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M. Bakri Musa

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As a young surgeon at the General Hospital Kuala Lumpur in the 1970s, I remember pleading with Tan Sri Majid Ismail, then Director-General of the Ministry of Health, for funding of my research project. A distinguished clinician turned policy maker, Tan Sri Majid was professionally interested in my proposal. Nonetheless he politely declined it, but not before offering me a comforting explanation. Between funding me and building a *Klinik Desa* (rural clinic) in Ulu Kelantan, the choice was clear, he gently told me. Besides, he assured me, I would have minimal difficulty securing funding elsewhere while those poor Kelantanese had no choice. Tan Sri Majid said something else that reverberates in me today. "Healthcare is a bottomless pit," he advised me, "but the resources to meet those literally endless worthy needs are limited, so society must set its priorities and draw the line somewhere." The job of government is to ensure a minimal acceptable level of care for all, he added, and beyond that it is for individuals to set their own limits with their own resources. Malaysia does this with its dual public and private healthcare systems. Tan Sri Majid was adamant in maintaining this clear separation lest there would be confusion in the respective missions and objectives.

America today is in the midst of a wrenching debate on healthcare reform, specifically its massive price tag and the provision for a "public option," a government-run insurance company (1). Similar debates occur elsewhere, Malaysia included. These deliberations would be elevated greatly if we were to heed Tan Sri Majid's observation on resources being necessarily limited and the necessity to set priorities. It is understandable for America, the richest country, to have difficulty acknowledging the first, and as for the second, the setting of priorities is too often confused with rationing, a highly emotive issue.

This need for setting priorities is never more urgent today. In the past, the best that physicians could do was to bring our patients back to their pre-morbid state. Today the goals go far beyond, from enhancing lives (cosmetic surgery) to eliminating genetic diseases through genetic engineering.

Consider the wonders of modern drugs. In the past they were for curative purposes in a limited setting, as with antibiotics for infections. Today the biggest expenses are for drugs in maintaining chronic conditions (anti-inflammatory medications), enhancing life (Viagra and oral contraceptives), and reducing risk of diseases (the statins) (1). Similarly with public health; in the past interventions were limited to specific communicable diseases as with childhood immunizations. Today we have the various screening tests for cancers.

Regular exercise, good diet, and smoking cessation too are also health enhancing and good preventive measures. Issues would arise however, if we insist that health insurers pay for our lean cuisine and health club membership. Where to draw the line, in public health as well as clinical setting, is the great challenge. Also often forgotten is that there is minimal correlation between outcomes and expenditures in healthcare. America spends twice as much as Britain (relative to the economy), yet it would be hard to argue that Americans are as healthy as the Brits, let alone twice that (2).

While the bulk of the healthcare dollar is expended on hospitals, pharmaceuticals, and physicians, nonetheless the costs are primarily physician-driven (3). Many are thus misled into believing that focusing on physicians specifically is the key to improving citizens' health and or controlling costs. In truth, much of our present good health is due more to civil engineering marvels like central sewer and water treatment plants, as well as modern refrigeration. Malaria,

still a scourge in the Third World, was eliminated in California's Sacramento Delta through the building of levees and consequent drainage of the swamps, not advances in parasitological research.

This observation is worth emphasizing. With rapid urbanization, the inadequacy of these basic infrastructures has turned Third World cities into public health time bombs (4). Stroll through an exclusive neighbourhood of Kuala Lumpur and you will see garbage strewn all over, stagnant drains spewing unbearable stench, and septic tanks leaking their waste. Aesthetics aside, those are real health hazards. These infrastructures are prerequisites for our good health, yet perversely they are not considered as healthcare expenses. Malaysia spent hundreds of millions on the aborted new bridge to replace the existing causeway in Johor Bahru, yet it does not have a water treatment plant. The returns on investment for a new water treatment facility would be much more in terms of health and thus productivity of citizens.

In between necessary infrastructure spending and providing basic medical care, there is a legitimate need for publicly-funded medical research even, if not especially, for a developing country like Malaysia. I did research in transplant immunology before returning home but felt minimal inclination to continue it in Malaysia even though the country then had an active kidney transplant program under the capable leadership of Drs. Hussein Awang and Bakar Sulaiman. For one, I did not think that we could compete intellectually and resource-wise with programs in the West. For another, I was more attracted to the neglected but more relevant area of immunology of parasitic infections. You can be assured that there is minimal interest in the West to undertake such research, hence the need for countries like Malaysia to undertake them. Besides, they are best done locally as we have the most at stake.

Incidentally, Dr. Hussein's brother Yahya, once my medical officer in Johor Bahru, would later perform the first heart transplant in the region. I am grateful to the wisdom Tan Sri Majid imparted on me. All of us involved in healthcare, from the policymakers to administrators and practitioners to researchers ought to participate in the exercise of acknowledging our limitations and setting our priorities.

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Role of Pioglitazone with Metformin or Glimepiride on Oxidative Stress-induced Nuclear Damage and Reproductive Toxicity in Diabetic Rats

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Abstract

Background: Oxidative stress due to improper control of blood glucose in chronic diabetes plays a major role in the development of secondary complications including cancer and birth defect. The aim of this study is to evaluate the protective effect of combination of pioglitazone with metformin or glimepiride against the experimental type-2 diabetes induced nuclear damage and reproductive toxicity in rats.

Methods: The combinations of Pioglitazone (Pio-1 mg/kg) with metformin (Met-50 mg/kg) or glimepiride (Gmp-0.2 mg/kg) given orally daily for 4 weeks were tested against nicotinamide (NA-230 mg/kg, ip)-streptozotocin (STZ-65 mg/kg, ip)-induced micronuclei (MN) formation and sperm abnormalities in male Wistar rats. The antioxidant status was evaluated by measuring the levels of serum lipid peroxidation (LPO), catalase (CAT) and superoxide dismutase (SOD).

Results: The administration of Pio+Met significantly ($P < 0.01$) reduced the number of micronucleated erythrocytes, increased the polychromatic: normochromatic erythrocytes (P/N ratio), reduced ($P < 0.001$) sperm morphology defects and increased ($P < 0.05$) the caudal sperm count compared to the untreated diabetic condition. Furthermore, the Pio+Met combination enhanced the antioxidant status in diabetic animals. However, Pio+Gmp did not attenuate the nuclear and sperm defects or oxidative stress.

Conclusions: The observations suggest that Pio+Met combination reduced nuclear damage and sperm abnormalities by enhancing the antioxidant status in the diabetic animals.

Keywords: antidiabetics, combination therapy, micronuclei, sperm abnormalities, health sciences

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease characterised by impaired insulin secretion and insulin resistance in the liver, adipose tissue and skeletal muscle. These combined abnormalities contribute to abnormal glucose metabolism. The degree and duration of hyperglycaemia is the main reason for the complications of T2DM (1). Chronic hyperglycaemia is the major cause of the generation of reactive oxygen species (ROS), which damage the components of host cells, including DNA. Mutation in the somatic cells often results in secondary problems such as aging, heart ailments, neurological defects and carcinogenesis (2). Damage to the germinal cells can result in male infertility, pre-term pregnancy loss and a variety of pathologies in the offspring, including childhood cancer (3). Genotoxicity testing

assumes importance since the consequences of DNA damage can cause defects in both the present generation and the offspring. Bone marrow micronucleus (MN) and sperm abnormality assays in rodents are important tools to assess the mutagenic and anti-mutagenic property of test compounds (3,4).

Data from the United Kingdom Prospective Diabetes Study (UKPDS) have established that tight glucose control reduces the risk of oxidative stress-related disorders in patients with T2DM. The UKPDS data also suggested that approximately 10% of patients do not maintain optimum glycaemic levels even when treated intensively with sulphonylureas (SUs), biguanides or insulin as monotherapy (5). Prior studies propose that addition of a second agent from a different class may improve the glycaemic control in patients who do not maintain glycated haemoglobin (HbA_{1c}) concentration of <7% (6).

However, combination of oral-hypoglycaemics may lead to unwanted side effects (7). The combination of SU with biguanide is the most preferred but this combination carries the risk of hypoglycaemia (8).

