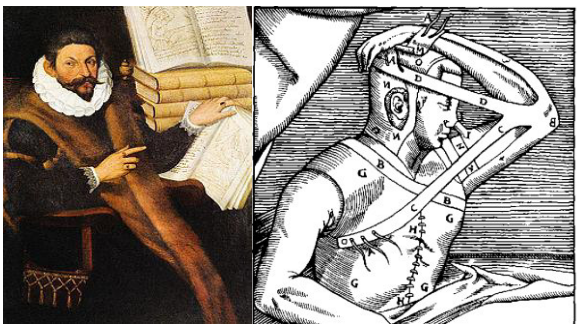

Figure 2. Tagliacozzi

The two world wars saw rapid progress in the field of Plastic surgery.

Not long afterwards, western world realised the potential of cosmetic surgery and the first rhinoplasty was performed in 1923 in USA[2]. In 1931 the first face-lift was performed. The first breast reconstruction was done by a German surgeon Vincenz Czerny in 1893 (published in 1895). He resected a large fibroadenoma and the space thus created was filled with patient’s own lipoma, which was present in the patient’s hip area[4].

In 1903, Charles Miller introduced the breast augmentation surgery in the USA. He used silk, celluloid and many other foreign materials as breast implants. However, the results were not satisfying[2].

Aesthetic surgical procedures

The various commonly performed aesthetic procedures are reviewed below.

Hair Transplant

This procedure is usually done to treat male pattern of baldness. Here hair follicles from the occipital region (known as harvesting) and transplanted in the fronto-temporal region of the scalp. One method is Follicular Unit Extraction (FUE) (Figure 3).[5]

Figure3. Hair transplant by FUE method

Aesthetic Rhinoplasty *(ῥίς rhis, nose + πλάσσειν plassein, to shape)* **(aka Nose job)**

John Roe, an American ENT surgeon was the first to describe endonasal rhinoplasty in 1887[6]. He corrected a deformity known as "Pug nose".

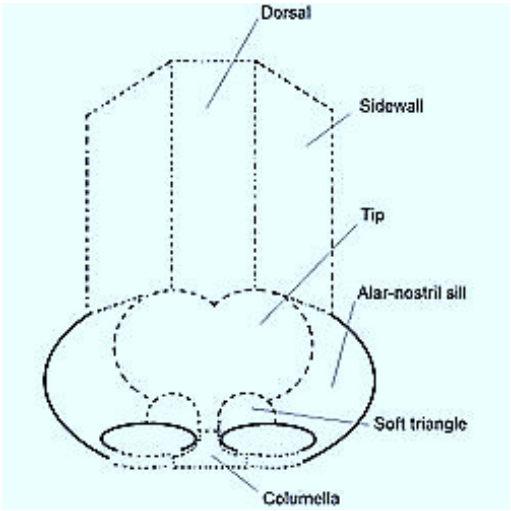

Figure 4. The surgical nose has six aesthetic nasal sub-units or segments:

Six aesthetic nasal segments are:

i. Dorsal
ii. Lateral nasal-wall
iii. Hemi-lobule or tip
iv. Soft triangle
v. Alar *and*
vi. Columellar

The structure of the nasal subunits—the dorsum, the sidewalls, the lobule, the soft triangles, the alae, and the columella, are configured differently according to the race and the ethnic group of the patient: African - platyrrhine (flat, wide nose); Asiatic - subplatyrrhine (low, wide nose); Caucasian - leptorrhine (narrow nose); and Hispanic - paraleptorrhine (narrow-sided nose).[7]

Aesthetically, the nose, from the nasion (the midpoint of the naso-frontal junction) to the columella-labial junction should ideally occupy one-third of the vertical dimension of the person's face; and, from ala to ala, it ideally should occupy one-fifth of the horizontal dimension of the person's face[8].

The angle between the frontal bone and the nasion usually is 120 degrees and it is called naso-frontal angle; it is more acute in the male face than in the female face. The slope of the nose relative to the plane of the face and the slope between the columella and the philtrum varies in men and woman. When seen from below (worm's-eye view), the alar base forms an isosceles triangle with the tip of the nose.

The Goode Method determines the extension of the nose from the facial surface by measuring the distance from the alar groove to the tip of the nose, and then comparing that measurement (of nasal-tip projection) to the length of the nasal dorsum[9].

The nose consists of skin and soft tissues which is separated from the underlying bony-cartilaginous framework during corrective rhinoplasty.

Basically, cosmetic rhinoplasty involves two types of procedures, viz. reduction rhinoplasty and augmentation rhinoplasty. These can be done by open or closed method.

Removal of nasal hump, narrowing of alar base/wide nostril, correction of saddle-nose deformity and nasal tip correction are some of the aesthetic rhinoplasty procedures.

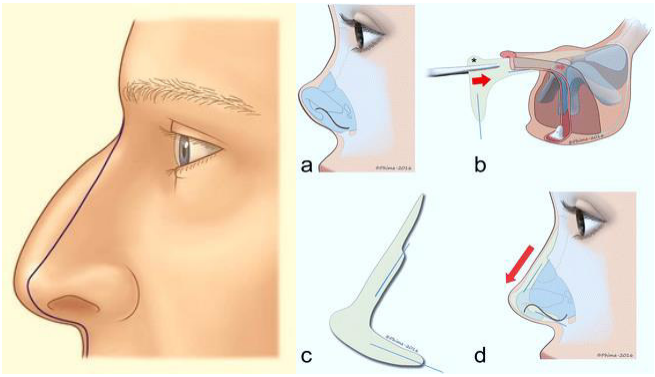

Figure 5. Reduction rhinoplasty / Augmentation rhinoplasty

Blepharoplasty (for Baggy eyes)
(Greek: *blepharon*, "eyelid" + *plassein*,"to form")
It is the surgical procedure for correction of baggy eyes caused by excess skin &/or excess adipose tissue in the upper and lower eyelids.

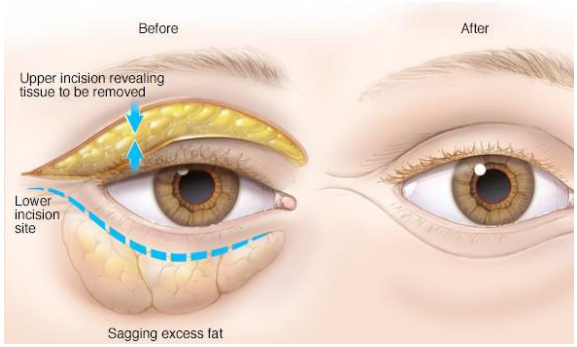

Figure 6. Blepharoplasty

Double-eyelid procedure is commonly done in Asian countries, especially South Korea[10]. In this procedure an extra fold is created in the upper eyelid.

Figure 7. Double eyelid surgery

Ptosis of upper eyelid can be congenital or can occur in myasthenia gravis. It can be corrected by shortening levator palpebrae superioris or frontalis sling[11] procedure.

Rhytidectomy (Face-lift)
Rhytidectomy (from Ancient Greek ῥυτίς (rhytis) "wrinkle" + ἐκτομή (ektome) "excision").
The first facelift was reportedly performed by Eugen Holländer in 1901 in Berlin[12].

There are eight types of "face-lift" techniques:

1. SMAS lift
2. Deep-plane facelift
3. Composite facelift
4. Mid face-lift
5. Mini-facelift
6. Subperiosteal facelift
7. Skin-only facelift
8. MACS facelift

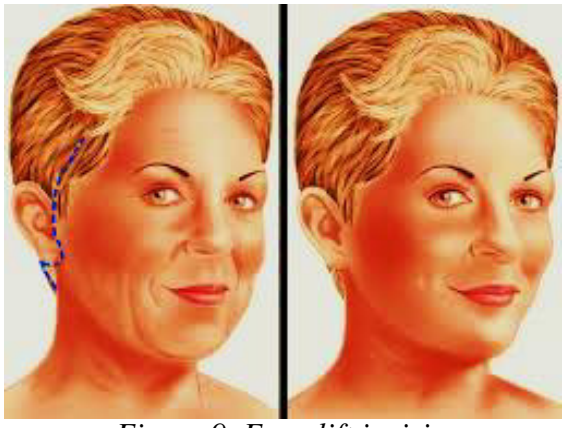

Figure 9. Face-lift incision

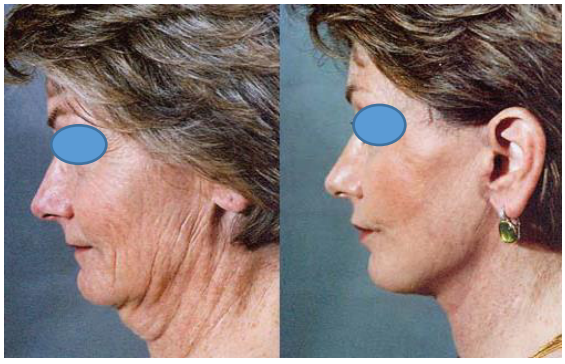

Figure 10. Face-lift Before & After

The aim of face-lift surgery is to smoothen the facial wrinkles to give a youthful look. SMAS and MACS are commonly done techniques. Laser and

collagen fills are also done to smoothen the wrinkles.

Otoplasty (for Bat-ears)

The pinna is prominent in some people. This can be corrected by excising an ellipse of skin posteriorly and scoring the cartilage.

Figure11. Bat ear repair Before & After

Mammoplasty (Augmentation/Reduction)

Augmentation mammoplasty is commonly performed to increase the size of the breasts and for sagging breasts (breast lift). This involves implanting breast implants which may contain silicone or saline fillers.

Reduction mammoplasty is commonly performed to reduce the size, change the shape, and/or alter the texture of the breasts. This involves the removal of excess skin and breast tissue.

Requirements of an ideal breast reduction have been put forth by Biesenberger[13] and have stood the test of time. They are as follows,

- The breast should be lifted to a youthful and natural form.
- The two breasts should be symmetrical.
- The nipple and areola should be translocated to an appropriate location.
- The blood supply to nipple and areola should be preserved.
- The scars should not be visible through normal clothing or be above the areola.
- The procedure should be a one stage operation

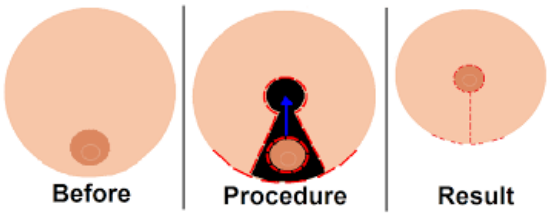

Figure 12. Reduction Mammoplasty for large & pendulous breasts

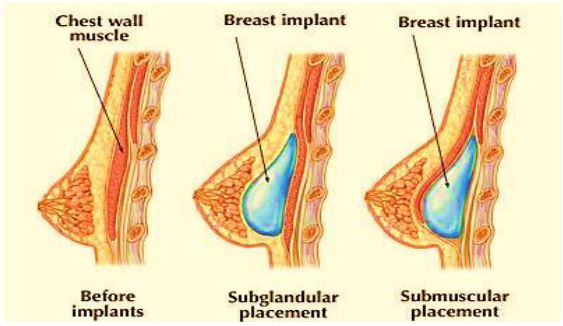

Figure13. Augmentation Mammoplasty

The implants can be placed deep to breast tissue or deep to pectoralis major. Incision can be made in the axilla or sub-areolar region.

Figure 14. Silicone and saline breast implants

Abdominoplasty or Apronectomy (Tummy tuck)

The surgery involves the removal of excess skin and fat from the middle and lower abdomen in order to tighten the muscle and fascia of the abdominal wall.

Figure 15. Abdominoplasty

Abdominoplasty is now replaced by liposuction in many instances. In conditions where there is excess skin and skin which has lost its elasticity, the patient would still require this procedure[14].

Liposuction

It is the most commonly performed cosmetic surgery.

Figure 16. Liposuction in progress

The procedure may be performed under general, regional, or local anaesthesia. A cannula is inserted deep to the skin in the sub-cutaneous layer of the body and negative pressure is applied to suck out fat. It is believed to work best on people with a normal weight and good skin elasticity[15].

While the suctioned fat cells are permanently gone, after a few months overall body fat generally returns to the same level as before treatment, because the remaining fat cells tend to hypertrophy. This is despite maintaining the previous diet and exercise regimen[16]. As such liposuction should not be advised as an alternative to bariatric surgery.

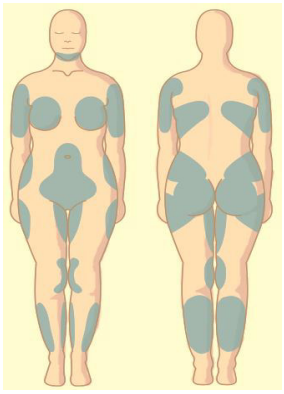

Figure 17. Areas that can be treated with liposuction

Primarily it is indicated to remove excess fat from unwanted areas of the body, viz. lower abdomen, gluteal region, thighs, triceps region and sub-mandibular region. Some even indicate for breast reduction mammoplasty[17].

Complications of liposuction varies from minor to major. They are skin bruising, paraesthesia/anaesthesia, deformities[18], fat embolism and rarely death.

Techniques of liposuction include tumescence, ultrasound assisted (pulsed delivery with third generation devices), laser assisted and cryo-assisted.

Psychological assessment[19] (of patients seeking aesthetic surgery)

Patients who seek aesthetic surgery are in their middle age and should ideally be seen by a psychologist to assess their characteristics, as they may have unrealistic goals or expectations, external motivations, identity concerns, negative self-image and other psychosocial issues such as body dysmorphic disorder.

The potential adverse outcomes the surgeon can face are as follows:

- Dissatisfaction with the outcome of the procedure
- Social isolation
- Relationship strain
- Requests for additional and unnecessary procedures
- Anger towards the service provider and staff
- Worsening of pre-existing mental health issues
- Risk of self-harm

Conclusion

A short review has been done regarding the history of aesthetic and plastic surgery. Also, an overview of the various techniques to modify the shape of various body regions have also been discussed.

It is also important to psychologically assess each patient's requirements and expectations pre-operatively and discuss the scope of surgery and its end result, with all possible complications.

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ORIGINAL ARTICLE

PERSONALITY TYPES AND DEPRESSION AMONG MEDICAL STUDENTS IN UniKL RCMP.

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Abstract

Background: The prevalence of depression among medical students is not uncommon. It usually happens because of the transition from a normal school environment to the medical college environment, where, the students need to be independent in taking care of themselves in terms of daily living and their studies. The aim of the study was to find out the association between the personality type and depression among medical students.
Methodology: The study was a cross-sectional study among 186 respondents, chosen based on convenience. A set of questionnaires consisting of three parts to assess their sociodemographic input, degree of depression and types of personality were prepared and distributed in the campus among the clinical year medical students only (Year 3, 4 and 5). The study was conducted over a period of 1 week in March 2017 in RCMP in Ipoh.
Results: Most of the students were found to be having the personality of openness to experience with the mean score of 32.98 and have normal degree of depression with the percentage of 73.7%. Female students were relatively more depressed than males. More students in Year 3 were depressed compared to the Year 4 and Year 5 and more Malay respondents were positive for depression compared to the other races. Overall, there was no significant association between these sociodemographic factors and the degree of depression and also between the gender and type of personality. Finally, it was found that the association between the types of personality and the degree of depression was statistically significant.
Conclusion: This study found that the type of personality of an individual would influence the degree of depression. However, more such studies should be conducted to explore more about the types of personality, the reaction towards stressor and development of depression as the type of personality is an important aspect in determining how they adapt to the stress, which, if they fail to handle, they may develop the symptoms of depression.
Keywords: Personality, Depression, Prevalence, Medical students.

Introduction

The prevalence of depression among medical students is not uncommon. It usually happens because of the transition from a normal school environment to the medical college environment where the students need to be independent in taking care of themselves in terms of daily living and their studies. On top of that, the subjects learned are also very different and new compared to the school syllabus and as the time goes by, the subjects get harder and need to be learnt in detail. These circumstances can lead to certain degrees of depression among students and each individual would usually have different type of adaptation to encounter the depression. As stated in one article entitled "correlates of depression, anxiety and stress among Malaysian university students", university students face not only challenges related with independent living, but also academic challenges. This predisposes them to depression, anxiety and stress, which are fairly common [1].

Another study which was done to determine the depression among medical students entitled Changes in life-style characteristics, health, and mood of freshman medical students by Wolf, T M and Kissling, G E stated that "Medical students are expected to learn and master a huge amount of knowledge and skills. The personal and social sacrifice they have to make in order to maintain good academic results in a highly competitive environment puts them under a lot of stress" [2] .

The study of the association between personality and depression is not new. In one study conducted by Roget T Mulder, Personality and Depression: A commentary (2008) stated that "ancient classifications focused on temperament with depression largely considered an epiphenomenon. Melancholic temperament was associated with individuals who were moody, pessimistic, and vulnerable to episodic depression"[3] . Another study had been done by the Black Dog Institution (2013), stated that "at the Institute we believe that personality and temperament contribute to depression, particularly *non-melancholic* depression. Certain personality types are more at risk of developing depression than others" [4]. It is believed that the personality of an individual may influenced their reaction and adaptation towards the stressors which could lead to the development of depression.

In this research, we are going to study the types of personality and the degree of depression of the medical students and whether their personalities have any relationship with the development of depression among themselves. We are going to use the Big Five Inventory and Beck Depression Inventory to achieve the objectives of our study. The Beck Depression Inventory (BDI, BDI-1A, BDI-II), created by Aaron T. Beck, is a 21-question multiple-choice self-report inventory, one of the most widely used psychometric tests for measuring the severity of depression. Its development marked a shift among mental health professionals, who had until then, viewed depression from a psychodynamic perspective, instead of it being rooted in the patient's own thoughts [5].

Materials and Methods

This was a cross-sectional study among the clinical year MBBS students in Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL RCMP). The study was conducted over a period of 1 week in March 2017. The total number of participants was 186. Samples were chosen based on convenient sampling in which the research group approached the students whoever was available from year 3 to year 5 at the time study. The study was conducted for few days till the total number of the proposed sample size was achieved. Inclusion criteria involved medical students in year 3 to year 5 (clinical years) and those who gave written consent to participate in the study.

The sociodemographic of the respondents were collected through part A of the questionnaire.

Whereas, part B of the questionnaire was concerned about the Beck Depression inventory where the respondents have to circle the score of 0 to 3 for the statements that, they think, suit what they feel about themselves. Part C of the questionnaire was about the Big Five Inventory which was basically used to determine personality types of the participants. The participants were required to score of 1 to 5 based on the Likert scale for each of the given statement. The raw data collected form the questionnaire was immediately processed and entered into the SPSS software (SPSS version 19.0). Descriptive statistics were used to describe the variables and the association between variables was tested by chi-square test. The association was primarily set to be statistically significant at the p-value < 0.05. Ethical approval was obtained from the Ethical committee of UniKL Royal College of Medicine Perak before conducting the study.

Results

This study included 186 respondents. Most of the respondents were females (69.9%). The highest percentage of respondents were studying in Year 4 (43.5%) followed by Year 3 students (32.8%) and only 23.7% of respondents, were year 5 students. There were 81.2% of respondents who were staying in Ipoh while the rest 18.8% were staying outside Ipoh area. Most of the respondents were not married (93.5%). Majority of the respondents were predominantly Malay (88.2%) followed by Indians (7.0%), other races (3.2%) and 1.6% were Chinese (Table 1).

In table 2, the means and standard deviations for the types of personality were shown. There were five major personalities which were listed in the Big Five Inventory: Extraversion, Agreeableness, Conscientiousness, Neuroticism and Openness to Experience. Based on the results obtained, most of the students have a personality type of openness to experience with the mean score of 32.98 followed by agreeableness (31.37), conscientiousness (28.06), extraversion (25.07) and neuroticism (24.34).

The degree of depression of the medical students in UniKL RCMP was explored. Basically, there are six classes for the level of depression: Normal, Mild, Borderline, Moderate, Severe and Extreme. Based on figure 1 below, most of the respondents have normal degree of depression with the percentage of 73.7% followed by mild depression (12.4%), moderate depression (7.5%), borderline depression (4.3%), severe depression (1.6%) and extreme depression (0.5%). The mean was 1.53 and the standard deviation was 1.05.

However when the categorical levels of depression among medical students were tested against the sociodemographic factors by Chi square test, no significant association could be observed. The P value was set at a level of 0.05. On the other hand, when the association between the type of personality and the degree of depression was examined, it revealed a significant finding with a P value of 0.029. (Table 3)

Discussion

Most of the respondents scored high in the personality of openness to experience and the lowest was in neuroticism type. The personality domain of openness to experience is made up of six sub-traits: Imagination, Fantasy, Aesthetics, Actions, Feelings and Values. This means, the respondents who scored high in openness to experience type of personality have high level of curiosity, imagination, creativity, interests, excitation and flexibility. Medicine is a very broad subject to be learned and without curiosity, interest and excitement, one would feel burdened and bored to keep studying in this field. A good imagination and creativity are also important especially for the subjects which the students need to memorize the graphics and at the same time understand what they are learning such as

anatomy and pathology. They are also important for the medical students when they use their own notes for better understanding. We all know that notes which, involve only words without any mind maps or pictures, will be less interesting to be compared to the notes which involve brainstorms, pictures and different colours. Flexibility is also essential as medical course takes a very long time to be completed compared to the other courses. Moreover, the learning aspects would never stop after the students are graduated. It is a lifelong course where the learning process continues even when they have reached the highest level of their medical career. The medical students have to know how to manage their time properly so that they have enough time to be spent for their studies, families, and friends as well as enough time for themselves.

As for the degree of depression, most of the respondents were having a normal degree of depression in which, their scores, were between 0-10. The normal degree of depression means they do have some ups and downs of emotional distress but they are still under control and considered as normal for them to continue daily activities smoothly. It is followed by mild and moderate degree of depression. One study by Sherina MS, which was addressing the prevalence of depression among medical students in Malaysia found that the prevalence of depression among medical students of University Putra Malaysia (UPM) at the Faculty of Medicine and Health Sciences was high (35.9%) and it was associated with the psychological pressure, they were exposed to, prior to the examination [2] . This was contrary to our study, where we found that most of the respondents have normal degree of depression which might be explained by the less pressure they were having as the examination was not approaching yet. On top of that, they might have certain ways to cope with the pressure they had such as hanging out with their friends after the class or doing some physical activities in the evening to release the pressure. However, there were still few of them who were having severe and extreme degree of depression. These few respondents with severe depression scores might be having some problems such as study difficulties or relationship issues with their family members or friends at the moment when the data was collected thus, influencing their degree of response.

If we consider any respondent who scored 11 and above for their degree of depression to be positive for depression, we could see that females are more depressed than males. Although the association between the gender factor and degree of depression was not statistically significant (p= 0.875), there was an evidence which suggested that early traumatic experiences may be partly responsible for a female preponderance in depression rates, since female are at greater risks of certain events and seem to be more sensitive to their depressogenic effects. Another study stated that the hypothalamic-pituitary-adrenal axis (a major neuroendocrine system that controls reactions to stress and regulates many body processes) seems to be more reactive to stress in females than in males, possibly due to a modulating role of gonadal hormones[6] . This means females' reactions towards the stressors are greater than the males making them more likely to get depressed in comparison to males.
Newly faced social and intellectual challenges may cause emotional pressure, which may lead to an increased risk for depression, anxiety and stress. In the literature, many studies point to the elevated risk of depression, anxiety and stress among first-year undergraduates [7]. As for this current study, we only focused on the clinical year students (Year 3, 4 and 5) and it is found that the students in Year 3 were relatively more depressed compared to the Year 4 and Year 5 students. This might be due to the transition from the pre-clinical phase (Year 1 and 2) to the clinical phase which requires a very different approach of study, and more load in terms of the daily academic tasks. The pre-clinical phase only involve the theories and practical on simulated patients while in the clinical phase, the students are needed to go to the

hospitals in order to apply and practice their knowledge skills on real patients under the supervision of their lectures and doctors. This transition might, one way or another, create a certain level of pressure on the clinical students especially to the Year 3 students because they need to adapt to their new environment. Apparently Year 4 and Year 5 students would presumably be more familiar and have already been adapted to the situation, which puts them under less pressure.

One study which was done at the same place of the current study but many years back found a substantial number of medical students (46.2%) in the study sample with high GHQ scores, indicating emotional disorders. The prevalence of emotional disorders were found to be significantly higher among Phase 1 students, students who faced severe pressure due to examinations and those who were not involved in a romantic relationship [8].

It was observed in the current study that, more Malay respondents were positive for depression compared to the other races. However, the association between the race factor and degree of depression was not statistically significant (p=0.054). This might be due to the imbalance number of respondents in terms of race as 88.2% of the respondents were Malay and if we wanted to compare the degree of depression based on their race, we should have the same number of respondents for each race.

The gender differences in personality traits can be detected in early childhood. In one of the studies done, researchers stated that women reported higher levels of neuroticism, extraversion, agreeableness, and conscientiousness than did men across most nations [9]. As for this study, we focused on the personality of openness to experience because most of the respondents scored highest in this personality type. There was a study showed that the gender differences in openness to experience were decidedly mixed across cultures. In 37 cultures, men scored higher than women in BFI Openness to Experience (in 8 cultures this difference was statistically significant), but in 18 cultures, women's self-reported openness to experience was higher than men's (in 4 cultures this difference was statistically significant). These conflicting results were not entirely unexpected as women have been found to be more open than men to feelings, whereas men tend to be more open to new ideas [9]. However, for this study it was found that the association between gender factor and the personality type was not statistically significant (p=0.08).

There is solid evidence at the individual level that personality traits are predisposing factors for a wide variety of psychiatric disorders. Several studies have shown that normal personality traits are systematically related to the development of Axis I disorders, such as mood, anxiety and substance abuse. Even stronger are the conceptual and empirical links between the Axis II personality disorders (PDs) and the broad factors and specific facets of the FFM [10]. It is also reflected in this study where the association between the type of personality and the degree of depression among the respondents is statistically significant with the p-value of 0.029. It is believed that individuals with high openness to experience personality have low risk of developing depression as they are very flexible towards any circumstances thus, they have better way of adaptation. Besides, the high level of curiosity and interest could influence the way of their thinking towards the stressors as they might take them as a challenge of life.

Conclusion

Depression among Medical students are getting more common as the pressure on them is getting higher. Having a flexible and open personality will be protecting you if you are studying Medicine. Coping with the pressure of a Medical study is essentially one way to prevent depression. However, medical students with a personality character of openness are those who will be more likely to stay away from depression.

Table 1: Distribution of sociodemographic factors

Sociodemographic factors	n	Percentage (%)
Gender		
Male	56	30.1
Female	130	69.9
Year of Study		
Year 3	61	32.8
Year 4	81	43.5
Year 5	44	23.7
Address		
Inside Ipoh	151	81.2
Outside Ipoh	35	18.8
Marital status		
Married	12	6.5
Not married	174	93.5
Race		
Malay	164	88.2
Chinese	3	1.6
Indian	13	7.0
Others	6	3.2

Table 2. Types of personality

Type of Personality	Mean	Standard Deviation
Extraversion	25.07	3.89
Agreeableness	31.37	4.63
Conscientiousness	28.06	3.99
Neuroticism	24.34	5.01
Openness	32.98	4.28

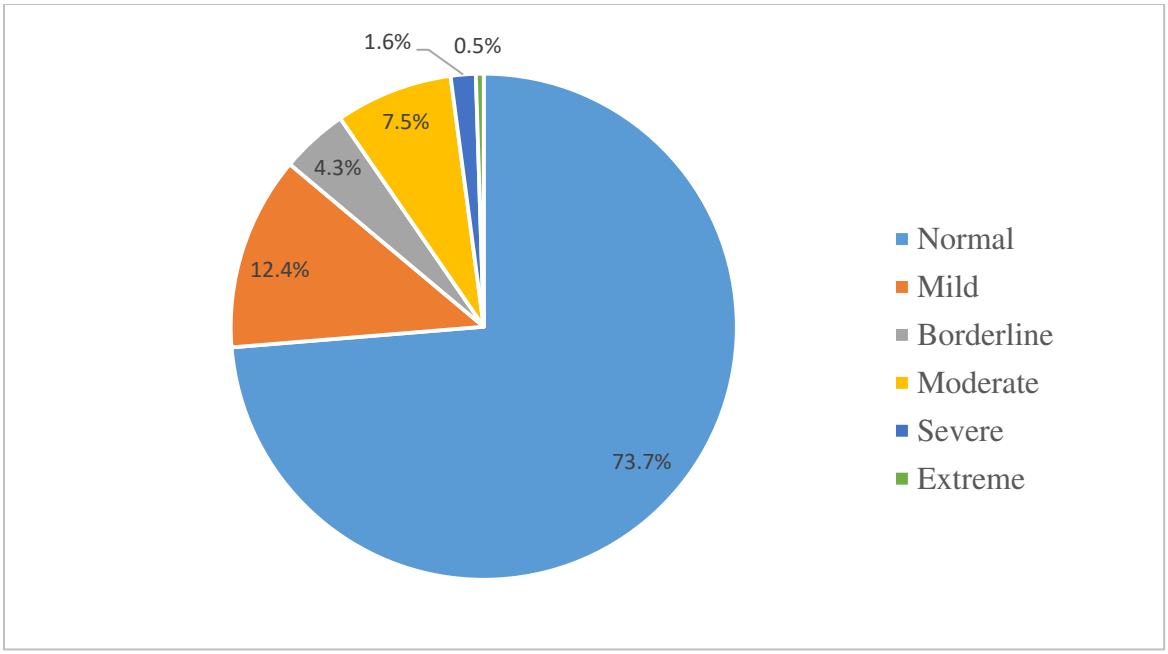

Figure 1. Degree of depression

Table 3. The Association between Sociodemographic Factors and Depression. Chi square test was used and the level of significance was set at level of 0.05.