Thiazolidinediones (TZDs) can be used in combination therapy with SUs or biguanide, and such combinations have been clinically established to be effective in reducing the HbA_{1c} concentration by 0.8% to 1.2% compared to the monotherapy of individual drugs (9). The combination of TZDs with SU/biguanides has been found to benefit diabetic patients in reducing hyperglycaemia and insulin resistance, in addition to improving cardiovascular complications such as dyslipidemia and endothelial dysfunction (10). However, monotherapy with pioglitazone (Pio), a member of the TZD class, has been reported to induce DNA damage in the hepatocytes and lymphocytes in rats. The mechanism suggested includes increased generation of ROS, especially from those cells that contribute to Pio metabolism and detoxification (11). On the other hand, metformin (Met) and glimepiride (Gmp) have been reported to decrease oxidative stress-mediated nuclear damage in diabetic rats (12,13). Considering the complications associated with genotoxic antidiabetic agents and the influence of the addition of an anti-mutagenic in the combination, this study was designed to evaluate the role of Met or Gmp in combination with Pio against nicotinamide (NA)-streptozotocin (STZ)-mediated nuclear defects and sperm abnormalities in male Wistar rats.

Materials and methods

Chemicals

Gift samples of Pio, Met and Gmp were obtained from Biocon Pvt. Ltd, Micro Labs Pvt. Ltd. and Bal Pharma Ltd., Bangalore, respectively. Staining reagents and other chemicals used in this study were of analytical grade and procured from the HiMedia Laboratories Pvt. Ltd., Mumbai.

Animals

Eight-week-old healthy, laboratory bred, male Wistar rats weighing 180 ± 10 g were maintained under standard laboratory conditions at a temperature of 20 ± 20 °C, 12 hour light / dark cycle and provided water and pellet food *ad libitum*. The experiments were conducted in a CPCSEA (Committee for the purpose of control and supervision of experiments on animals, Chennai, India) approved animal house after obtaining the prior approval from the Institutional Animal Ethics Committee (AACP/IAEC/P-31/2005).

Dosage, treatment and sampling

The animals were divided mainly into the following groups:

- Group 1:** Control (0.5 mL/kg saline, by mouth (p.o))
- Group 2:** Untreated diabetic (230 mg/kg NA and 65 mg/kg STZ)
- Group 3:** Diabetic + Combination-1 (1 mg/kg Pio + 50 mg/kg Met, p.o)
- Group 4:** Diabetic + Combination-2 (1 mg/kg Pio + 0.2 mg/kg Gmp, p.o)
- Group 5:** Diabetic + α -tocopherol (20 mg/kg, p.o)
- Group 6:** Diabetic + insulin (1 IU/kg, s.c)

The doses of Pio (15), Met (16) and Gmp (17) were selected as per previous reports and depending on their individual concentrations found in the antidiabetic combination formulation meant for clinical use (18,19). The drugs were administered once daily for 4 weeks after the induction of diabetes. The control and untreated diabetic animals were administered saline (0.5 mL/kg) daily throughout the treatment period. In this study, α -tocopherol (20) and insulin (21) were used as the standard antioxidant agent and hypoglycaemic agent, respectively. Before the administration, Pio, Gmp and α -tocopherol were suspended in 1% w/v carboxy methyl cellulose (CMC), insulin was reconstituted in water for injection and Met was dissolved in distilled water to obtain the required dose. In all of the groups, a 12 h fasting condition was maintained before the experiment, wherein the animals were provided only water *ad libitum*.

Bone marrow micronucleus test

The modified method of Schmid was followed to perform the bone marrow MN test (4). Following the treatment, animals were sacrificed by cervical dislocation under light ether anaesthesia (2 mL/kg, open drop method) (22). Animals were cut open to excise the femur and tibia. Bone marrow MN slides were prepared by using the modified method of Schmid. Marrow suspension from the femur and tibia bones of both sides were prepared in 5% bovine serum albumin (BSA), centrifuged at 1000 rpm for 8 min and then the pellet was resuspended in a required quantity of BSA. A drop of this suspension was placed on a clean glass slide and a smear was prepared and air dried. The slides were fixed in absolute methanol, stained with May-Grunwald-Giemsa and MN were identified as dark bluish coloured, round fragments in two forms of RBCs (polychromatic erythrocytes as PCEs and normochromatic erythrocytes as NCEs) (23) (Figure 1). However,

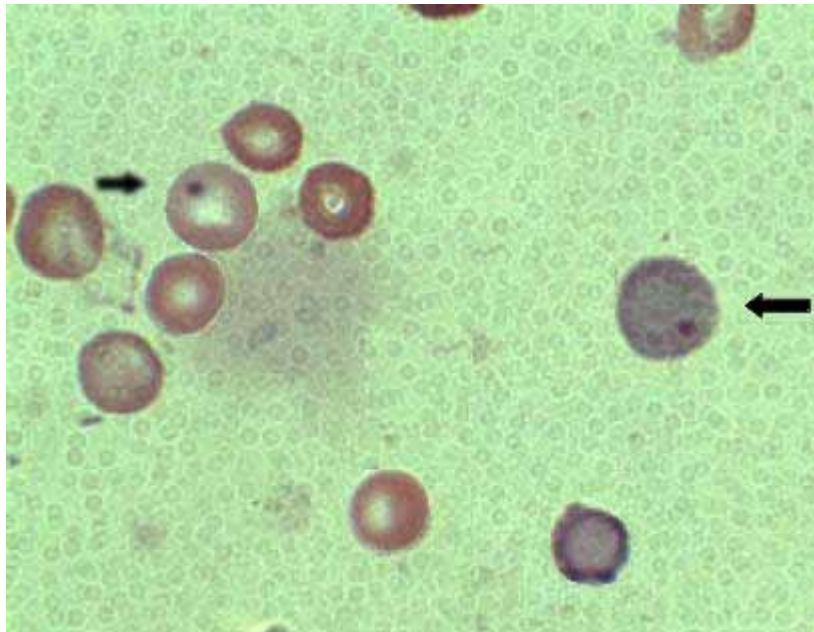


Figure 1: Micronucleated polychromatic erythrocytes [arrow indicates the micronucleus in the polychromatic erythrocytes with normal normochromic erythrocytes, stained with May-Grunwald-Giemsa, 100X magnification]

a few exceptions could be possible, especially with high doses of chromosome breaking agents, in which MN could appear as almond-shaped or half-moon-shaped (23). About 2,000 PCEs and corresponding NCEs were scanned for the presence of MN to calculate P/N (Polychromatic: normochromic erythrocytes) ratio using 100X oil immersion objective.

Sperm morphology and sperm count assay

The procedure described by WYROBEK and BRUCE (1975) (24) was followed to study the sperm shape abnormalities in the cauda epididymis of the rats. One thousand sperm per animal were screened to find the different types of abnormalities in one of the cauda epididymis. Six types of abnormalities including amorphous, hookless, banana shape, coiled, double-headed and double-tailed (Figure 2) were evaluated and the total abnormality was represented as % abnormal sperm (25).

The caudal sperm count test was performed according to the method described by D'SOUZA (26). The spermatozoa count was obtained by counting the number of sperm cells in the four chambers of a Neubauer slide.

In vivo antioxidant activity

Blood samples were collected from the retro-orbital plexus under light ether anaesthesia (22). The serum was separated by centrifugation (1000 rpm) and immediately analysed to determine the antioxidant enzyme activity.

Serum lipid peroxidation (LPO)

The procedure described by YAGI (27) was followed to estimate the lipid peroxidation. The principle depends on the reaction between thiobarbituric acid with malondialdehyde, a secondary product of lipid peroxidation at pH 4. The development of a reddish-pink colour, which indicates the extent of peroxidation, was estimated at 532 nm. The extent of lipid peroxidation was expressed as $\eta\text{mol/mg protein}$ (27).

Catalase (CAT)

The estimation of catalase (EC 1.11.1.6) activity was done by determining the decomposition of H_2O_2 at 610 nm in an assay mixture containing phosphate buffer (0.25 M, pH 7). One international unit of catalase utilised is that amount which catalyses the decomposition of 1 mM H_2O_2 per min at 37°C and is expressed in terms of unit/mg protein (28).

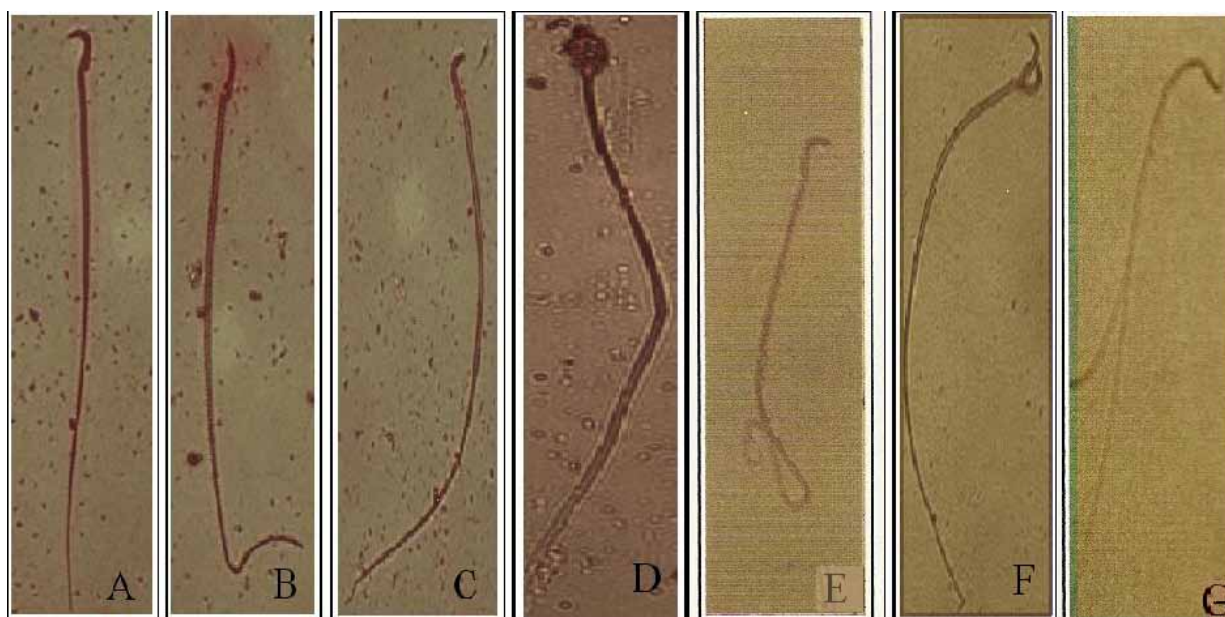


Figure 2: Different types of sperm shape abnormalities [(A: normal; B: hookless; C: banana; D: amorphous; E: curved, F: double head and G: double tail) stained with 1% aqueous eosin yellow, 40X magnification].

Superoxide dismutase (SOD)

The principle for measuring the SOD (EC 1.11.1.1) depends on the detection of superoxide ions generated during auto-oxidation of hydroxylamine. During the oxidation, nitro blue tetrazolium (NBT) is reduced and nitrite is produced in the presence of EDTA, which can be detected colourimetrically at 560 nm. The concentration of SOD is expressed as units/mg protein (29).

Blood glucose estimation

Fasting blood glucose estimation was done using the glucometer (Ascensia ENTRUST, Bayer Healthcare Ltd, Mumbai). A drop of blood collected from the tail vein was gently applied over the test zone of the glucometer and the blood glucose level was recorded immediately as mg/dL.

Statistics

The statistical analyses were done by One-way ANOVA followed by a multiple comparisons test with Bonferroni test for the bone marrow MN test and Newman-Keuls for the antioxidant study. However, data on epididymal sperm shape abnormalities and sperm count were analysed employing a non-parametric test, the Mann-Whitney U test. $P < 0.05$ was considered to indicate a significant difference.

Results

Effect of the combination of Pioglitazone with Metformin or Glimepiride on the frequency of bone marrow micronuclei in NA-STZ-induced diabetic rats

The NA-STZ induced T2DM significantly ($P < 0.001$), increased the frequency of MN in PCEs and NCEs and reduced the P/N ratio compared to the control animals. Combination of Pio+Met inhibited the percentage of MN in PCEs ($P < 0.001$) and NCEs ($P < 0.01$), in addition to enhancing the P/N ratio ($P < 0.05$) compared to the untreated diabetic rats. The percent inhibition was 14.9% for MN PCEs, 21.8% for MN NCEs and 11.4% for P/N ratio compared to the untreated diabetic group. Administration of α -tocopherol reduced ($P < 0.001$) the number of MN in PCEs (17.2%) and NCEs (22.6%), along with an increase ($P < 0.001$) in the P/N ratio (11.4%) compared to the untreated diabetic group. However, Pio+Gmp and insulin treatments did not alter the incidence of micronucleated erythrocytes and P/N ratio in NA-STZ diabetic rats (Table 1).

Effect of the combination of Pioglitazone with Metformin or Glimpiride on the sperm morphology and sperm count in NA-STZ-induced diabetic rats

Administration of NA-STZ significantly increased the occurrence of sperm shape abnormalities ($P<0.001$) and reduced the sperm count ($P<0.001$) compared to the control animals. Administration of combination of Pio+Met significantly reduced ($P<0.001$) sperm shape abnormalities and increased ($P<0.05$) the sperm count compared to the untreated diabetic group. The percent inhibition was 19.5% for sperm abnormalities and 6.7% for sperm count compared to the untreated diabetics. Similarly, α -tocopherol diminished ($P<0.001$) the sperm abnormalities (26.6%) and sperm count (14.8%) compared to the untreated diabetics. However, Pio+Gmp and insulin treatments did not alter the reproductive damage induced by the diabetic state (Table 2).

Effect of the combination of Pioglitazone with Metformin or Glimpiride on the serum antioxidant status and glucose level in NA-STZ-induced diabetic rats

The experimental T2DM significantly ($P<0.001$) increased the oxidative stress and blood glucose level compared to the control animals. Diabetic animals treated with Pio+Met combination showed a decreased level of LPO ($P<0.05$) and enhanced concentrations of CAT ($P<0.001$) and SOD ($P<0.01$) compared with the untreated diabetic condition. The percent change was 14.3% for LPO, 68.9% for CAT and 72.7%

for SOD compared to untreated hyperglycaemic group. Administration of α -tocopherol elevated the antioxidant status by decreasing LPO level ($P<0.001$, 28.3%) and improving CAT ($P<0.001$, 68.9%) and SOD ($P<0.001$, 95.5%) concentrations compared to untreated experimental T2DM. However, Pio+Gmp and insulin did not produce significant changes in the oxidative stress. In addition, all of the treatments significantly ($P<0.001$) reduced the hyperglycaemia, α -tocopherol being the least potent ($P<0.05$) among them (Table 3).

Discussion

The present study indicated that administration of NA-STZ increased the micronuclei frequency, sperm abnormalities, oxidative stress and glycaemia and reduced P/N ratio. The normal P/N ratio is reported to be 1:1 in bone marrow. A n increase in NCEs signals a cytotoxic effect whereas an increase in PCEs reflects a stimulation of erythrocyte proliferative activity (30).

The elevated blood sugar level was observed to be moderate (180 ± 8 mg/dL) and this can be attributed to the role of NA during the development of T2DM. NA functioning as an antioxidant is reported to partially protect β -cells against the cytotoxic damages of STZ (14). The oxidative stress generated during hyperglycaemia is reported to involve several pathways such as accelerated formation of advanced glycation end products (AGEs), polyol pathway, hexosamine and protein kinase-C (PKC) (31,32).