Sociodemographic factors	p value
Gender	0.875
Year of Study	0.096
Address	0.704
Marital status	0.390
Race	0.054
Type of personality	0.029

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ORIGINAL ARTICLE

KNOWLEDGE AND ATTITUDE TOWARDS BASIC LIFE SUPPORT AMONG MEDICAL AND NURSING STUDENTS IN UNIVERSITI KUALA LUMPUR ROYAL COLLEGE OF MEDICINE PERAK.

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Abstract

Background: This study provides insight into the outcome of Basic life support (BLS) training in medical and nursing students through analysis of their level of knowledge and attitude towards BLS. It is aimed at serving as reference for future improvement in the training and exposure of BLS among the students.
Methodology: This was a cross-sectional study, using stratified random sampling. A structured questionnaire consisting of three parts - socio-demographics, knowledge and attitude on BLS, was used.
Results: Medical students had a significantly higher knowledge score compared to nursing students. Female students had a significantly better attitude score compared to male students. Semester 5 nursing students showed a significantly better attitude than the semester 6 students. Some students (11%) felt reluctant to perform CPR, main reasons being fear of causing harm and lack of confidence.
Conclusion: The knowledge and attitude of medical and nursing students towards BLS were found to be adequate but varied according to academic level of study. Early exposure with more practical training on BLS would improve the students' knowledge, as well as perception. Thus, periodical reinforcement and refresher training courses on BLS are needed.

Keywords: Basic life support, Knowledge, Attitude, Medical students, Nursing students

Introduction

Basic Life Support (BLS) is an emergency procedure that provides training to identify the manifestations of cardiac arrest, stroke, heart attack and foreign body airway obstruction[1]. It also includes the role of CPR and defibrillation. The rate of immediate survival and return of spontaneous circulation have been reported to show a significant increase and improvement in post-BLS stage[2]. With the number of emergencies increasing daily, health care professionals are under pressure of heavier workload. They also are facing high expectations from the public regarding their performance because of the increased awareness of the public on CPR. This calls for the willingness on the part of health care professionals to learn to improvise better techniques[3].

Even though BLS is believed to substantially recover the social health, a study found out that in spite of the medical students being provided with a proper and structured training they still had a poor knowledge of BLS in emergency situations, especially in a difficult and chaotic scenario[4]. The situation evokes a fear in medical students including the final year students which makes it difficult for them to respond to emergency situations. They are hesitant and unprepared to start the resuscitation[5]. Consequently, junior doctors are incompetent to handle real emergency situations and do not meet the required level as stated in the guidelines for practice of medical education in the Netherlands[6]. There was also a high percentage of low attitude towards BLS among the practitioners as they had inadequate training, which led to lower self-confidence in performing BLS[7].

A study done by Vausedvan et al. (2016) on knowledge of BLS resuscitation algorithm among medical and nursing students of Medical College Kottayam, Kerala showed that final year medical and first year nursing students had higher knowledge as compared to other students[8]. Aroor et al. (2014) stated that the BLS and other resuscitation skills should be a part of the undergraduate curriculum[9].
Another study found that trained groups of undergraduate, graduate and post-graduate medical and nursing students had greater scores in theoretical knowledge and practice of BLS as compared to the untrained groups[10]. One study found that 59.6% of medical and nursing students had weak knowledge regarding BLS and 44% were even unable to define the abbreviation of BLS[11]. Therefore, with the lack of knowledge and awareness, it created a group of graduates who were incapable of conducting BLS or educating the community.

In one study, it was stated that more than one third of the first-year residents at three U.S. training sites never performed CPR and most of them also had never conducted any BLS which reflected lack of retention of skills among the postgraduate[12]. This may lead to reluctance of junior doctors to be engaged with the CPR and BLS procedures. Thus this study was aimed at analyzing the level of knowledge and attitude towards BLS among medical and nursing students of UniKL Royal College of Medicine Perak.

Materials and Methods

This study was done on Year 4 and Year 5 medical students and Semester 5 and Semester 6 nursing students of UniKL Royal College of Medicine Perak (UniKL RCMP). A cross-sectional study using stratified random sampling was done. From the total study population of 321 students, random selection was done using the random number generator in Open Epi.com and the *minimum* sample size required was 176. After considering 10% non-responders and incomplete questionnaires, minimum sample size was finally determined as 194.

A structured questionnaire was used to assess the levels of knowledge and attitude towards BLS.

The questionnaire consisted of 3 parts; socio-demographics (7), knowledge (11) and attitude (8) on BLS. The questionnaire covered areas on BLS, Emergency Medical Services (EMS), Automated External Defibrillator (AED), CPR, and prior experience and exposure to BLS training. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 24.0. Categorical variables were reported as numbers and percentages while continuous variables were expressed as means and standard deviations. Knowledge and attitude scores among the participants were expressed as mean and standard deviation. The mean scores among students in different years/semesters of study were compared using independent sample t-test and one-way ANOVA test. A p-value of less than 0.05 was considered significant. Ethical approval was obtained from the Institutional Ethical Committee of UniKL RCMP before conducting this study. Written informed consent was obtained from all the participants and all the information gathered was kept confidential.

Results

In the present study, 93.8% (182) of students had exposure to the Basic Life Support (BLS) as it was introduced in their curriculum and repeated in certain medical posting. Although 6.2% (12) of 4th year medical students were not exposed yet, probably due to busy posting schedules their scores regarding knowledge as well as attitude showed no significant difference with the remaining students (Table 1).

Regarding the knowledge, medical students had a significantly higher score compared to nursing students (p=0.001) (Table 2).

Regarding the attitude, female students had a significantly higher score compared to male students (p=0.015) (Table 3).

On post-hoc analysis among 182 students who had prior exposure to BLS, an association was noted between the mean attitude score and the academic levels in 5th and 6th semester nursing students ($p < 0.048$). (Table 4).

In the present study, out of 194 students 178 participants (91.8%) were confident of providing chest compression, 99 (51.0%) were confident of providing mouth to mouth ventilation but 22 (14 medical, 8 nursing) were reluctant to perform CPR and the reasons being; fear of causing harm (59.1%), not confident (22.7%), fear of acquiring infection (9.1%) and fear of taking responsibility (9.1%). Regarding participants' opinion on inclusion of BLS in the medical and nursing programme curricula majority (98.8%) had agreed to the proposal.

Discussion

Our study showed that medical students had a higher knowledge score compared to nursing students (p=0.001) and this is similar to a study done in Tamil Nadu[13] which also found that more than 20% of medical students attained higher than 70% marks while 81% of nursing students only managed to score less than 50% marks.

In the present study the knowledge score of 6th semester nursing students was found to be higher than the 5th semester nursing students showing that the performance improved as the duration of clinical exposure increased. This finding was similar to studies done in Tamil Nadu[13] and Nepal[14].

In the present study the knowledge score of year 5 medical students was found to be lower than that of the 4th year medical students showing a reduction in retention of memory. A study done in the University of Maribor also reported a similar reduction in retention of skills related to BLS[15].

Overall, it indicated that periodic exposure to BLS increased both the awareness and attitude of students towards BLS. There is a need for optimal refresher training[16] or repeated refresher training

especially for individuals who are not practicing resuscitation on a regular basis[17].

In the present study, 91.8% of participants were confident of providing chest compression in contrast to the study done in Universiti Sains Malaysia[18] where only 57.1% of the participants were confident in providing chest compression alone. However, there were few students who felt reluctant to perform CPR and the main reasons were fear of causing harm and lack of confidence. Similar reasons were also reported in other studies[14].

In this study 98.8% of participants felt that BLS should be included in medical and nursing programme curricula which was in accordance with other studies[19]. There is the need of teaching BLS to medical students. Though being a real important issue there is still less attention within the curriculum at medical universities for teaching life support skills in an attractive way[20]. There was a significantly high attitude score (p=0.021) among those who had prior BLS training compared to those who had not. The finding is in consistence with other studies [21, 22].

Limitations

Some limitations were encountered in this study. Although the participants were trained in BLS none of them were engaged in active patient care. Despite questions on attitude included evaluation of their confidence in performing BLS, the study did not assess the practical skills of participants. The present study provided an insight into the state of BLS training outcomes among students in UniKL RCMP which could enable further improvement in the outcomes. However, it will be more informative if the assessment on the knowledge and attitude can be done among the general public untrained in BLS skills. Including only medical and nursing students seriously limits the usefulness of the study.

Conclusion

There was adequate knowledge and appropriate attitude of medical and nursing students towards basic life support (BLS) but varied according to academic level of study. As the present study was a questionnaire-based study, the practical skills of BLS were not assessed. To improve the students' knowledge, attitude as well as their skill, more hands-on practical training on BLS is needed. Thus, implementation of periodical reinforcement and refresher training courses on BLS should be encouraged.

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Table 1: Mean knowledge and attitude scores between medical and nursing students

Student group	Knowledge			Attitude		
	Frequency	Mean ± SD	P value	Frequency	Mean ± SD	P value
Total	194	0.6996 ± 0.12330	0.001	194	1.6458 ± 0.29525	0.162
Medical	157	0.7209 ± 0.11468		157	1.6624 ± 0.29302	
Nursing	37	0.6093 ± 0.11904		37	1.5753 ± 0.29831	

Table 2. Association of knowledge scores with other factors - gender, BLS exposure and practice.

Variable	**Number**	**Knowledge**		
		Mean score	SD	P value
Gender				
Male	55	0.6959	0.15572	0.572
Female	139	0.7011	0.10848	
Prior exposure to BLS				
Yes	182	0.6998	0.12393	0.671
No	12	0.6970	0.11843	
Practised BLS procedure				
Yes	188	0.7045	0.1169	0.062
No	6	0.5455	0.21513	

Table 3. Association of attitude scores with other factors - gender, BLS exposure and practice, reluctance.

Variable	Number	Attitude		
		Mean score	SD	P value
Gender				
Male	55	1.7091	0.31583	0.015
Female	139	1.6208	0.28401	
Prior exposure to BLS				
Yes	182	1.6538	0.27901	0.569
No	12	1.5238	0.48093	
Practised BLS procedure				
Yes	188	1.6558	0.28978	0.021
No	6	1.3333	0.32156	
Reluctant to perform resuscitation				
Yes	22	1.3442	0.30435	0.002
No	172	1.6844	0.27168	

Table 4. Association of knowledge and attitude scores with academic levels of participants with prior exposure to BSL (n=182).

Academic level	Knowledge			Attitude		
	Frequency	Mean ± SD	P value	Frequency	Mean ± SD	P value
4th Year Medical	69	0.7352 ± 0.12832	0.111	69	1.7019 ± 0.26584	0.177
5th Year Medical	76	0.7117 ± 0.10001		76	1.6485 ± 0.27547	
5th Semester Nursing	13	0.5944 ± 0.04717	0.123	13	1.7143 ± 0.22588	0.048
6th Semester Nursing	24	0.6174 ± 0.14431		24	1.5000 ± 0.30956	

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ORIGINAL ARTICLE

A DESCRIPTIVE STUDY ON OESOPHAGEAL CANCER IN HOSPITAL UNIVERSITI SAINS MALAYSIA.

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Abstract

Background: Oesophageal cancer is one of the cancer-related deaths in Malaysia. To date, neither the incidence nor the prevalence of oesophageal cancer has been documented especially in Kelantan, Malaysia.
Objective: This study aimed to determine the basic features of oesophageal cancer patients registered in Hospital Universiti Sains Malaysia (USM).
Methodology: A retrospective cohort study was carried out where the records of 55 oesophageal cancer patients registered in Hospital USM were retrospectively reviewed. The oesophageal cancer patients aged above 18 years old were included in the study whereas the patients with an incomplete medical record were excluded. Descriptive analysis was used.
Results: The mean age (standard deviation) of oesophageal cancer patients was 63.5 (12.3) years. Thirty five of oesophageal cancer patients were males (63.6%) while other 20 patients were females (36.4%). Out of 55 patients, 45 of them were above 60 years of age (81.8%). Smoking was found in 42 oesophageal cancer patients (76.4%). Dysphagia was the main presenting symptom in all patients. Adenocarcinoma was the commonest histology type among oesophageal cancer patients (52.8%).
Conclusion: Oesophageal cancer developed more in older and male patients. Most patients presented with common symptom of dysphagia and adenocarcinoma type of cancer.

Keywords: Adenocarcinoma, Dysphagia, Oesophageal cancer, Kelantan

Introduction

Oesophageal cancer is one of the cancer-related deaths with developing nations making up more than 80% of total cases and fatalities.[1] The incidence of oesophageal cancer is rapidly increasing[2] since it is considered as a serious malignancy concerning fatal outcome in most of the cases.[3] However, in Malaysia, oesophageal cancer is uncommon case among patients admitted to hospital.

Since oesophageal cancer cases were rare in Malaysia, especially in Kelantan region, therefore, the population also very subtle. In our area of study, only 55 patients were diagnosed with oesophageal cancer. Majority of oesophageal cancer patients usually detected at advanced stages. Due to it, remedial treatment cannot be undertaken at the time of diagnosis. Therefore, it showed a grim prognosis attributable to the late presentation in most patients. Early detection of oesophageal cancer and knowing the extent of spread of the disease ensures the option for a cure.

Considering the serious and fatal nature of oesophageal cancer and its prevalence in Malaysian population along with the importance of its early diagnosis in the initial stage, the study aimed to evaluate the basic features of oesophageal cancer among patients in Hospital Universiti Sains Malaysia (USM). Hopefully, the result of this study could help to develop targeted strategies and activities for the early management of oesophageal cancer and references for the future studies.

Materials and Methods

Study design and subjects

A retrospective cohort study was conducted at Hospital USM where fifty five oesophageal cancer patients aged above 18 years old and were registered at Hospital USM were recruited. The medical record of all oesophageal cancer patients were reviewed retrospectively.

Data collection method

Age, gender, race, clinical presentation, risk factor, histology type and tumour location were recorded in structured proforma. The location of the tumour was classified as upper, middle and lower oesophagus according to the distance from the cricopharynx to the oesophagogastric junction. The study included all oesophageal cancer patients aged above 18 years old while those with incomplete medical records were excluded from the study.

Statistical analysis

Data entry and analysis was conducted using the Statistical Package for the Social Science (SPSS) version 24.0 for Window. As a first step, normal distribution of the sample was analysed. Normal distribution was represented by mean and standard deviation (SD) whereas skewed distribution was expressed by median and interquartile range (IQR). Descriptive analysis was used to determine the basic features which provide simple summaries of oesophageal cancer patients in our setting.

Ethical consideration

The study was approved by the Human Research Ethics Committee of USM. Permission to access patient's folder was obtained from Hospital Director of Hospital USM.

Results

Demographic particulars

The basic socio-demographic features of the patients are summarized in Table 1.

Oesophageal cancer had predominance in males (63.6%) rather than females (36.4%). The majority of the patients diagnosed with oesophageal cancer were above 60 years old

(81.8%). The mean age (SD) of patients was 63.5 (12.3) years. The oldest patient was 87 years old and the youngest 31 years old. For ethnicity; 76.4% were Malays, 18.2% were Chinese, and 5.4% were Siamese. This finding may reflect the local population, which is made up primarily of Malays..

Clinical presentation

Dysphagia was found in all the oesophageal cancer patients (100%), followed by weight loss (65.5%), coughing (16.4%), hoarseness of voice (12.7%) and odynophagia (9.1%). With regard to oesophageal cancer subtypes, 52.8% of patients had adenocarcinoma while another 47.2% of patients had squamous cell carcinoma. Almost half of the patients (60.4%) had lower third tumour location followed by middle third (26.4%) and upper third (13.2%). Most of the patients had moderate grade of cancer (64.3%) and stage IV of cancer (43.4%).

Risk factors

Most oesophageal cancer patients (76.4%) gave a history of smoking, and only the six patients (10.9%) gave a history of alcohol consumption. A small percentage (3.6%) of patients was diagnosed as having a previous Barrett's oesophagus (3.6%).

Discussion

The current study was conducted in a tertiary level teaching hospital located in the north-east of Peninsular Malaysia. Over period of the study, the researchers have seen a fairly small number of patients with oesophageal cancer in the tertiary hospital in Kelantan. As oesophageal cancer is a complex disease and almost always referred to a major hospital, the researchers were able to capture most of the cases in this area even though oesophageal cancer patients are in a small population.

The study revealed that the percentage of adenocarcinoma and squamous cell carcinoma are almost the same which are 52.8% and 47.2% respectively. In the United States, the incidence of squamous cell carcinoma is declining, however, the incidence of adenocarcinoma has increased more than 6-fold in the last three decades.[4]

Reports from Asian countries, such as Singapore and China have shown a decline in the incidence of squamous cell carcinoma.[5] These observations are not surprising since erosive reflux disease is rare in this part of the world.[6] The present study showed adenocarcinoma and squamous cell carcinoma occur more frequent in patients above 71 years old just like the report from the United States, where the incidence of squamous cell cancer of the oesophagus increases with age as well and peaks in the seventh decade of life.[7]

Oesophageal cancer occurred more often in men compared to women[8]. It was similar to the present study where the incidence of oesophageal cancer was predominant in men compared to women with overall male to female ratio 1.75:1. The National Cancer Registry 2007 reported the incidence of oesophageal cancer in Malaysia is slightly higher in males compared to females.[9] For males, oesophageal cancer was the fifth most common cancer[10] and the crude incidence rate was 30.44/100,000 population.[8]

The incidence of oesophageal cancer is very low in those under 40 years of age, but it increases in succeeding years of life. The overall incidence increases with age and for our study, it reached a peak in the sixth decade. In China, aging population is a major cause of the increasing burden of oesophageal cancer[11]. Jemal et al., (2011) also revealed that the incidence of oesophageal cancer has been found to increase in a continuous manner with age[12]. The increasingly aging population makes it inevitable that more elderly patients will manifest oesophageal cancer.

The most common symptoms of oesophageal cancer in the study is dysphagia. Dysphagia is often mild when it starts, and over time, it

becomes worse as the opening inside the oesophagus become narrower. People had to change their diet and eating habits when their swallowing problem becomes severe. They will take smaller bites and chew their food more carefully and slowly. They may start eating softer foods which can pass through their oesophagus more easily. The swallowing problem may even get worse that some people stop eating solid food completely and switch to a liquid diet. Patients with oesophageal cancer tend to be more susceptible to develop malnutrition due to dysphagia and anorexia.[13]. These symptoms also may affect their weight where 65.5% of oesophageal cancer patients in the study had lost their weight. It happened because their swallowing problems prevent them from eating adequate food.

Amongst the well-recognized risk factor, cigarette smoking was found in most oesophageal cancer patients in our study. It was similar to the study in Malawi where Mlombe et al., (2015) concluded that smoking is a well-described risk factor for oesophageal cancer[14]. The present study found that 76.4% of patients were smokers and they faced an increased risk of both squamous cell carcinoma and adenocarcinoma of the oesophagus. There is a direct correlation between the number of cigarettes a smoker smokes per day, the length of time the smoker spends smoking, and the risk of oesophageal cancer.[15] Tobacco contains many carcinogens particularly nitrosamines and when a smoker ingested tobacco condensates, it causes nitrosamines to react with the oesophageal mucosa.[8] Cigarette smoking is more like a promoter than a mutagenic initiator. The most predominant chemicals in cigarette smoke are known promoters as they share mechanistic characteristics of known tumour promoters. For examples, they have threshold levels of action, they are reversible in action, and their biological effects can be overridden by anti-tumour promoters, anti-oxidants and chemo preventive agents in the diet.[16, 17]

Alcohol consumption has been consistently associated with increased risk of oesophageal cancer.[18, 19] However, only small portion of patients in the study were consuming alcohol. Alcohol and its metabolic pathway played an important role in predisposing individuals to oesophageal cancer.[20]

Lower oesophageal cancer appeared to be the commonest site of oesophageal cancer. These findings are in good conformity with the observation in Indian by Cherian et al., (2007) where lower oesophageal cancers outnumbered the middle and upper and appeared to be the commonest site of oesophageal malignancy.[5] While the study in China found that squamous cell carcinoma of the oesophagus was located mainly in the middle of the oesophagus and most of the adenocarcinoma of the oesophagus were located in the lower oesophagus.[21]

Conclusion

In conclusion, oesophageal cancer was predominant in men and majority of them was in sixth decades of life. The common histology subtype of oesophageal cancer was adenocarcinoma. Cigarette smoking and drinking hot tea and coffee was found in most oesophageal cancer patients.

Table 1: Socio-demographic of Oesophageal Cancer Patients in Hospital USM (n=55)

Variable	Frequency (%)
Age	
Below 40 years old	1 (1.8)
41-50 years old	3 (5.5)
51-60 years old	6 (10.9)
61-70 years old	16 (29.1)
Above 71 years old	29 (52.7)
Gender	
Female	20 (36.4)
Male	35 (63.6)
Race	
Siamese	3 (5.4)
Malay	42 (76.4)
Chinese	10 (18.2)
Occupation	
Government	4 (7.3)
Self-employed	18 (32.7)
Unemployed	33 (60.0)

Table 2. Clinical Presentation of Oesophageal Cancer Patients in Hospital USM (n=55)

Variable	Frequency (%)
Dysphagia	
No	0 (0)
Yes	55 (100)
Odynophagia	
No	50 (90.9)
Yes	5 (9.1)
Loss of Appetite	
No	25 (45.5)
Yes	30 (54.5)
Weight Loss	
No	19 (34.5)
Yes	36 (65.5)
Coughing	
No	46 (83.6)
Yes	9 (16.4)
Hoarseness of voice	
No	48 (87.3)
Yes	7 (12.7)
Vomiting	
No	33 (60.0)
Yes	22 (40.0)
Histology Subtypes	
Adenocarcinoma	28 (52.8)
Squamous Cell Carcinoma	25 (47.2)
Grade of Cancer	
Well	6 (21.4)
Moderate	18 (64.3)
Poor	4 (14.3)
Stage of Cancer	
II	14 (26.4)
III	16 (30.2)
IV	23 (43.4)
Tumour Location	
Upper third*	7 (13.2)
Middle third	14 (26.4)
Lower third	32 (60.4)

*including both cervical oesophagus and upper third

Table 3. Risk Factors of Oesophageal Cancer Patients in Hospital USM (n=55)

Variable	Frequency (%)
Smoking Status	
No	13 (23.6)
Yes	42 (76.4)
Alcohol Consumption	
No	49 (89.1)
Yes	6 (10.9)
Barrett's Oesophagus	
No	53 (96.4)
Yes	2 (3.6)

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ORIGINAL ARTICLE

ATTITUDE TOWARDS TRADITIONAL, COMPLEMENTARY AND ALTERNATIVE MEDICINES (T&CAM) AND ITS USE AMONG WOMEN DURING ANTENATAL AND POSTNATAL PERIOD.

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Abstract

Aim: This study investigated women's attitude towards the use of traditional complementary and alternative medicine (T&CAM) during pregnancy and postnatal period and their practices of T&CAM during that period and its association with socio-demographic variables.
Methodology: A cross-sectional descriptive study conducted among antenatal and postnatal clinic attenders at MCH clinic of Klinik Kesihatan Manjoi. Data were collected by using structured prevalidated questionnaire.
Result: Out of total 103 respondents, 66.02% were antenatal and 33.98% were postnatal women with the mean age of 29.72 years. Prevalence of T&CAM among the participants was 25.24%. T&CAM use was not prevalent among pregnant or breast feeding mothers ($p<0.05$). There was no significant association of use of T&CAM with sociodemographic variables. The majority (95.15%) of the respondents demonstrated good attitude towards T&CAM use. Dietary method (restraining some food) was the most commonly practiced method. "The rest methods" were used by 30.10% of the respondents, followed by massage and hot stones (24.27%), herbal bath (21.36%), herbal drinks (9.71%) and abdominal wrap (5.83%).
Conclusion: The prevalence of T&CAM among our study population is lower than that reported by previous studies. The respondents, irrespective of their sociodemographic back ground, demonstrated good attitude towards the use and they prefer safe practices. There is need to study the details of individual methods to understand more about the rationale of using those specific methods.

Keywords: Attitude, Practice, T&CAM, Pregnancy, Postnatal, Breastfeeding

Introduction

Traditional complementary and alternative medicine (T&CAM) has been playing a major role in providing healthcare to the mankind since the last century. It is getting more popular and will become an important component in our healthcare system with the reason to improve the level of health and quality of life along with modern medicine.[1] Herbal medicine is one of the most commonly used form of T&CAM among individuals in primary health care setup in both developing and developed countries. The World Health Organization reported that 70% to 80% of the world population relies mainly on herbal medicines for their primary health care needs.[2]

Some herbal medicines are believed to be useful for multiple purposes such as to facilitate labour, to promote a baby's physical health and intelligence, to enhance sexual pleasure and for abortion. A review reported the extensive use of herbal medicines to treat pregnancy related illness and to improve health and well-being during pregnancy [3]. However, previous studies indicated a lack of evidence for the safety and efficacy of herbal medicines popularly utilized during pregnancy[4]. Majority of Malaysians believe that herbal products do not contain harmful chemicals and are free from side effects compared to pharmaceutical drugs.[5]

In Malaysia, the uses of herbal medicines are based on practical experiences, observations and rituals derived from socio-religious beliefs passed down from one generation to another. These practices used within the Malay communities are claimed to be important for health and well-being, including being beneficial during pregnancy and postnatal period. Although various studies had been published on medications used during pregnancy, there is lack of evidence for safety and efficacy on these herbal medicines during pregnancy.[6]

Prevalence of herbal medicines use during pregnancy was 52.4% in a Malaysian district although the negative attitude towards herbal medicines had prevented women from using herbal medicines during pregnancy.[7]

The study of T&CAM among pregnant and post-natal women has been limited but the usage has been increased.[8] The World Health Organization (WHO) reported that prevalence of herbal medicine use is about 80% [9].

According to a US national survey, 37% of pregnant women and 28% of postpartum women reported using T&CAM in the last 12 months compared with 40% of non-pregnant/non-postpartum women [10]. According to a study from Saudi Arabia, the source of knowledge of CAM in 46.5% participants was mass media (e.g. T.V., newspapers and radio) while family members, relatives and friends were sources in about 46.3% of participants. Other rare sources included educational organizations (3.8%) and internet, as well as books and hospitals [9].

Women always take care of their health during postpartum period to restore good health and to avoid future ill health both in them and babies. A research done in few districts in Malaysia found that women believed that their bodies are dirty during postpartum due to baby formation during pregnancy and cold since they lose a lot of blood during delivery. During the confinement, Malay women practice rituals like bathing (mandi teresak), bedian, massage, bertungku, avoidance of sexual intercourse, abstinence from some food, rest, body wrap and take some hot medicines (traditional herbs) [11]. Another concern to be highlighted is whether women are using only T&CAM or along with prescribed medication during pregnancy and post-delivery. Data on the current patterns of use and effectiveness of various T&CAM treatments being used alone and in combination with modern medicines are inadequate. Even though a vast informal and silent healthcare sector exists in all countries, there are no available comprehensive data regarding the existence of this sector in any country[9]. Based on a research done among pregnant women in Nigeria, over half the

respondents did not support combining herbal medicines with conventional drugs to prevent drug-herb interaction. About one third respondents believed herbal medicines possess no adverse effects while 30% were of the opinion that adverse/side effects of some herbal medicines could be dangerous[12]. Therefore, this study was done to determine the belief, attitude and practice of the usage of T&CAM during antenatal and postnatal period among women attending Klinik Kesihatan Manjoi, Ipoh, Perak, Malaysia. We also investigated whether the T&CAM use was along with prescribed medication and the source of information regarding T&CAM.

Materials and Methods

This cross-sectional study was carried out among women attending Mother and Child Health Clinic Klinik Kesihatan Manjoi for antenatal and postnatal care in the period between 24th August and 9th October 2015.

Sample size was calculated as 100 based on the findings of a previous study from Hospital Universiti Sains Malaysia, Kubang Kerian (HUSM KK), with 95% confidence interval (CI). All women attending the clinic for their antenatal or postnatal visits during the period of study were selected except those who had mental illness and who refused to participate in the study. The information on our study written in English and Bahasa Melayu was read over and explained to the participants, and a written consent was obtained from each of them. The structured, pre-validated questionnaires were used to collect demographic information, reproductive profile, breastfeeding status, and their belief, attitude and practice on usage of T&CAM.

For the scoring, 1 mark was given to those who answered 'yes' for the question and 0 mark was given to those who answered 'no'. After calculating the total score, the respondents were grouped into two categories, either good or poor using the median score as a cut-off point.
Data was processed using SPSS software. Association between dependent variables and independent variable were determined using chi-square test and the association is said to be statistically significant if the *p* values is <0.05.

The ethical approval from institutional ethical committee of UniKL Royal College of Medicine Perak (UniKL RCMP) and necessary permission from the clinic in-charge was obtained before conducting the study.