Table 1: Effect of the combination of Pioglitazone with Metformin or Glimpiride on the frequency of bone marrow micronuclei in NA-STZ-induced diabetic rats

Bone marrow micronucleus test	Treatment and Dose (mg/kg)					
	Control (Saline-0.5 ml/kg)	NA (230 mg) + STZ (65 mg)	NA-STZ + Pio (1 mg) + Met (50 mg)	NA-STZ + Pio (1 mg) + Gmp (0.2 mg)	NA-STZ + α -Tocopherol (20 mg/kg)	NA-STZ + Insulin (1 IU/kg)
% MN in PCEs	0.39 \pm 0.01	1.41 \pm 0.08 ^a	1.20 \pm 0.06 ^a *	1.42 \pm 0.08 ^a	1.17 \pm 0.14 ^b *	1.47 \pm 0.02 ^b
% MN in NCEs	0.41 \pm 0.02	1.24 \pm 0.12 ^a	0.97 \pm 0.09 ^c **	1.02 \pm 0.26 ^a	0.96 \pm 0.15 ^b **	1.27 \pm 0.10 ^b
P/N ratio	1.08 \pm 0.03	0.79 \pm 0.02 ^a	0.88 \pm 0.07 ^b ***	0.80 \pm 0.02 ^a	0.88 \pm 0.07 ^b *	0.76 \pm 0.04 ^b

Values are expressed as Mean \pm SD, MN – micronucleus, PCE – polychromatic erythrocytes, NCE – normochromatic erythrocytes, NA – Nicotinamide, STZ – Streptozotocin, Pio – Pioglitazone, Met – Metformin, Gmp – Glimpiride, N=8
Statistics: One-way Anova followed by Bonferroni test.

^a $P<0.001$, ^b $P<0.05$ compared with the Control

^{*} $P<0.001$, ^{**} $P<0.01$, ^{***} $P<0.05$ compared with the untreated Diabetic group

Table 2: Effect of the combination of Pioglitazone with Metformin or Glimepiride on sperm morphology and sperm count in NA-STZ-induced diabetic rats

Sperm abnormality test	Treatment and Dose (mg/kg)					
	Control (Saline-0.5 ml/kg)	NA (230 mg) + STZ (65 mg)	NA-STZ + Pio (1 mg) + Met (50 mg)	NA-STZ + Pio (1 mg) + Gmp (0.2 mg)	NA-STZ + α-Tocopherol (20 mg/kg)	NA-STZ + Insulin (1 IU/kg)
Total % Abnormality	1.04 ± 0.02	1.64 ± 0.02 _a	1.32 ± 0.05 _b *	1.54 ± 0.04 _c	1.21 ± 0.12 _c *	1.59 ± 0.03 _c
Sperm count (10 ⁶)	33.18 ± 0.49	27.77 ± 0.46 _c	29.64 ± 0.45 _b **	28.31 ± 0.41 _c	31.87 ± 0.98 _*	27.69 ± 0.79 _c

Values are expressed as Mean ± SE, NA – Nicotinamide, STZ – Streptozotocin, Pio – Pioglitazone, Met – Metformin, Gmp – Glimepiride, N=8

Statistics: Mann-Whitney U test,

*P<0.05, ^bP<0.01, ^cP<0.001 compared with the Control

[†]P<0.001, ^{††}P<0.05, compared with the untreated Diabetic group

Table 3: Effect of the combination of Pioglitazone with Metformin or Glimepiride on serum antioxidant status and glucose level in NA-STZ-induced diabetic rats

Serum antioxidant status and glucose level	Treatment and Dose (mg/kg)					
	Control (Saline-0.5 ml/kg)	NA (230 mg) + STZ (65 mg)	NA-STZ + Pio (1 mg) + Met (50 mg)	NA-STZ + Pio (1 mg) + Gmp (0.2 mg)	NA-STZ + α-Tocopherol (20 mg/kg)	NA-STZ + Insulin (1 IU/kg)
Lipid peroxidation (nmol/mg protein)	2.39 ± 0.20	3.35 ± 0.22 _a	2.87 ± 0.34 _b *	3.09 ± 0.28 _a	2.40 ± 0.37 _{**}	3.36 ± 0.11 _a
Catalase (units/mg protein)	6.39 ± 0.34	3.12 ± 0.38 _c	4.49 ± 0.29 _c **	3.11 ± 0.40 _c	5.27 ± 0.66 _b **	3.11 ± 0.05 _a
SOD (units/mg protein)	0.46 ± 0.05	0.22 ± 0.06 _a	0.38 ± 0.06 _b ***	0.22 ± 0.07 _a	0.43 ± 0.05 _{**}	0.23 ± 0.09 _a
Blood glucose (mg/dl)	92.3 ± 3.44	174.3 ± 6.32 _a	121.65 ± 8.62 _a **	148.22 ± 5.97 _a **	157.4 ± 6.47 _a *	143.8 ± 5.93 _a **

Values are expressed as Mean ± SD, NA– Nicotinamide, STZ – Streptozotocin, Pio – Pioglitazone, Met – Metformin, Gmp – Glimepiride, N=8

Statistics: One-way Anova followed by Newman-Keuls

*P<0.001, ^bP<0.05, ^cP<0.01, compared with the Control

[†]P<0.05, ^{††}P<0.001, ^{†††}P<0.01, compared with the untreated Diabetic group

Administration of Pio+Met reduced the incidence of MN formation in PCEs, NCEs and enhanced the P/N ratio in the diabetic animals (Table 1). The combination also reduced the incidence of sperm shape abnormalities and increased the sperm count in the hyperglycaemic rats (Table 2). The antioxidant profile indicated that the combination of Pio+Met elevated the serum levels of CAT and SOD and reduced the LPO, along with a significant anti-hyperglycaemic action (Table 3). As reported, SOD is an enzyme that catalyses the dismutation of superoxide ion to oxygen and hydrogen peroxide, thus protecting the cell from the superoxide toxicity (29,32). CAT

efficiently promotes the conversion of hydrogen peroxide to water and molecular oxygen (28,33). LPO occurs when ROS attack the polyunsaturated fatty acid residues of phospholipids of the cell membrane, which is extremely sensitive to oxidation. Spermatozoa are highly susceptible to damage by excess concentrations of ROS due to a high content of polyunsaturated fatty acid within their plasma membrane (27,33).

Additionally, α-tocopherol treatment reduced the nuclear breaks in erythrocytes and minimised spermatozoa abnormalities in addition to reducing the oxidative stress and hyperglycaemia. As a potent antioxidant, α-tocopherol has been

reported to reduce ROS-mediated MN formation, sperm abnormalities and hyperglycaemia (34–36). Considering these observations, it can be suggested that the antioxidant property of a compound could play a significant role in averting the nuclear injury and sperm aberrations caused by diabetes (2,33).

Previous research has indicated that Pio and Met possess antioxidant potential (37,38). TZDs were found to suppress the generation of ROS by affecting the activation of NF- κ B and interfering with the MAPK signalling cascade (37). Met is reported to modulate the activity of PKC and NADPH oxidase, which in turn counteract ROS by elevating antioxidant enzymes like catalase, SOD and glutathione peroxidase (GPx) (38). As reported earlier, Pio monotherapy has been shown to increase the nuclear damage in hepatocytes and to a small extent, in lymphocytes. This action can be related to the hepatotoxic property of TZDs, including troglitazone and Pio (11), although the mechanism for lymphocyte damage caused by Pio remains to be elucidated. Our data indicate that inclusion of Met with Pio reduced the nuclear damage, suggesting that this combination is effective in combating the ROS-induced nuclear imperfections in the diabetic state.

On the other hand, Pio+Gmp did not protect from nuclear damage and sperm abnormalities in NA-STZ diabetes and the lack of free radical scavenging action can be considered as the possible rationale. The non-significant reduction in the micronuclei and sperm abnormality frequency after the administration of Pio+Gmp and insulin indicated the importance of antioxidant potential in addition to the antidiabetic effect in minimising the hyperglycaemia-mediated oxidative stress and cellular damages. Gmp is reported to possess antioxidant properties (39), but the present study suggests that the dosage and duration of co-exposure with Pio may not be sufficient to exploit the free radical scavenging potential of this drug.

Conclusion

The combination of Pio with Met prevented NA-STZ-mediated oxidative stress and erythrocyte and sperm abnormalities. With optimal control of hyperglycaemia, the combination could play an important role, especially in young diabetic patients, in avoiding the nuclear complications related to hyperglycaemia and oxidative stress.

Author s contributions

Data collection and assembly: SIR, KD.

All authors contributed have contributed equally to the conception and design of the study, data analysis and interpretation, as well as drafting and critical revision of the article.

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Abstract

Background: Although around 70% of HIV+ cases used to have ocular manifestations, the late reporting of cases often results in severe forms of ocular morbidity that would otherwise have been prevented. The objective of this study was to describe the ocular manifestations of HIV and AIDS-related patients who had been admitted to TM Jafferji Hospital, Dar-es-Salaam, Tanzania.