Results

A total of 103 women, 66.02% antenatal and 33.98% postnatal, were included in the study. The mean age was 29.72 years. Fifty six respondents (54.37%) were working either in government or private sectors, or were self-employed. The largest proportion (48.54%) of the respondents had secondary education. Among the participants 25.24% were having their first child and 38.83% were having 2 to 4 children. Most of the respondents (96.12%) were Malays. Among them 40.78% were currently breastfeeding.

Twenty six women (25.24%) were using T&CAM. Nearly 40% of them were first time users. Currently pregnant or breast feeding mother were not using T&CAM ($p<0.05$) (Table1). T&CAM use was not associated with sociodemographic variables (Table 2).

Family or friends (87.38%) were the major source of information related to T&CAM followed by newspaper or magazine, health centres, television and radio (14.56%) (Figure 1). More than half of the respondents (68.93%) received recommendation from those who had already used T&CAM during pregnancy or after delivery.

Their attitude towards use of CAM during pregnancy and post-natal period was assessed using six questions with Likert scale of 5 from

strongly disagree to strongly agree. The Majority of the respondents (95.05%) exhibited positive attitude towards usage of T&CAM.

To the statement "one should ask and discuss with the doctor before taking any traditional herb medications during pregnancy or after delivery" 37.86% of participants strongly agreed and 2.91% strongly disagreed. Besides that, 11.65% of them were interested to drink or eat any traditional herb medications during pregnancy or after delivery and 30.10% answered "not sure". Only 5.83% strongly disagreed to recommend to family or friends who wants to drink or eat any traditional herbs during pregnancy or after delivery and 11 (10.68%) strongly agreed, while 37 (35.92%) were not sure. A good proportion of the respondents (43.69%) strongly agreed that government, especially the Ministry of Health is responsible to make sure that traditional herbs and herbal products are of good quality and safe to be used. Half of the respondents (50.49%) strongly agreed that health personnel such as the doctors, nurses or midwives should give the information regarding the side effects of the traditional herbs to the foetus. Fifty eight (56.31%) of the respondents were not sure if the traditional medications or practices are better than conventional medicines and seven (6.80%) of the respondents strongly disagreed.

However, there was no significant difference found between attitude towards antenatal and postpartum T&CAM use and their socio-demographic variables.

Among seven types of listed T&CAM, dietary method was the most commonly practiced method used by 33.98%. "The rest methods" were used by 30.10% of the respondents, followed by massage and hot stones (24.27%), herbal bath (21.36%), herbal drinks (9.71%), abdominal wrap (5.83%) and others for 0.97%. According to the respondents, for diet, there was list of food that was inedible during the 40 weeks of confinement period such as some vegetables, chicken, eggs, some fruits and others. However, some of them did not agree as the food stated as inedible can help in healing the wound inside and hasten the recovery.

T&CAM was used along with prescribed medicines by 72.82%. However, 27.18% of them use only medicines prescribed by the doctor starting from early pregnancy (Figure 2).

Only 26 (25.24%) reported consumption of traditional herbs from the early pregnancy until delivery. Most of them (33.98%) were practicing diet or good nutritional care and a few were practicing abdominal warp.

More than half of the respondents (68.93%) received recommendation from those who practiced T&CAM earlier during pregnancy or after delivery. Most of them (61.17%) were recommended by their family members. A total of 41 (39.81%) respondents answered that they were using T&CAM for the first time.

Those who used T&CAM for few times reported that T&CAM promote physical and mental health (46.60%) and increase sexual drive (6.80%). All of them agreed that there were no side effects such as arrhythmia, miscarriage or foetal death, whereas 35.92% believed that there could be side effects like allergy, rashes and kidney failure and 40 (38.83%) respondents believed that it could cause foetal deformity. Besides, about 21.36% of the respondents were taking T&CAM for months, which is until the end of confinement period of 240 days. Almost all the respondents were taking conventional medicines prescribed by the doctor during pregnancy or after delivery and only 28 (27.18%) of them were taking it together with T&CAM.

Discussion

According to our analysis, the majority of the respondents demonstrated to have good attitude towards the usage of T&CAM. A previous study

suggest that user's attitude is one of the factors that influence the usage of herbal medicines during pregnancies[13]. Generally, it can be postulated that a good attitude will lead towards good practice. However, our study findings suggested that there was no association between attitude and practice of T&CAM among antenatal and postnatal women attending KK Manjoi. Besides, there was no association between the attitude and any of socio-demographic variable among our study respondents.

In the aspect of practice, our study revealed that only 5.83% of total respondents are having good practice of the T&CAM while 57.28% of them are poor in practice of T&CAM. This finding is in line with a report that stated that 70% of women do not receive any postpartum care in developing countries[14]. However another study revealed high awareness and practice of traditional postpartum care [15]. It is believed that both the mother's and child's health are greatly influenced by postpartum maternal healthcare during the confinement period [16].

In our survey, we have found seven types of common T&CAM practiced among Malaysians. The most common type is post-partum diet. A previous study found that encouragement of food intake or postpartum diet is less practiced than the other methods and they also proposed to discourage prolonged immobilization to prevent unwanted complications such as deep vein thrombosis among postnatal mothers[17]. Abdominal wrap or corset remain the least practiced method of T&CAM among all other choices and this finding is similar to the study done in Penang [18]. A study done in 2014 in North-East Scotland revealed that one third of total 332 respondents were using herbal products in various stages of pregnancy [19].

According to previous studies, the most common source of information related to T&CAM use is family and friends of the respondents[2, 18, and 19]. Similarly, our respondents had chosen their family and friends as the most reliable source of information regarding their use of T&CAM during pregnancy and post-natal period. The respondents of a study reported that they would advise their children on the importance of practising traditional postpartum care [18]. The second most common source of information were midwives in a previous study from New York[20]. However, in a study done by Jamal, Zakiah and Khairana revealed that Malay traditional practitioners are not having any formal training regarding preparations and usage of local medicinal plants to provide postnatal care [21].

Among our respondents, only 27.18% of them were using T&CAM along with doctor-prescribed medicines. This may be due to the safety concern of the T&CAM especially the oral traditional herbs that were not experienced by most of our young respondents. A previous study also reported that only 12.7% pregnant women were using herbal medicines along with conventional medicines [13].

Limitations

The study was conducted as a student research project in one health centre (KKM) within a short period of time which limited the number and diversity of participants.

Conclusion

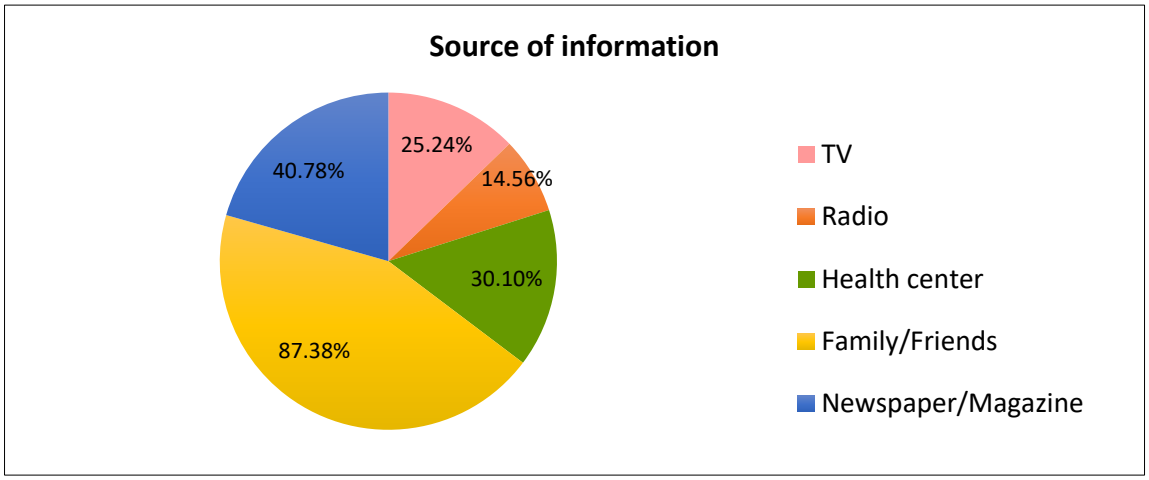
In conclusion, the prevalence of T&CAM among our study population is lower than that reported by previous studies. The respondents demonstrated good attitude towards T&CAM and they prefer safe practices. No user reported side effects. There is need to study the details of individual methods to understand more about the rationale of using those specific methods in large number of participants representing different communities and ethnic groups.

Table 1: T&CAM use among antenatal, postnatal women and breast feeding mothers

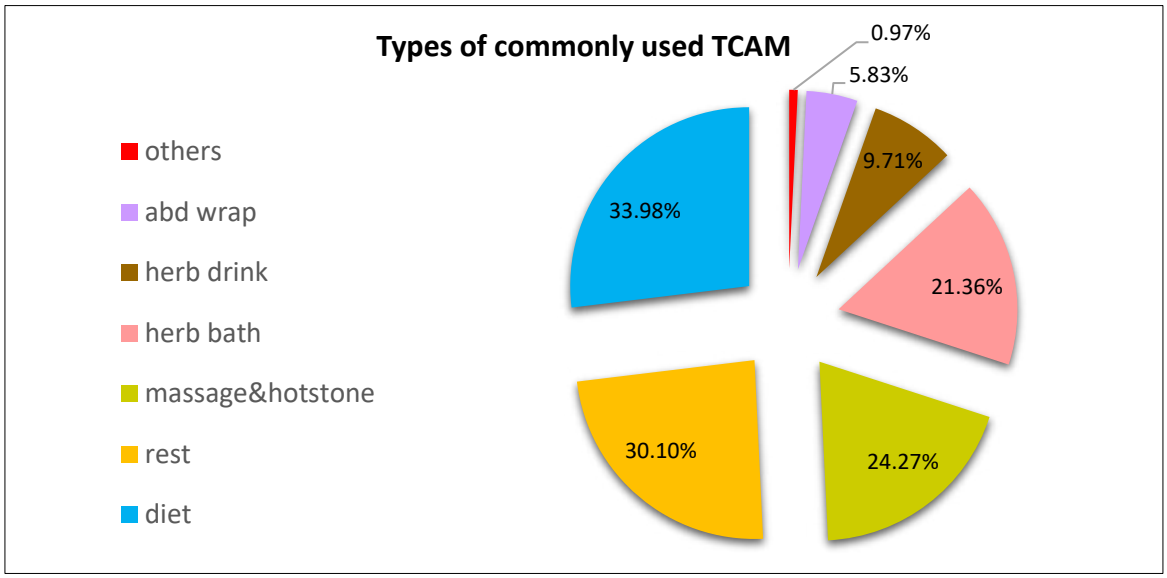
Variable	User (n=26) %	Non-user (n=77) %	*p*-value
Status			
Antenatal	12	56	0.013
Postnatal	14	21	
Breastfeeding			
Yes	16	26	0.013
No	10	51	

Table 2: Association between the T&CAM use and sociodemographic variables

Variables	User (n=26)%	Non-user (n=77)%	*p*-value
Age Group			
20-29	16	42	
30-39	9	32	0.223
40-49	1	0	
50-59	0	3	
Occupation			
Government	6	16	0.978
Private	6	18	
Self-employ	2	8	
Unemployed	12	35	
Education			
No education	0	0	
Primary	0	4	0.305
Secondary	11	39	
Tertiary	15	34	
Religion			
Islam	26	75	0.709*s
Indian	0	1	
Christian	0	1	
Number of children			
Nullipara	4	22	
Primipara	10	21	0.547
Multipara	10	30	
Grand multipara	2	3	
Great grand multipara	0	1	
Ethnicity			
Malay	26	73	0.495
Indian	0	2	
Others	0	2	



[Figure 1]



[Figure 2]

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ORIGINAL ARTICLE

ASSOCIATION OF PEAK EXPIRATORY FLOW RATE WITH AGE AND HEIGHT AMONG MALAYSIAN ADULTS.

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Abstract

Peak expiratory flow rate is a person's maximum flow produced during maximal force of expiration starting after a full inspiration. Subsequently, any respiratory disease such as asthma can be detected by comparing the readings with the normal. This study is aimed to determine the association between peak expiratory flow rate with age and height among normal adults in UniKL Royal College of Medicine Perak (UniKL RCMP). A cross-sectional study on association between peak expiratory flow rates was conducted among adults belonging to age group of 20-30 years and 40-50 years. All participants' heights were measured using the calibrated standard clinic scale without shoes. Peak flow meter was used to measure the PEFR. Results were analyzed using ANOVA test and the Independent Sample t test. Peak expiratory flow rate decreased as the age advanced (49%). However, the decrease of PEFR with increase age was not statistically significant. But for the height, the peak expiratory flow rate increased as the height increased and it was statistically significant (30.5%). The results of our study conclude that age and height have effects on the peak expiratory flow rate among normal adults. Peak expiratory flow rate decreases as age increases. Height has a positive association with peak expiratory flow rate in individuals.

Keywords: Age, Height, Peak flow meter rate, Normal adult.

Introduction

Peak expiratory flow rate (PEF) is defined as the maximum expiratory flow delivered with maximum force with maximal lung inflation.[1] It is an essential measure in monitoring lung function in patients with bronchial asthma. It is also used to check pulmonary function in estimating ventilator capacity. It's a crude measure of lung function in addition to spirometry. Peak flow meter is a simple instrument that is easily handled as well and also affordable, makes it suitable for self-measurement. The patient should know about the device handling in order to avoid errors in evaluating PEF readings[2]. Several factors such as age, sex, height and environmental factors like smoking and having pets can affect the readings of PEF.

When PEFR is associated with age, the highest peak flow reading occurs between the age of 30-40 years where a reading of 400- 600 l/min is considered normal.[3] The average height for Malaysian male and female was found to be 1.67 m and 1.50 m. According to the previous studies, based on average height, the PEF rate was 6.65 at the age of 25 years old and 5.40 at the age of 50 years old.[4] Past studies regarding gender differences on using the peak flow meter revealed that males gained faster correct techniques compared to females. Men scored higher than women for the steps of "inhale fully" and "exhale as hard and as fast as you can" in the first attempt. Percentage change in PEF improved from the second attempt to third attempt in women but not in men[5]. The study found out that men learned the correct technique for using peak flow meter and attained their best PEF more quickly than women. Taking all those factors into an account, the present study was carried out to examine the relationship of PEFR with age and height among Malaysian adults. Rationale of this study is aimed to determine the association between peak expiratory flow rate with age and height among normal adults.

Materials and Methods

Study population

We conducted the study among adults in UniKL RCMP. Both men and women between 20 to 30 years old and between 40 to 50 years old took part in the study.

Study type

This was a cross-sectional study on the association between peak expiratory flow rate with age and height. Convenient sampling method was used and healthy adults participated in the study. Adults with physical disabilities and respiratory diseases including asthma were excluded from the study.

Study variables

Study variables were age and height with its scale of measurement and PEFR.

Method of data collection

A written consent was obtained from all the participants as a proof of their willingness to participate in the study. All Participants' height was measured using the standard clinic skill without shoes. Each participant was required to sit and blow into the peak flow meter using the right technique (i.e., with maximal force after full inspiration) three times, and the PEFR values were noted and the mean of three values was calculated. The technique was personally supervised with standardized instructions. The confidentiality of participant's data was ensured to avoid any misuse of the data. Institutional ethical committee's approval was obtained prior to the conduct of study.

Data analysis

Data was collected and tabulated in Microsoft Excel. Data was analyzed with SPSS version 23 software. The software was used to tabulate the data. Student't'-test and Analysis of Variance (ANOVA) were used to analyze the data.

Results and Discussion

This study was aimed to determine the association between peak expiratory flow rate with age and height among adults and to learn how age and height reflects the lung function through peak flow meter. Distribution of study population by age and height is shown in Table 2.

When comparing the age, the distribution was 50.80% participants were in between 20 to 30 years old and 49.20% participants were between 40 to 50 years. The distribution according to the height was found as 5.1% participants below 149 cm, 32.20% participants in between the height of 150 cm to 159 cm, 32.20% participants in between the height of 160 cm to 169 cm, and 30.50% participants more than 170 cm. The peak expiratory flow rate (PEFR) was taken in three readings for each participant and average of expiratory flow rate was calculated. On calculation, the mean and standard deviation of the average peak expiratory flow rate was found to be 387.34±125.31. Based on the average value, peak expiratory flow rate was associated with age and height. Association of PEFR with age was shown in Figure 1.

Average peak expiratory flow rate for 20 to 30-years-old of participants was found to be 403±123 whereas for 40 to 50-years-old, average peak expiratory flow rate was 371±128 as shown in Figure 1. The peak expiratory flow rate would decrease as the age advance. However, the age factor did not significantly affect the peak expiratory flow rate. Based on the data from the Mann Whitney test, the average peak expiratory flow rate ($p = 0.275$) in 20 to 30 years age group (mean rank = 32.40) was not significantly higher than in 40 to 50 years age group (mean rank = 27.52). Association between average peak expiratory flow rate and height categories were shown in Table 3.

Peak expiratory flow rate increased as the height increased as shown in Table 3. A turkey post hoc test revealed that the peak expiratory flow rate was significantly higher at the height category of more than 170 cm compared to the other height categories, below than 149 cm (291.11±75, $p = 0.01$), between 150 cm – 159 cm (316.14±80, $p=0.00$) and between 160 cm – 169 cm (364.56±105, $p=0.00$). However, there was no significant difference between the height categories below 149 cm with 150 cm – 159 cm ($p=0.98$) and 160 cm – 169 cm ($p=0.63$). The height category of 160 cm – 169 cm did not have significant difference with 150 cm – 159 cm ($p=0.44$).

While testing the respiratory function, there will be a normal decline in the flow rate as the age increases, as part of aging process. There will be degeneration in thoracic-abdominal compartment with decreased muscle strength followed by decrease in lung elasticity and joint mobility[6]. This reduced PEFR reflects of tightening airways and can be used to verify the clinical status. In case of children, with increase in age, PEFR increases and reverse happens in adults, as the PEFR decreases after 30 years[7]. This fact was proved in the present study, as PEFR declined with increased age. However, this decline was not statistically significant in the two age groups we studied i.e. 20 to 30 years and 40 to 50 years. Similar findings were observed in a study done by Sagher *et al*. showed increased PEFR with both age and height[8]. In older people, PEFR predicts important outcomes. It was found that in order to report pulmonary function in the older people, standardized residual percentage method is better.[9]

Association between PEFR and height was significant, with mean PEFR values of taller participants were more than the shorter participants. With this correlation of height with PEFR, it can be used to predict the flow rate in children. But in another study, there was no significant difference between the height and age of adults with PEFR[10]. Our results are in accordance with the previous study done by Jayanti *et al.* where similar results are noted and

is due to high muscular effort with more chest volume. [11] Most significant correlations between height and PEFR was noted similarly in other experiment done by Malik *et al.* where the relation between PEFR and other parameters such as weight, arm span, body surface area and body mass index were also studied. [12]

Conclusion

Peak flow meter is a simple test to assess the airway obstruction and also to find the response of patient towards the therapy which helps in the management of the patient. It can also be used in the field studies. In this study, there was a significant relation between PEFR and height was observed with increased PEFR in taller participants. But there was no association between age and PEFR. However, further study with large sample size is needed to determine the association of PEFR with age. This study is considered as a baseline for larger studies in the future.

Acknowledgement

Authors acknowledge the cooperation of all the participants of this study and Universiti Kuala Lumpur Royal College of Medicine Perak, for giving permission in doing this project in their campus.

Conflict of interest

None

Table 1: Study variables used in the study

Conceptual definition of the variables	Operational definition of the variables
1. Peak Expiratory Flow Rate (l)	The participant's PEFR measured by peak flow meter.
2. Height ~~(cm)~~	The participant's measured by height scale
3. Current age from birth	The participant's age based on their Identification Card (IC)

Table 2. Distribution of study population by age and height

Factor	size	Percentage
Age		
20 – 30	30	50.80
40 – 50	29	49.20
Total	59	100.00
Height (cm)		
Below than 149	3	5.10
150 – 159	19	32.20
160 – 169	19	32.20
More than 170	18	30.50
Total	59	100.00

Table 3. Average peak expiratory flow rate in relation with height

Height (I)	Height Category (J)	Mean Difference (I-J)	Std Error	Sig.	Mean ± SD
below 149	between 150 to 159	-25.03	61.42	0.98	291.11±75
	between 160 to 169	-73.45	61.42	0.63	
	more than 170	-211.48*	61.66	0.01	
between 150 to 159	below 149	25.03	61.42	0.98	316.14±80
	between 160 to 169	-48.42	32.08	0.44	
	more than 170	-186.45*	32.52	0.00	
between 160 to 169	below 149	73.45	61.42	0.63	364.56±105
	between 150 to 159	48.42	32.08	0.44	
	more than 170	-138.03*	32.52	0.00	
more than 170	below 149	211.48*	61.66	0.01	502.59±112
	between 150 to 159	186.45*	32.52	0.00	
	between 160 to 169	138.03*	32.52	0.00	

*The mean difference is significant at the 0.05 level.

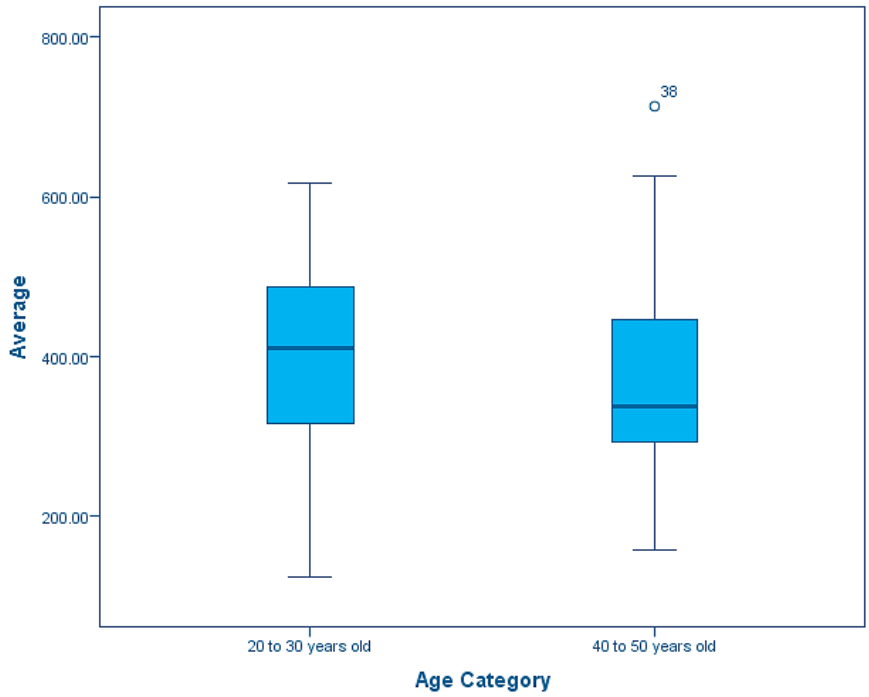

Figure 1. Average peak expiratory flow rate in relation with age.

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SHORT COMMUNICATION

ROLE OF 'REDUNDANT' OR 'PSEUDO' CLINICAL VIGNETTES IN FORMATIVE ASSESSMENT.

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It is true that though students can escape bad teaching they would still be victims to bad assessment.[1] Assessment based on real life happenings, issues which the student would find themselves during the vocation they are being trained for is the ideal assessment method rendering validity and authenticity.[2] They are also termed as fit for purpose 'assessment tasks[3].

We speak of, **Assessment of learning** often referred to as 'summative assessment' used to grade students. **Assessment for learning** or 'formative assessment' is done to inform the learners their level of academic progress[4].

Students can utilise examinations to be aware of their strengths and deficiencies. With prompt feedback received from their teachers they can improve their academic abilities[5]. The onus is in the form of the assessment and how the information gathered is used to improve teaching and learning[6].

Assessment as learning happens when the assessment is used to instruct the learners.[6] Students are more focussed during assessments than during the teaching learning sessions. Use of clinical scenarios, meaningful questions and prompt feedback can make learning and assessment aligned.[7] Use of clinical scenarios which do not reflect real life scenarios would not be beneficial to the learners. For these questions with the redundant scenarios, the learner needs only to read the lead-in statement to answer the question.[8]

To cite an example:

A 40 year old male with AIDS develops intractable diarrhoea. 1% modified acid fast staining reveals the presence of an acid fast oval protozoa. The organism is identified as:

A. *Pneumocystis jiroveci*
B. *Cryptosporidium hominis*
C. *Entamoeba histolytica*
D. *Mycobacterium avium intracellulare*
E. Rotavirus

The above question with a 'redundant' scenario; the student needs only to read the lead-in in order to answer the question ignoring the pseudo clinical scenario. A direct way of asking this question would be 'Which among these organisms are modified acid fast?'

However, the question serves **AS** learning, linking AIDS and intractable diarrhoea with an opportunistic infection.

During a low achievers counselling session, at the university I am affiliated to, a year two student stated that while basic facts are taught in teaching learning sessions, clinical vignette-based questions are asked in the formative assessments. The students felt that more practice or mock scenario questions would make them better prepared for the formative assessment. The learner was addressing a perceived gap and non-alignment between the teaching sessions and the examination. Though the student's argument here may not be relevant, the feedback cannot be ignored. Would the pseudo clinical vignettes, considered ineffective, serve as an interphase between the teaching sessions and the formative assessment? The basic science question then would be clear to the novice student and the pseudo clinical vignette (without which the learner can still answer the question) would serve as assessment for learning.

Example of a basic science fact as taught in class

This is a question that features from a session on 'Basic bacterial physiology'. The intended learning outcomes include

Describe the relationship of different bacteria to their nutritional requirements, oxygen, and temperature and pH demands

The basic question-**Which one of the following bacteria grows well in colder temperature?**

A Listeria monocytogenes
B Clostridium botulinum
C Salmonella typhimurium
D Bacillus cereus

Example of how the same topic could feature in the formative assessment

Psychrophiles are bacteria that grow and multiply in low temperature. Storage of psychrophiles contaminated dairy products and meat in the refrigerator can increase the risk of gastroenteritis and diarrheal outbreaks.

Which one of the following bacteria grows well in colder temperature?

A *Listeria monocytogenes*
B *Clostridium botulinum*
C *Salmonella typhimurium*
D *Bacillus cereus*

Another example of a question which would make the learner realise the significance of and apply a basic science fact.

Gastroenteritis (diarrhoea and vomiting) due to Vibrio species are associated with sea food intake. Vibrio is a/an

A Acidophile B. Neutrophile C. Alkalophile

Assessment **AS** and **FOR** learning is known to influence higher order thinking skills in the students.[9] Most literature strongly recommends the use of assessment as a scope and as an opportunity to reinforce and enhance learning.[10]

Medical students will benefit from questions which require a meaningful sequence, an algorithm, a right approach, an immediate response to a clinical situation.

For instance questions like 'Explain tetanus' is best avoided. Even better framed questions like 'Describe the post exposure prophylaxis of tetanus" does not specify the exact scenario. Stating a specific clinical scenario where a patient has been exposed to tetanus and what would be needed to be done then would serve as an ideal assessment.

For instance, neonatal tetanus prophylaxis will differ from the prophylaxis of an adult who was involved in a road traffic accident. A pseudo scenario is better than no scenario. More information about the use of pseudo clinical vignettes as an interim between teaching basic science facts and testing with clinical scenarios in the formative assessment will serve as a needs analysis before implementation.

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CASE REPORT

LEFT LUNG AGENESIS IN AN ADULT – A RARE ANOMALY.

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Abstract

Pulmonary agenesis is a rare congenital anomaly and only a few cases are reported in the literature. Adult cases present with a heterogeneous spectrum of manifestations and radiological findings. Historically, the diagnosis was made during autopsy, but with modern imaging technology, the diagnosis can be confidently made based on radiological findings.

We present a 72 year old lady with left lung agenesis, diagnosed at the age of 40 years old. This is the first case to be reported in Malaysia.

Key words: Agenesis, lung, Congenital, Incidental, Opaque lung

Introduction

Lung agenesis is a rare condition with a prevalence of approximately 1 in 100,000 births[1]. Bilateral lung agenesis is extremely rare and not compatible with life while unilateral agenesis is also very uncommon in adults. In childhood, it is usually accompanied by other system anomalies.[2,3] The oldest patient reported by Oyamada *et al*. was 72 years old and younger patients reported were 19 and 24 years old respectively.[4,5] We report a case of left lung agenesis in a 72 year old lady who had remained in reasonably good health despite this condition being diagnosed when she was 40 years old.

Case report

A 72-year-old lady with no co-morbid had been diagnosed with left lung agenesis at the age of 40 years when she presented with non-productive cough and wheezing. She had no significant childhood history of recurrent chest infections and no symptoms suggestive of reflux esophagitis or hiatus hernia. Physical examination of the chest revealed reduced breath sounds and dullness on the left side with right sided expiratory wheeze. Examination of the cardiovascular system was unremarkable. Lumbar scoliosis was noted.

Chest radiograph revealed a homogenous opacity of the left hemi thorax (Figure 1). Thoracic computed tomography (CT) demonstrated a hyper expanded right lung with, marked tracheal and midline shift to the left and a non- aerated left lung accompanied by small pulmonary vessels. (Figure 2, 3).

She was not able to complete the pulmonary function studies. Other laboratory evaluation, including tuberculosis screening was unremarkable. She was empirically treated for obstructive lung disease with budesonide inhaler.

Discussion

Lung agenesis is a rare congenital anomaly due to failure of pulmonary system development during embryogenesis [6, 7] and is usually associated with other cardiovascular anomalies.