Methods: Proven cases of HIV were recruited in this study. Detailed slit lamp examination and fundoscopy using a +90D lens were carried out in all cases after thoroughly dilating the pupil with 1% Tropicamide eye drops.

Results: Around 90% of the recruited cases were in clinical stage III and IV HIV. The notable ocular manifestations included micro-vasculopathy of the retina in 25%, uveitis in 8%, CMV retinitis in 7%, neuro-ophthalmic manifestation in 6%, Herpes zoster ophthalmicus in 5%, Kaposi's sarcoma in 3% and conjunctival carcinoma in 2% of cases. Fifty-three percent of the cases had other anterior segment disorders like conjunctivitis, blepharitis and corneal ulcers.

Conclusion: Most of the cases recruited in our study were in the late stages of HIV. A significantly high number of cases (70%) had ocular manifestations. Around 53% had additional anterior segment disorders like conjunctivitis, blepharitis and corneal ulcers.

Keywords: AIDS, CMV retinitis, HIV, micro-vasculopathy, medical sciences

Introduction

A World Health Organisation (WHO) report estimated that currently around 32 million people including around 2 million children have been infected with human immunodeficiency virus (HIV) worldwide (1,2). Of the total cases of HIV, 58% are thought to be sub-manifestations of HIV infection involving the anterior or posterior segment of the eye. Anterior segment findings include tumours of the peri-ocular tissues and a variety of external infections. Posterior segment changes include an HIV-associated retinopathy and a number of opportunistic infections of the retina and choroid. The increasing longevity of individuals with HIV disease may result in greater numbers of patients with opportunistic infections of the retina.

HIV and AIDS-related ocular manifestations may affect 45–75% of HIV+ individuals, although the types of manifestations seen in developing nations varies in comparison to those reported in developed countries (3,4,5,6). A study on HIV+ individuals in India reported around 45% having ocular manifestations (7,8). Most notably, while antibodies against cytomegalovirus (CMV) are detectable in 90% of people living with HIV and

AIDS (PLWHA), CMV retinitis is rare (less than 5%) in AIDS patients in developing countries (6,9). However, ocular manifestations affecting only one eye, like Herpes zoster ophthalmicus (HZO) and conjunctival squamous cell carcinoma, are relatively common in developing countries (10). Such variations in distribution are most likely because of the early and high mortality rate in PLWHA in developing countries and possibly differences in HIV subtype, race, and the influence of co-morbidity diseases. The earlier WHO clinical staging of HIV recommended in 1990 was modified in 2005. Clinical stage I represents mostly asymptomatic cases in which the CD4 T-cell count remains around 1000, and the common ocular manifestations noted in this stage are dry eyes and an inflamed conjunctiva. Clinical stage II constitutes early HIV manifestations in which the CD4 T-cell count is usually between 500 and 1000, and the common ocular features are allergic conjunctivitis, intermediate uveitis, retinal vasculitis, HIV retinopathy and optic neuropathy. Clinical stage III is known as the intermediate stage in which the CD4 T-cell count is usually between 200–500, and the common ocular manifestations noted are dry eyes, blepharitis, bacterial and follicular conjunctivitis, Kaposi's

sarcoma, molluscum contagiosum, HZO, herpes simplex, HIV retinopathy and Aspergillosis. Clinical stage IV represents the stage of AIDS in which the CD4 T-cell count stays below 200 and the ocular manifestations are due to on various opportunistic infections (11,12,13). The goal of the present study was to discover the types of ocular manifestations and their severity in HIV cases referred for ophthalmological examination.

The objective of this study is to describe the ocular manifestations of HIV and AIDS-related patients who had been admitted to TMJ Hospital, Dar-es-Salaam, Tanzania.

Materials and Methods

This cross sectional study was performed in a specialty hospital of Tanzania called TMJ Hospital. TMJ Hospital in Dar-es-Salaam, Tanzania is a tertiary care hospital as well as a teaching hospital. It has an outpatient department that provides services in various disciplines. The hospital has a bed capacity of 100 and a Voluntary Counseling and Testing Clinic where both self-referred individuals and physician-referred patients are tested for HIV. Hospital policy requires all admitted cases of diagnosed HIV / AIDS to undergo ocular examination.

A total of 150 diagnosed cases of HIV that were referred to the Department of Ophthalmology from March 2005 to August 2005 were recruited for this study. For the laboratory diagnosis of HIV, serum samples were considered positive only if they were found to be repeatedly reactive by the rapid enzyme immunoassays (Serocard and Tridot screening tests). Diagnosis was then confirmed by the Enzyme-linked immunosorbent assay (ELISA). In a few equivocal cases, the western Blot test was carried out for further confirmation. A CD4 T-cell count was performed in all cases. The cases were staged as per WHO staging criteria.

All cases underwent a detailed anterior segment and posterior segment slit lamp and +90D lens examination. Fundoscopy was performed after thoroughly dilating the pupil with Tropicamide eye drop. Fundus photographs were taken for cases showing posterior segment changes. When indicated, conjunctival and lid masses were subjected to histo-pathological examination. Blindness was defined as a visual acuity (VA) less than counting fingers (CF) at three meters with the better eye. Data collection and analysis was performed using a standard format.

Results

One hundred and fifty adult serology proven HIV/AIDS patients were enrolled in the study. The mean age was 34±13 years old, ranging from 18–82 years, and 69 of the patients were male. About 90% of the patients were in WHO stages III and IV, indicating that a very high proportion of the patients visiting the hospital were seriously sick and had marked immune suppression.

No patients in stage I were observed (Table 1). Enrolled patients (n=150) had a median CD4 cell count of 190 cells/μL. The majority of cases in the present study had a CD4 cell count between 200–500 cells per microlitre of blood. Two cases (1.3%) had CD4 T-cell counts below 200 cells per microlitre of blood.

Ocular involvements were documented in 105 (70%) individuals. The ocular manifestations observed included retinal micro-vasculopathy in 26 (25%), neuro-ophthalmic disorders in 7 (6%), uveitis in 9 (8%), herpes zoster (HZO) in 6 (5%), CMV retinitis in 8 (7%) and conjunctival carcinoma in 3 (2%) cases. Kaposi's sarcoma in the eyelid was found in 4 (3%) of the cases. Around 56 (53%) of the cases presented other anterior segment manifestations like conjunctivitis, blepharitis and corneal ulcers (Table 2). Two patients had bilateral blindness due to CMV. Six patients had unilateral blindness. The most common cause of unilateral blindness was HZO in three patients, followed by toxoplasma-induced retinochoroiditis in two patients and anterior uveitis of unknown aetiology in one individual. Cotton wool spots were observed in 80% of the patients with micro-vasculopathy, and retinal haemorrhage and perivascular sheathing were also found in a few patients. The most common presentations of neuro-ophthalmic disorders were papilloedema, followed by optic atrophy and cranial nerve palsy (III & VII). Two of the patients with papilloedema had cryptococcal meningitis. Two patients had sub-conjunctival haemorrhage. The haemorrhage in one patient subsided spontaneously. The most common opportunistic disease was tuberculosis (40%).

Table 1: Percentage of cases in various stages of HIV infection.

WHO stage	No of patients (%)
I	0 (0%)
II	15 (10%)
III	90 (60%)
IV	45 (30%)

Table 2: Various ocular manifestations and the percentages of involvement.

Ocular findings	No of cases (%)
Micro-vasculopathy	26 (25%)
Uveitis	9 (8%)
Cytomegalovirus retinitis	8 (7%)
Neuro-ophthalmic manifestations	7 (6%)
Herpes zoster ophthalmicus	6 (5%)
Kaposi sarcoma lid	4 (3%)
Conjunctival carcinoma	3 (2%)
Sub-conjunctival haemorrhage	2 (1%)
Others (conjunctivitis, blepharitis, corneal ulcer)	56 (53%)

Discussion

The present study indicates that most of the HIV/AIDS patients (90%) referred to the eye department were in late stages of the disease. About two thirds of the patients had ocular complications of HIV. Most of the cases with ocular manifestations had a CD4 T-cell count in the range of 200–500. These findings are similar to the frequency of ocular complications reported in a study carried out in Senegal, (14) but are higher than previous reports from Burundi and Malawi (Table 3). A recent report from one of the studies conducted in western India reported that around 45% of patients had ophthalmic manifestations (7). The fact that more than 90% of the patients were in the later stages of the disease might partially explain the higher occurrence of eye manifestations in this study.