The exact aetiology is still unknown although genetic, and teratogenic factors have been implicated[8] including viral agents, and dietary deficiency of Vitamin A during pregnancy. Agenesis of the lung was originally classified into three groups by Schneider and was subsequently modified by Boyden. Lung agenesis is classified by Boyden[9] into three categories.

Type 1 (Agenesis) - Complete absence of lung bronchus and no vascular supply to the affected side.

Type 2 (Aplasia) - Rudimentary bronchus with complete absence of pulmonary parenchyma.

Type 3 (Hypoplasia) - Presence of variable amounts of bronchial tree, pulmonary parenchyma and supporting vasculature.

Our patient will be classified as type 3 as a small pulmonary artery is present within a non-aerated lung. There was a case report in Malaysia of an isolated pulmonary artery agenesis in a young man who underwent pneumonectomy.[10] The incidence and prevalence of lung agenesis was found to be similar in both genders. Right lung agenesis has a shorter life expectancy compared to the left anomaly.[11] Our patient was only diagnosed at the age of 40 when she presented with respiratory symptoms.

The clinical manifestations vary from being asymptomatic to severe respiratory distress depending on the extent of malformations and presence of comorbidities. Recurrent chest infection is the most common presentation leading to the diagnosis and usually begins in childhood. Clinical findings may pose a diagnostic challenge especially in adults since there are other diagnosis to be considered such as lung collapse, pleural thickening, hiatus hernia and pleural effusion.

The CT scan is an important diagnostic tool for this rare entity as it will demonstrate the pulmonary architecture in great detail.

Lung agenesis is often associated with anomalies in the musculoskeletal, cardiovascular and

gastrointestinal systems.[12] Our patient presented with sciatica which is attributed to her lumbar scoliosis.

Conclusion

This case highlights the diagnostic challenge for clinicians, and one must have a high index of suspicion in patients presenting with repeated unexplained respiratory symptoms. CT or MRI/MRA are usually diagnostic. Treatment and intervention is usually indicated only for symptomatic patients.

Informed Consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient.

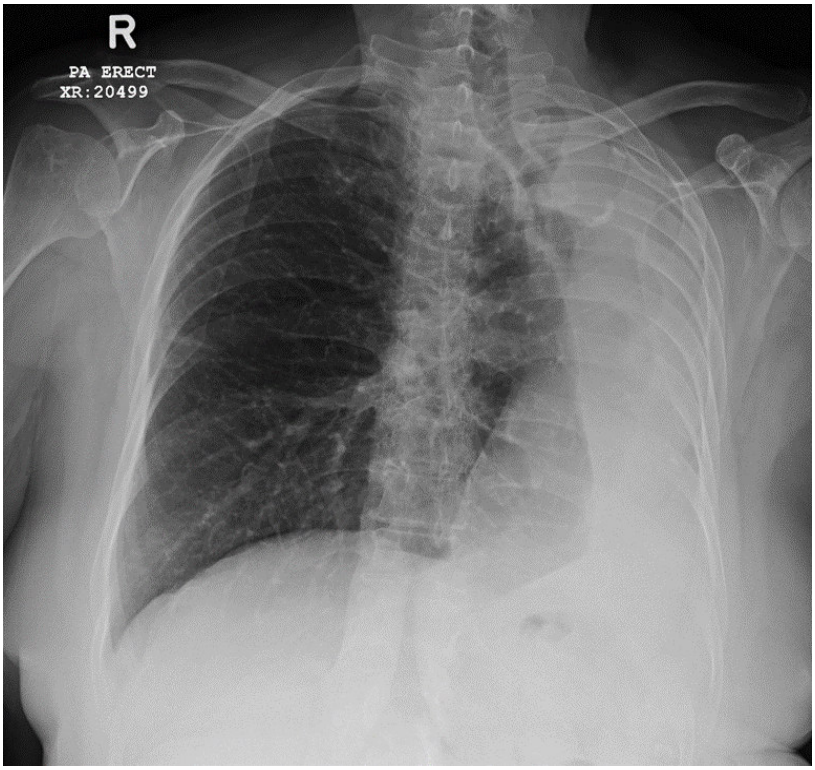

Figure 1: Plain Chest radiograph showing hyperinflation of the right lung with herniation towards the left thorax. There is gross tracheal and mediastinal shift to the left and crowding of ribs of the left thorax.

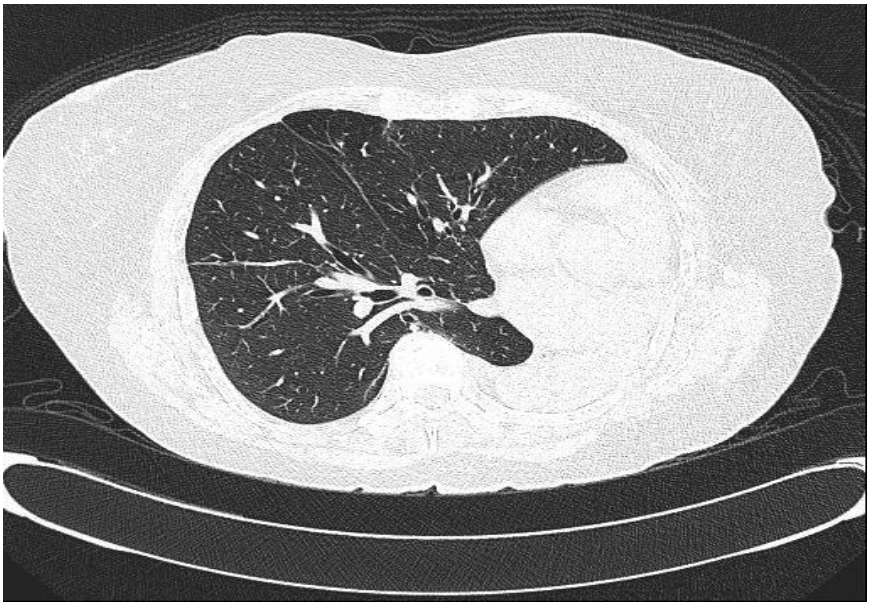

Figure 2. Computed axial tomography scan of the thorax showing the mediastinal shift to the left with hyper expansion of the right lung. Smaller left hemi thorax is present.

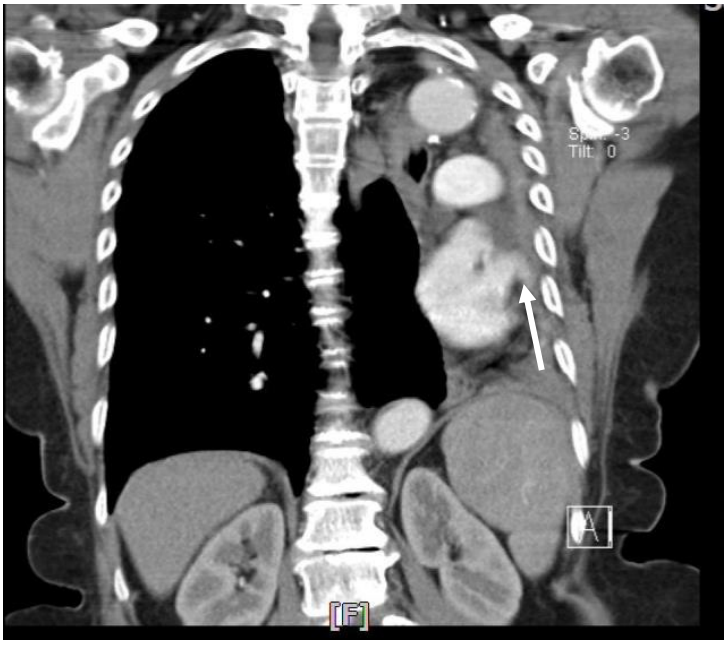

Figure 3. Contrast enhanced coronal CT Thorax showing the tracheal and mediastinal shift to the left with absent of the left lung parenchyma. Small left pulmonary artery seen (*Arrow*)

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CASE REPORT

GRAVES' DISEASE WITH NON-FUNCTIONING PITUITARY ADENOMA.

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Abstract

Pituitary adenoma may be associated with hyperthyroidism if there is excess production of thyroid stimulating hormone (TSH). However, the occurrence of Graves' disease and this slow-growing benign pituitary tumor (1% of functioning adenomas producing TSH) is rare. We report a case of difficult to control Graves's disease with myopathy diagnosed for the past 1 year. Pituitary adenoma was incidentally found when patient developed Addisonian crisis complicating severe gastroenteritis.

Key words: Graves' disease, Nonfunctioning pituitary adenoma, Incidentaloma, Addisonian crisis.

Introduction

Nonfunctioning pituitary macroadenoma (NFPA) is a benign tumour [1,2] and it is the most common of pituitary adenomas (28% to 37%).[3,4] There is a wide variation in progression and is frequently diagnosed in patient above 50 years and the symptoms may be subtle. The rare coexistence of Graves' disease and TSHoma has been described in previous case reports.[5,6,7] We present a patient with Graves' disease who developed Addisonian crisis which led to an incidental finding of a pituitary macroadenoma.

Case history

A 59-year old Chinese man was diagnosed as Graves' disease in early 2018 when he presented with loss of weight and episodic proximal myopathy. He had no other classical symptoms of hyperthyroidism. He did not have any ophthalmic symptoms, headache or goiter. He was easily fatigued and had changes in mood, being easily irritable. He also admitted to having erectile dysfunction. He had a history of hypertension and hypercholesterolemia for more than 20 years.

Neurological examination revealed proximal myopathy affecting predominantly both his lower limbs. He did not have a goiter, there was no bruit heard over his neck and there were no other signs of thyrotoxicosis. The reflexes were normal. Other systemic examination was unremarkable. His blood pressure was well controlled.

His initial thyroid function test showed markedly raised free thyroxine (FT4) 60.8 pmol/L (normal 9.1 – 24.4), free triiodothyroinine (FT3) 18.14 pmol/L (normal 2.23 – 5.35) and undetectable thyroid stimulating hormone (TSH) <0.01 mIU/L (normal 0.30 – 4.64) respectively. The thyrotropin TSH receptor antibody was raised, 2.74 IU/L (normal less than 1.75).

The creatinine kinase was normal. The serum sodium (Na+) and potassium (K+) levels were normal then. He was given carbimazole 20 mg daily. The following month, his FT4 and FT3 decreased to 13.8 pmol/L and 4.43 pmol/L respectively with resolving lower limb weakness and he gained weight. Clinically he was euthyroid. Over the ensuing two months, he was in a hypothyroid state with FT4 4.1 pmol/L and FT3 1.87 pmol/L with polymyalgia and cold intolerance but no constipation. Carbimazole was stopped but within 2 months the FT4 and FT3 increased to 18.0 and 8.19 respectively and the TSH remained undetectable (<0.02) and he developed recurrent episodes of proximal weakness. The creatinine kinase and other electrolytes remained normal. Subsequently he developed multiple joint pain and stiffness for 2 weeks but there was no clinical evidence of synovitis. He experienced excessive fatigability and blamed this on his travelling related to his job.

In late 2018, he was diagnosed with Addisonian crisis when he presented with severe gastroenteritis and persistent hyponatremia ranging from 112 – 114 mmol/L, and normal potassium. Urine sodium was 41 mmol (normal 54-150). The serum osmolarity was normal. Septic workout was negative. The thyroid function test was normal (FT4 10.5 pmol/L, FT3 4.35 pmol/L, TSH 0.61 mIU/L). However, he suddenly developed a syncopal episode without any other significant neurological deficit. There was no seizure noted. Computed tomography scan of the abdomen revealed normal adrenals. Magnetic resonance imaging (MRI) of the brain revealed a tumor mass arising from the pituitary fossa consistent with an adenoma (Figure 1A, 1B). Hormonal studies were done, his prolactin level was 18.61 ng/mL (normal 1.61 – 18.77), arginine vasopressin 0.5 pg/mL (normal < 4.3). The serum cortisol level remain low (1.0 ug/dL). The follicular stimulating hormone (FSH) and luteinizing hormone (LH) were normal.

The anti-thyroglobulin antibody (anti-TG) 0.4 IU/mL (normal less than 115), and anti-Thyroid

peroxidase (anti-TPO/AMC) 0.4 IU/mL (normal less than 34.0).

He underwent successful surgical resection by the transphenoidal approach. Histopathology showed cohesiveness of the tumour cells arranged in garland, festoons, cords and sheets with intervening thin vascularized stroma exhibiting uniform rounded nuclei and moderate amount of pinkish cytoplasm which was consistent with pituitary adenoma.

He remained euthyroid clinically and biochemically with normal hormonal studies post operatively.

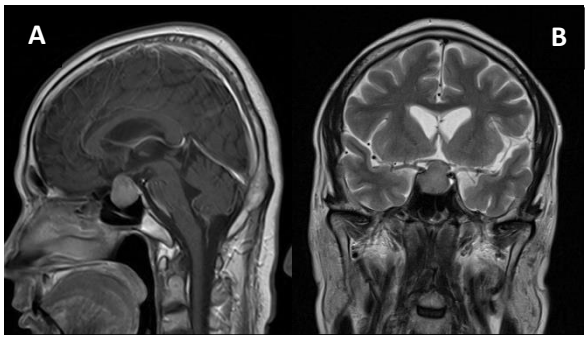

Figure 1. Magnetic resonance imaging sagittal (A) and coronal (B) sections of the brain showing a sellar mass measuring 18.6 mm x 17.9 mm x 20.2 mm resulting expansion of the pituitary fossa suggestive of pituitary macroadenoma.

Discussion

Graves' disease is classically associated with negative feedback suppression of TSH in response to increase in FT3 and FT4. The TSH may fall to undetectable level as illustrated in our patient. It has been described in the literature and case reports of a rare occurrence of coexistence of a state known as syndrome of inappropriate secretion of TSH (SITSH) in which the TSH level is usually increased. This was not the case in our patient although his thyroid condition was difficult to control as shown by a fluctuating clinical course and levels of FT3/ FT4.

The diagnosis of gastroenteritis with persistent hyponatraemia was treated as infective in origin though the possibility of uncontrolled hyperthyroidism or masked thyroid storm was entertained.[8,9]

The MRI findings were highly suggestive of pituitary macroadenoma. This was a non-functioning adenoma in our patient. His symptoms were very non-specific and he had no headaches. Macroincidentaloma of the pituitary has established diagnostic and management guidelines.[10] Successful surgery usually results in complete remission of symptoms though hormone replacement therapy specifically levothyroxine and cortisone may be necessary. In asymptomatic patients, surgery may be deferred with regular follow up, endocrinological assessment and neuroimaging. Symptomatic patient which neurological signs such as the visual field defects due to compression effect, pituitary apoplexy or hormonal hypersecretion warrant surgical intervention.[10]

Conclusion

This case highlights the diagnostic challenge for clinicians, and one must have a high index of suspicion in patients presenting with repeated unexplained respiratory symptoms. CT or MRI/MRA are usually diagnostic. Treatment and intervention is usually indicated only for symptomatic patients.