In this study, the most common ocular manifestation observed was retinal micro-vasculopathy (25%). Previous cross-sectional studies from other African countries found micro-vasculopathy to be the most common manifestation, ranging between 10% and 42% (15). A report from India found micro-vasculopathy in 50% of the study subjects (16). On the other hand, prospective cohort studies from developed countries showed a high prevalence of micro-vasculopathy (70%–80%) (17). The most common types of retinal micro-vasculopathy were cotton wool spots, but their magnitude may be underestimated because they are typically transient and asymptomatic. Common presentations in neuro-ophthalmic parts were papilloedema followed by optic atrophy & cranial nerve (CN III & VI) palsy. This is in agreement with the rates reported elsewhere (3). Three of the

patients had uveitis due to toxoplasmosis, while the cause of the uveitis was not established in the remaining six patients. Kaposi's sarcoma of the eyelid was found in 3% of the patients, which may be slightly lower than the results of other studies. Sub-conjunctival haemorrhage was observed in two patients. In one of the patients, the haemorrhage was drug-induced (Fansidar) pancytopenia, and the problem gradually disappeared when the patient stopped taking the drug. The haemorrhage in the second patient might represent an early sign of conjunctival Kaposi's sarcoma. Blindness due to CMV retinitis was present in only 2% of patients, comparable to reports from other African countries (Table 3).

Other important observations in the present study were the other anterior segment ocular manifestations, including conjunctivitis, blepharitis and corneal ulcer. These observations were probably due to most of our recruited cases having opportunistic infections. A recent report from a study in India described only a few cases with problems involving the conjunctiva and eyelid (7,8). All of the recruited cases in this study were admitted cases in various inpatient departments of the hospital that had been referred for ophthalmological examination which explains the higher percentage of cases having eye manifestations as well as the severity of HIV infection in this study. Although the ocular manifestations found in this study are consistent with most of the documented eye manifestations found in the literature (11,12,13), a bigger sample size especially from a community-based study would have revealed a more accurate picture.

Table 3: Comparative analysis of ocular manifestations in the present study and two other studies conducted in other parts of Africa.

Eye Lesions	Present study	Burundi study by Cochereau et al. (5)	Malawi study by Gharai et al. (8).
Percentage of eye involvement	70%	19%	20%
Retinal micro-vasculopathy	25%	16%	17%
HZO	5%	1%	Not available
Anterior uveitis	8%	4%	2%
CMV Retinitis	7%	1%	1%
Neuro-ophthalmic manifestations	6%	Not available	Not available
Others (conjunctivitis, blepharitis, corneal ulcer)	53%	Not available	Not available

Conclusion

Most of the cases recruited in our study were in the late stages of HIV, as defined by WHO clinical staging of HIV. A significantly higher number (70%) of cases had ocular manifestations. Our study reported a higher number of retinal manifestations in comparison to two studies performed in other African nations. Around 53% of the cases had non-specific manifestations like dry eyes, conjunctivitis, and blepharitis, compared to studies reported from India. Increased numbers of people living with HIV and AIDS have been a general threat to society. Furthermore, the visual disabilities add to the woes of the patients and the society as a whole. Therefore, routine eye examinations need to be done in all diagnosed cases of HIV to avoid visual morbidity; similarly, any suspicious ocular lesions need to be screened for HIV.

Author s contributions

Conception and design, collection and assembly of data, data analysis and interpretation, drafting of the article, critical revision of the article: SS

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Assessing Patient Pain Scores in the Emergency Department

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Abstract

Background: Pain management in the Emergency Department is challenging. Do we need to ask patients specifically about their pain scores, or does our observational scoring suffice? The objective of this study was to determine the inter-rater differences in pain scores between patients and emergency healthcare (EHC) providers. Pain scores upon discharge or prior to ward admission were also determined.

Methods: A prospective study was conducted in which patients independently rated their pain scores at primary triage; EHC providers (triagers and doctors) separately rated the patients' pain scores, based on their observations.

Results: The mean patient pain score on arrival was 6.8 ± 1.6 , whereas those estimated by doctors and triagers were 5.6 ± 1.8 and 4.3 ± 1.9 , respectively. There were significant differences among patients, triagers and doctors ($P < 0.001$). There were five conditions (soft tissue injury, headache, abdominal pain, fracture and abscess/cellulites) that were significantly different in pain scores between patients and EHC providers ($P < 0.005$). The mean pain score of patients upon discharge or admission to the ward was 3.3 ± 1.9 .

Conclusions: There were significant differences in mean patient pain scores on arrival, compared to those of doctors and triagers. Thus, asking for pain scores is a very important step towards comprehensive pain management in emergency medicine.

Keywords: emergency medicine, pain assessment, pain management, pain score, neurosciences

Introduction

Pain is a complex phenomenon in which an individual's response is determined by the interactions of physical, psychological, cultural and sociodemographic factors (1). Pain itself is one of the most common presenting complaints in the Emergency Department (ED) (2). Pain assessment is of prime importance because it helps to determine the appropriate type of analgesia to administer and the urgency of the pain relief needed (3). Its contribution to improvements in patient satisfaction is also well-established (4).

Many studies have shown that assumptions about patient pain intensity are inaccurate in many settings, and documentation of pain assessment has improved pain management (5,6). Encouraging patients to communicate about their pain is also part of pain management (7). However, the assessment and management of pain in the ED is difficult and is a constant

challenge to emergency healthcare providers, including emergency physicians (8).

There are currently several reliable, valid pain assessment tools or pain scores available for use with adult patients in the acute pain setting. Although multidimensional pain scales are excellent, it can take up to 45 minutes to fully complete the questionnaires, rendering them impractical and cumbersome in the emergency setting (9). Therefore, a numeric rating scale (NRS) was used in this study, as the advantages include ease of administration and scoring, multiple response options and no age-related difficulties (Figure 1) (10). The words 'no pain' and 'worst possible pain' comprised the 0 and 10 ends of the scale, respectively.

In Malaysia, the development of comprehensive emergency medical and trauma services is still in process. Most government hospital EDs are staffed by junior doctors with no postgraduate training or qualifications. Therefore, pain assessment and management are largely

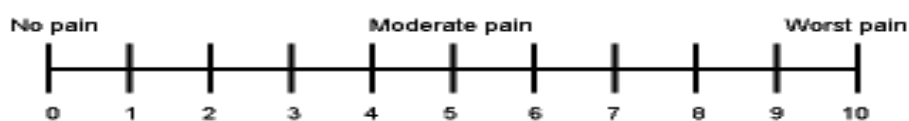


Figure 1: Numeric Rating Scale (NRS)

based on limited personal experience, as well as on the experiences of senior physicians.

The first step for pain management is to identify the patient who is in pain, so that the appropriate management can be delivered quickly. Do we need to ask patients specifically about their pain scores or do our observational scores suffice? The objective of this study was to determine the difference in pain scores between patients and emergency healthcare (EHC) providers. Pain scores upon discharge or prior to ward admission were also to be measured.

Materials and methods

A cross-sectional study was conducted from September, 2004 to October, 2004 on varied shifts and days, based on convenience sampling in the ED of the Hospital Kuala Lumpur (HKL). ED HKL was a busy government hospital that receives an average of 650 to 700 patients per day and is managed by five to six medical officers per eight-hour shift. Ethical approval was obtained from the Universiti Sains Malaysia (USM), Human Ethics Committee, as the researchers were from USM. Adult patients (age 18 years or older) with acute pain who presented to the ED HKL were included. Head injury cases with Glasgow Coma Scale ratings less than 15/15, intoxicated patients, haemodynamically unstable, significant language barrier, in a pain state of more than 72 hours, or were on any type of analgesia within the preceding four hours were excluded.

All patients provided informed consent prior to their participation in this study. Patients were given a formatted form and were asking to rate their pain scores after primary triage. Upon discharged to home or admission to the ward, the patient pain scores were assessed by the managing physicians. A horizontal 0 to 10 NRS was used to measure the pain score. Pain severity was defined in the following manner: mild, 1–4; moderate, 5–7; and severe, 8–10.

The EHC providers would rate the patients' pain scores at the same time at the primary triage. The EHC providers were doctors and triagers. In our hospital, triagers were nurses or medical assistances with more than five years

of experience working in the ED. Pain scores of the patients, doctors and triagers were obtained independently and blindly. At no time were the research personnel allowed to intervene in the patients' management. As there were no proper guidelines for acute pain management in the ED, pain management depended on doctors' professional experiences.

Based on the data collected, the chief complaint or diagnosis of the patients was divided into eight categories. It consists of soft tissue injury (STI), musculoskeletal pain (such as back pain), headaches, abdominal pains, abscesses or cellulitis, ischaemic heart disease (IHD), fractures and foreign bodies. The data were collected and analysed using SPSS (Version 12). T-tests were used to analyse the differences in pain score severity between patients and EHC providers. The non-parametric Wilcoxon Signed-Rank Test was used to compare the difference between patient and EHC provider pain scores based on the chief complaint/diagnosis. The patients' pain scores were considered as a reference.

Results

A total of 107 patients were enrolled in this study. However, 20 patients had to withdraw from the study due to inadequate pain score data upon discharged or ward admission. Thus, there were 87 patients, of whom 56 (64.4%) were male and 31 (35.6%) were female. Among the male patients, 2 (3.6%), 39 (70%) and 15 (26.4%) were having mild, moderate and severe pain, respectively. Among the female patients, 21 (67.7%) and 10 (32.3%) of them were having moderate and severe pain. None of the female patients reported having mild pain. There was no statistical significant difference in pain severity scores between genders.

The mean age was 38.4 ± 11.3 years old; the range was from 19 to 65 years old. Patients of Malay ethnicity (46.0%) formed the majority of the study population, followed by Indian (39.1%) and Chinese (14.9%) patients. Most of patients presented with moderate pain (69%), followed by severe pain (28.7%). Upon discharge to the home or admission to the ward, the majority of patients were experiencing mild pain (51.7%), and almost

half of them were having moderate pain (44.8%) (Table 1). The mean pain score of patients on arrival was 6.8 ± 1.6 , whereas the mean pain scores of doctors and triagers were 5.6 ± 1.8 and 4.3 ± 1.9 , respectively. The mean differences between patients and doctors were 1.2 ± 1.6 and 2.5 ± 1.7 (Table 2). Paired t-tests showed significant differences between patients, triagers and doctors. The mean pain score of patients upon discharge or admission to the ward was 3.3 ± 1.9 .

There were significant differences between patients' pain scores and EHC providers' pain scores in relation to the chief complaint or diagnosis (Table 3 and 4). There were five conditions—STI, headache, abdominal pain, fracture and abscess/cellulites—that were related to significant differences in pain scores. Both doctors and triagers were underscoring these diagnoses.

Discussion

Patients with pain comprise 60–70% of ED visits (11). It is a well-accepted fact that pain is an individual experience and should be established by the individual's self-report of pain (7). The Joint Commission on Accreditation of Healthcare Organisation (JCAHO) guidelines recommend the use of a pain score appropriate to the patient population to measure the intensity of a patient's pain and to practice proper documentation. For

adult populations, the JCAHO recommended the use of the ten-point NRS (12).

Good assessment and documentation lead to good pain management (12, 13). Good documentation should cover the initial and subsequent assessment (14). In our study, there were 20 patients who were withdrawn from the study due to no documentation of the pain score upon discharge or at ward admission. Poor documentation of subsequent pain assessments also occurs in developed countries (14).

The majority of the patients were male. Although there was no statistical significant difference in pain severity scores by gender, a higher percentage of female patients experienced severe pain, and none were experiencing mild pain. These data are consistent with current human findings regarding sex differences in the perception of experimental pain that indicate greater pain sensitivity among females compared to males (15). However, other research examining subjects in Singapore showed that the median pain score was not affected by gender (16).

People of the Malay ethnicity comprised the majority of the study population followed by the Indian and Chinese ethnicities. This ethnic distribution was not representative of the general Malaysian population (17), suggesting that financial constraint might have been a factor. HKL is a busy government hospital with minimum charges. With a charge of RM 1, all the hospital costs were covered, including consultations,

Table 1: Frequency and percentage of patients' pain scores by severity on arrival and upon discharge/ward admission

Pain Severity (NRS)	On arrival	Upon discharge/ward admission
	n (%)	n (%)
None	0 (0)	3 (3.4)
Mild (1–4)	2 (2.3)	45 (51.7)
Moderate (5–7)	60 (69.0)	39 (44.8)
Severe (8–10)	25 (28.7)	0 (0)

Table 2: Result of paired t-tests between patients' vs. doctors' pain scores and patients' vs. triagers' pain scores on arrival

	Paired Differences					t	Df	Sig. 2-Tailed
	Mean	SD	SEM	95% CI				
				Lower	Upper			
Patients' vs. Doctors' pain scores	1.2	1.6	0.17	0.86	1.53	7.10	86	<0.001
Patients' vs. Triagers' pain scores	2.5	1.7	0.18	2.08	2.79	13.6	86	<0.001

Table 3: Result of Wilcoxon Signed-Ranks Test comparing the differences between patients' and doctors' pain scores based on chief complaint/diagnosis

Chief complaint/ Diagnosis	n (%)	z	P-value
Soft tissue injury	30 (34.5)	-3.87	<0.001
Headache	4 (4.6)	-2.00	0.046
Musculoskeletal	4 (4.6)	-1.89	0.059
Abdominal pain	23 (26.4)	-2.20	0.028
Ischaemic Heart Disease	5 (5.7)	-1.41	0.157
Fracture	13 (15.0)	-3.11	0.002
Abscess/cellulitis	6 (6.9)	-2.23	0.026
Foreign body	2 (2.3)	1.41	0.157

Table 4: Result of Wilcoxon Signed-Ranks Test comparing differences between patients' and triagers' pain scores based on chief complaint/diagnosis

Chief complaint/ Diagnosis	n (%)	z	P-value
Soft tissue injury	30 (34.5)	-4.15	<0.001
Headache	4 (4.6)	-2.00	0.046
Musculoskeletal	4 (4.6)	-1.89	0.063
Abdominal pain	23 (26.4)	-4.05	<0.001
Ischaemic Heart Disease	5 (5.7)	-1.41	0.157
Fracture	13 (15.0)	-3.20	0.001
Abscess/cellulitis	6 (6.9)	-2.00	0.046
Foreign body	2 (2.3)	-1.41	0.157

medications and even CT scans.

Most of the patients presented with moderate pain, followed by severe and mild pain. Upon discharge to home or ward admission, only 3.4% of the patients were experiencing no pain. Yet, 44.8% of them were experiencing moderate pain, and none were experiencing severe pain. This is comparable with another local study that reported 14.3% and 33.3% of patients having severe and moderate pain upon discharge, respectively (18). This figure is suggestive of the clinical significance of pain undertreatment among our patients.

There is cause for concern in this scenario. The doctors anecdotally revealed that their major concern was in treating acute life-threatening conditions. Pain was considered as a minor condition and therefore less attention was thought to be needed. Another reason for this under-treatment of pain was ED overcrowding. ED overcrowding was a known independent factor for the undertreatment of pain (19). When the ED gets busy, staff may be less responsive to the needs of individual patients, and as a result,

patients have a higher likelihood of experiencing delays in treatment and inadequate pain relief.

We detected a significant difference in pain scores among patients and EHC providers. We also found comparable results of greater underscoring by the triagers than by the doctors (6). A potential reason for this condition was that the teaching and training of pain management during the undergraduate level in medical school was inadequate (20); thus the highest education level for triager was a diploma. Pain assessment and management were among the least importance skills for them during their three-year course.

To look for possible factors that might account for the observed results, we examined differences based on the chief complaints. There were five conditions (soft tissue injury, headache, abdominal pain, fracture and abscess/cellulites) that were significantly different in pain score between the patients and EHC providers. Other conditions, such as musculoskeletal pain, ischaemic heart disease (IHD) and foreign bodies (FB), showed no significant difference in pain

score. A potential reason for this was due to the small numbers of patients having those chief complaints.