Conflict of interest

Authors declared no conflict of interest.

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CASE REPORT

TORSION OF TESTIS – REPORT OF TWO CASES WITH A BRIEF REVIEW OF LITERATURE.

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Abstract

The torsion of testis is an acute vascular event, one of the emergency presentations seen in young adolescent males. The spermatic cord becomes twisted and rotated on its axis and results in gangrene of testis due to vascular ischemia. There may be chances of loss of normal spermatogenetic function if there is any delay in the management of testicular torsion.

We had 2 cases of torsion testis with classical signs and symptoms with acute pain over the scrotum, elevated testis & swelling on affected side. Emergency ultrasound and Doppler were done and reported as torsion testis with ischemia. The cases were managed with orchiectomy since the patients reported to us late. Patients were comfortable in post-operative period and discharged.

In conclusion, testicular torsion should be considered in undescended testis. The emergency Ultrasound and Doppler investigations have to be done in all cases of acute scrotum who have acute pain over scrotum.

Key words: Testis, Torsion, Doppler, Orchiectomy, Orchidopexy.

Introduction

Though it is common in adolescence, torsion of the testicle is not unusual as a cause of acute scrotum in the elderly population[1]. A 65-year-old Malay gentleman with a background history of Parkinson's disease once had presented with torsion of testis in one hospital in Malaysia[2]. The acute scrotal diseases are medical emergency which involves the scrotum and/or the intra-scrotal contents and later require proper medical or surgical management[3]. Cases of Torsion testis may present as an acute onset of severe and unbearable scrotal pain. If there is any delay in diagnosis of testicular torsion, patient may land with gangrene of testis which requires orchiectomy. Sometimes it may lead to medico legal issues which would focus about delayed management. The main differential diagnosis is usually epididymo-orchitis which requires only conservative (medical) line of management. The vascular and inflammatory causes are important for the cases of acute scrotum and the importance of a differential diagnosis between them[4].The testicular torsion in the intravaginal form ("bell clapper deformity"[4]) is a condition that characterizes itself for the free rotation of the testicle due to the anomaly of testicular fixation.

Case No. 1

A 23-year-old young man presented to the accident and emergency unit of SIBI Hospital, India with complaints of pain in the right side of the scrotum for 20 minutes duration. Pain was severely aching in nature without radiation. There was no history of trauma over the scrotum and lower abdomen. There was no history of urinary symptoms and fever. No history of previous episode of similar presentation and urinary tract infection were noted. There was no past history of surgery. He is not a known case of diabetes and hypertension. On examination, he was in painful distress and afebrile. His left side of the scrotum was normal with findings of absence of swelling and normal skin with normal rugae. The right side scrotal examination revealed elevated right testis, swelling (Fig-1) and tenderness with loss of rugae. Prehn's sign was negative.

Figure 1. Right sided scrotal swelling and elevated right testis.

Positive Prehn's sign indicates the relief of pain on lifting the affected testicle and points towards epididymitis. Cremasteric reflex was absent. Examination of penis revealed no abnormal discharges through urethra. Pulse Rate was 76 beats per minute, regular, with normal volume; blood pressure was 114/76 mmHg. Respiratory, abdominal and cardiac examinations were normal. Diagnosis of torsion testis-right sided was made. The patient's condition did not support in favour of right epididymo-orchitis as the testis was not warm and Prehn's sign was negative.

Doppler ultrasound (Fig-2) showed decreased blood flow to right testis and minimal fluid collection in tunica vaginalis suggestive of right testicular torsion.

Patient was explained about his condition and informed consent was obtained for removal of right testis. An explorative surgery was performed under general anaesthesia and left orchidopexy was done. Then right side of scrotal

skin was explored and gangrene of the right testis was noted (Fig-3). Right orchiectomy was performed. Post-operative period was uneventful. Patient is still under our follow up.

Figure 2. Doppler ultrasound test showing no demonstrable vascularity in the right testis.

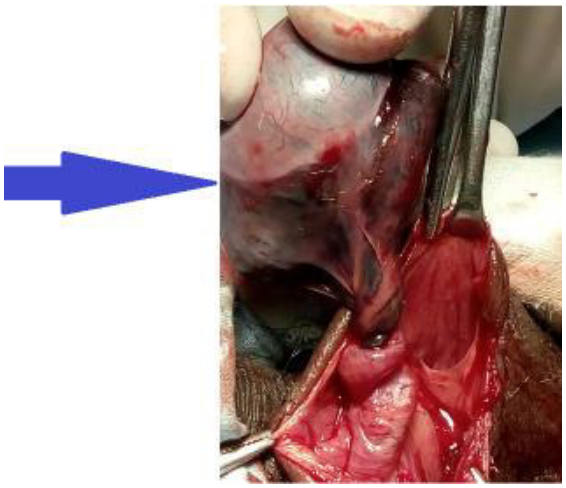

Figure 3. showing the torsion and gangrene of right testis (arrow mark) during scrotal explorative surgery.

Case No. 2

A 15 year- old boy, presented to the accident and emergency unit of SIBI Hospital, India with complaints of pain of thirty minutes duration over left inguinal region with radiation to left loin. Absence of left side testis was noted and history revealed that it was absent since birth. He noticed small swelling in his left inguinal region when he was 11 years old. There were no issues over left inguinal region till he came to hospital for this episode. There was no history of trauma over the scrotum and inguinal region. There was no history of urinary tract infection. He had not undergone surgery for left inguinal region swelling. He did not have any co-morbidity like diabetes or hypertension. On examination, he was afebrile and was in distress of pain. His right side scrotum was normal with normal testis. There was absence of scrotal pouch on his left side. Swelling was noted over left inguinal region (Fig-4). The size of the swelling was 2 x 1.5 inches and it was tender but not warm. Examination revealed normal penis and no abnormal urethral discharge was noted. Pulse Rate was 80 beats per minute, regular, with normal volume, blood pressure was 120/74 mm of Hg. The examination of respiratory, abdomen and cardiovascular systems were found to be normal. Diagnosis of torsion of left undescended testis was made and other possible causes were ruled out. There were no points to support left epididymo-orchitis. The ultrasound and Doppler study showed no demonstrable blood flow to the undescended left testis suggesting left undescended testis with testicular torsion (Fig-5).

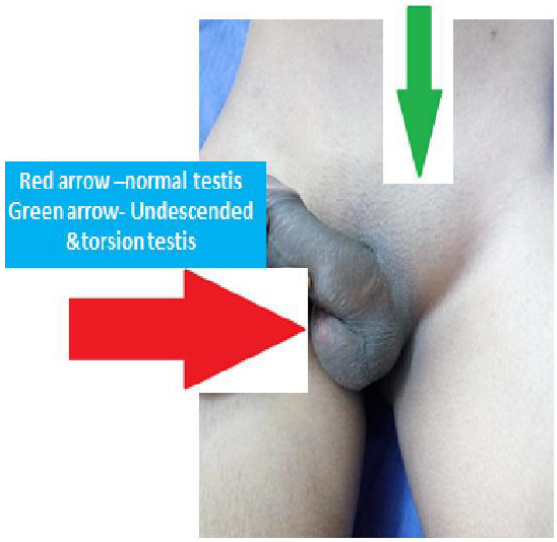

Fig -4 showing absence of left scrotal pouch and left inguinal swelling suggesting left undescended testis.

Figure 5. Doppler ultrasound test–showing no demonstrable vascularity left testis.

Father of the patient was explained about the condition and informed consent was obtained for removal of left testis. An explorative surgery was performed under general anaesthesia and gangrene of the left undescended testis was noted (Fig-6). Right orchidopexy and left orchiectomy were performed. Patient was well during his post-operative period and was discharged on time without any further complications. He is still under our follow up.

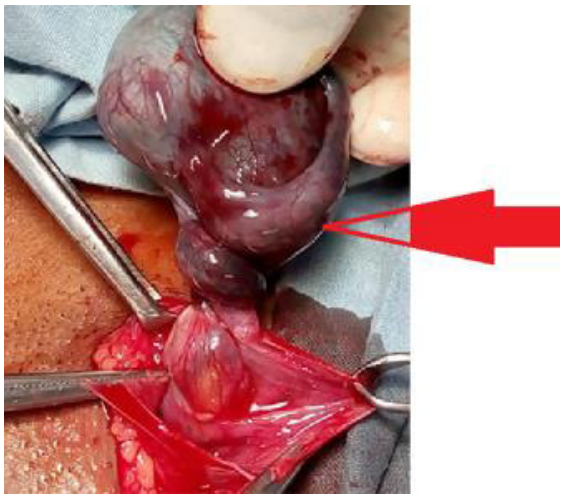

Figure 6. showing torsion and gangrene (Red arrow) of undescended left testis during the surgery

Discussion

Torsion of the testis is more common in adolescent period. Acute and sudden pain over any one side of scrotum is mostly due to torsion testis. It is explained that there is twisting of the spermatic cord resulting in acute pain over one side of scrotum due to ischemia of testis[5]. Testicular torsion is more common because of anatomic anomalies of tunica vaginalis and epididymis which would allow excessive testicular mobility inside the scrotal pouch. The intravaginal torsion (bell clapper deformity) is the most frequently occurring type[6, 7] Testicular torsion can manifest at any age and incidences are more common compared to testicular tumours. The increasing age is the sole identifiable risk factor for orchiectomy[6, 8]. Rotation and torsion of testis mostly medial rotation ranging from 360° to 720° in its own axis can cause interruption of the testicular blood supply. There is one type (Type1) where the head and tail of epididymis are attached to the testes[9]. The common signs and symptoms of torsion testis are redness, swollen oedematous scrotum and acutely tender testicle, though there is no history of trauma and the testis may lie

horizontally and inflammatory signs may or may not be present[10,11]

Children are usually brought to the emergency department with pain and acute swelling in scrotum and there are diverse pathologies that present themselves as acute scrotum on emergency. The pathology of these conditions are usually inflammatory and vascular causes. The probable causes of pain and acute scrotal oedema are testicular torsion, appendices testis torsion, epididymitis and orchitis[12]. Differentiating them is difficult, because there is no trust worthy clinical sign which can be considered as pathognomonic to these conditions[13]. There is no standard and classical clinical presentation for testicular torsion and it can present similar to epididymitis[14]. A significant number of proven testicular torsion cases present with gradual onset discomfort, whereas alternative causes of scrotal pain, such as epididymitis, can present with sudden discomfort in up to 51% of cases[15]. Finally, circumstances surrounding the presentation may not reveal the ultimate diagnosis. Testicular torsion is attributed to direct trauma in 4–8% of reported cases, and more frequently occurs during sleep, as a result of spontaneous cremasteric contractions[16]. Since there is a wide variety and overlap of symptoms and circumstances surrounding testicular torsion, it is imperative to not rely on historical features alone to guide further evaluation. Presence or absence of cremasteric reflexes, scrotal oedema/erythema, pain along the upper pole of the testicle or epididymis, enlarged epididymis, transverse lie, Prehn's sign (relief of pain when the examiner is lifting testicle), and retraction of testicle all fail to give a definitive answer. Even when experienced urologists combine all these exam findings, their initial impressions are frequently erroneous[15].

When surgery is performed early within the first 6 hours from the appearance of signs and symptoms, there would be 90% chance of recovery. This would go down to 50% after 12 hours and to 10% after 24 hours lapse before surgical treatment[17]. Clinical examination has an important role to diagnose the testicular torsion[18]. A study involving 245 boys with acute scrotum, observed a 100% correlation between the presence of the cremasteric reflex and the absence of testicular torsion. It confirmed that the presence of the cremasteric reflex is very important clinical finding to rule out testicular torsion and the absence increases suspected diagnosis[19]. The radiological study used in the hospital for confirming the diagnosis is the Doppler ultra sound, which has a 96.8% sensitivity, a 97.8% specificity, a positive predictive value of 92.3% and a negative predictive value of 99.1%. They conclude that clinical assessment combined with Doppler ultrasound are most reliable confirmative procedures to arrive at proper diagnosis of the testicular torsion[20].

Nonsurgical management (Manual de-rotation) can be tried if there is no evidence for ischemia or gangrene of affected testis which would be assessed by clinical parameter and Doppler study. Manual de-rotation can be done when the surgery is not an immediate option[21]. It can also be tried during the preparations of surgery for the patient and it should not be supersede or delay surgical interventions[22, 23]. Manual de-torsion should not replace surgical intervention or exploration[24, 25]. The testes are typically de-torsed from the medial to lateral side, turning the physician's hands as if "opening a book"[26]. Usually general anaesthesia is not necessary to do this simple and short duration of re-torsion procedure. Intravenous analgesic drug administration or sedation are enough to tackle this procedure. Sometimes we can give spermatic cord block which would

support for de-torsion by relaxing cremasteric muscle fibres. The testicle is typically twisted more than 360 degrees, so more than one rotation may be required to completely de-torse the testicle[26]. Though we succeed by doing de-torsion to save the testis, we need to monitor the testis through clinical and Doppler study. Completion of the treatment would be attained by doing orchidopexy in both sides to prevent re-torsion. Sometime surgeon may not be able to take concrete decision for surgery. Delaying the time may worsen the patient's condition. It is safer to proceed surgical exploration of scrotum and decide accordingly on the table. From a surgeon's point of view, it is always safe to counsel the patient for potential need of orchiectomy and get the consent before surgery [25, 27,28,29,30.] Many studies said that patients with physical findings strongly suggestive of testicular torsion should be referred for surgical exploration regardless of ultrasound findings[25, 27,31,32,33].

Orchidopexy of other testis should also be done though surgery for affected side could be orchidectomy or orchidepexy[34]. The type of bell-clapper deformity increases testicular mobility so that the risk of torsion in both sides increases in 80% of patients[10]. It is assumed to be present contra laterally in all patients with testicular torsion[35, 28, 30]. There are rare incidences of recurrent torsion after many years in some patients those who had undergone orchidopexy. These patients and their parents have to be warned regarding the risk of recurrences and consequences and they have to be under follow-up.

Conclusion

The family physician and doctor in emergency department have to take more care whenever they get the patient with scrotal pain or lower abdominal pain. These patients need proper physical examination and have to be submitted for ultrasound/Doppler studies whenever there is any doubt regarding torsion testis or epididymo-orchitis. Rarely Doppler study of epididymo-orchitis may show reduced blood to testis. The compartment syndrome is the cause for ischemia to testis and the early incision over tunica albuginea (capsulotomy) would save the testis before it goes for irreversible necrosis. There is nothing wrong to refer these patients to a specialist –urologist to get opinion to avoid medico legal issues. Surgeon can go for early exploration of scrotum whenever the Doppler report is inconclusive. Patient and the parents have to be counselled well regarding possible orchiectomy before scrotal exploration.

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