Conclusions

There were significant differences between patients' mean pain scores on arrival, compared to those of doctors and triagers. Clinical conditions that had significant differences in pain assessment were soft tissue injury, headache, abdominal pain, fracture and abscess/cellulites. It is obvious that more needs to be done for patients who present to the ED with pain. EHC providers need to be educated regarding pain assessment and pain management while not compromising the ED's task of treating emergent, life-threatening conditions.

Introducing pain as a fifth vital sign, along with blood pressure, pulse rate, respiratory rate and temperature, is a method to improve pain management. It also allows EHC providers to reassess patients' pain scores sequentially to evaluate the effectiveness of the ED's pain management. Thus, asking for pain scores is a very important step toward excellent and comprehensive pain management in Emergency Medicine.

Author s contributions

Conception and design, KAB, NASNH, NM
Data-collection, assembly, analysis and interpretation: KAB, NASNH
Provision of study materials or patients: NASNH
Drafting of the article: KAB
Critical revision of article: NM
Final approval of the article: RA, NHNAR
Statistical expertise: RA

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Treatment Outcome of Superficial Cerebral Abscess: An Analysis of Two Surgical Methods

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Abstract

Background: The purpose of the study is to compare the two surgical methods (burr hole and craniotomy) used as treatment for superficial cerebral abscess and its outcome in terms of radiological clearance on brain CT, improvement of neurological status, the need for repeated surgery, and survival and morbidity at three months after surgery. This report is a retrospective case review of the patients who were treated surgically for superficial cerebral abscess in Hospital Kuala Lumpur (HKL) and Hospital Sultanah Aminah (HSA) over a period of four years (2004 to 2007).

Methods: Fifty-one cases were included in this study: 64.7% of patients were male and 35.5% were female. Most of the patients were Malay (70.6%); 28 patients (54.9%) had undergone craniotomy and excision of abscess, and the rest had undergone burr hole aspiration as their first surgical treatment.

Results: This study reveals that patients who had undergone craniotomy and excision of abscess showed a significantly earlier improvement in neurological function, better radiological clearance and lower rate of re-surgery as compared to the burr hole aspiration group ($P < 0.05$). However, with respect to neurological improvement at 3 months, morbidity and mortality, there is no significant difference between the two surgical methods.

Conclusion: The significance of these findings can only be confirmed by a prospective randomised series. Further study will be required to assess the cost effectiveness, intensive care needs, and possibility of shorter antibiotic usage as compared to burr hole aspiration.

Keywords: burr hole aspiration cerebral abscess, craniotomy excision, neurosciences

Introduction

A brain abscess is defined as a focal suppurative process within the brain parenchyma (1). With advances in the development of new and more potent antibiotics and earlier diagnosis, we are seeing less intracerebral abscesses in Malaysia. Antibiotics, faster diagnostic confirmation and newer surgical methods have dramatically reduced the mortality rate from about 30–60% to 4–24% (2). However, it is still a challenge in treating this disease, which can still result in significant morbidity and mortality.

The basic principles of brain abscess treatment are early diagnosis, prompt surgical removal of pus, simultaneous eradication of

the primary source and high-dose intravenous antibiotics. The definitive methods of surgical drainage are still not finalised (burr hole or craniotomy) and until now there has been no large prospective randomised controlled study done that can show which is the most effective surgical method.

The purpose of this study was to determine the association between two surgical methods used (burr hole and craniotomy) in the treatment of superficial cerebral abscess (SCA) as measured by survival of the patients, improvement of neurological status, radiological clearance of abscess, re-surgery and morbidity among the survivors.

Materials and methods

This was a retrospective case review of patients who were treated surgically for SCA in Hospital Kuala Lumpur (HKL) and Hospital Sultanah Aminah (HSA) over a period of four years (2004 to 2007). HKL and HSA are both using the same computer database system in the operation theatre (OT). This system is called the Computerised Operation Theatre Database System (COTDS). With this Microsoft Excel system, data for all the patients who underwent neurosurgical procedures in the OT were recorded. The database consisted of the patient's name, age, gender, registration number, date of operation, surgeon's name and operative diagnosis. By typing the diagnosis "brain abscess" in the search box, a complete list of the patient's data appeared on the computer screen. From these data, all patients who were diagnosed as brain abscess post-operatively were included in the study. By using their registration number, the patient's notes and films were traced and studied. Those patients who fulfilled the criteria were included in the study.

Inclusion criteria

- Intracranial supratentorial abscess >2.5 cm
- Stage 3 or 4 abscess (Britt Staging)
- Superficial margin of the abscess <1 cm from the cortex
- First surgical treatment for supratentorial abscess was either burr hole aspiration or craniotomy excision
- Patient's notes and CT brain films were available in the record office

Exclusion criteria

- Deep-seated or infratentorial abscess
- Preoperative American Society of Anesthesiologists (ASA) >3
- Less than 12 years old

Sample size calculations were calculated for each independent variable; the calculation used gave us the highest sample size using PS software (Dupport and Plummer). There were only 78 brain abscess patients available for this study in HKL and HAS. However, 27 patients did not fulfil the criteria and certain data were, rendering an actual sample size of 51 ($n=51$).

The burr hole and drainage procedure was defined as making a small opening in the skull using a twist drill (e.g. Hudson brace) up to a maximum diameter of 16 mm to allow a small opening of the dura mater so that a cannula

could be inserted into the abscess to aspirate out the pus. In this procedure, pus was aspirated without any excision of its capsule. In this study, all the patients who had undergone the burr hole procedure and pus aspiration are categorised in the "burr hole" group.

Craniotomy and excision of the abscess was defined as a surgical procedure with a wide opening of the skull and dura, which exposed the full margin of the abscess. A high-speed craniotome was used to allow evacuation of pus and excision of the abscess wall under direct examination. In this study, all patients who had undergone craniotomy or craniectomy and excision of the abscess with its capsule were categorised in the same "craniotomy" group.

In this study the neurological status of the patients was assessed preoperatively and postoperatively using a Modified Rankin Scale (MRS). The neurological deficit after the first surgery was compared with the pre-operative status. Those patients who showed improvement in neurological status were categorised as the "yes" group. Those who did not have any neurological improvement following surgery were categorised as the "no" group.

Patients were also divided in two groups based on radiological clearance of the abscess. The first group was the "satisfactory" group where there was no residual abscess seen or only minimal residual abscess (<50% of pre-surgery volume). The second group exhibited residual abscess more than 50% of the pre-surgery volume (3).

Data from the case notes and films were studied and collected using a standardised questionnaire (see Appendix III). Analysis of the data was done using SPSS version 12.0 with the guide of our statisticians. Most of the data were categorical except for age, duration of illness and volume of abscess on brain CT. Descriptive analysis was performed for all data variables.

For all the study objectives, univariate analysis was performed using Chi-square test or Fisher exact test; P-value of < 0.05 was considered to be significant.

Results

Over the period of four years (from January 2004 until December 2007), seventy-eight patients with brain abscess were operated upon in the HKL and HSA neurosurgical OT. Out of these cases, only 51 cases of brain abscess fulfilled the criteria and were included in the study. Sixteen cases were excluded due to the exclusion criteria and 11 cases were excluded from this study due to

incomplete data or missing case records. In this series the youngest patient included was 13 years old and the oldest was 65 years old. The mean age of the patients was 36.6 years old. Thirty-nine patients were below 50 years old (76.5%). Thirty-three patients (64.7%) were male and only 18 patients (35.3%) were female. The male to female ratio was 1.8:1.

Altered sensorium was noted to be the most common clinical presentation for brain abscess, occurring in most of the patients (82.4%) and followed by fever (66.7%), headache (62.7%), vomiting (39.2%) and focal neurological deficit (33.3%). The range of duration of symptoms prior to admission was mostly less than a week (66.7%); 21.6% of patients had symptoms for 1–2 weeks before seeking treatment in the hospital and 11.8% presented after 2 weeks. In the majority of cases, there was a predisposing factor (80.4%). In sixteen patients (31.4%), the source of infection was from the heart, either due to cyanotic heart disease or infective endocarditis. Eleven patients (21.6%) had history of trauma and/or head surgery; 4 patients (7.8%) had meningitis; 5 patients (9.8%) had ear infection (3 with mastoiditis) and 3 patients (5.9%) had lung abscess. In 19.6% of cases the source was not determined.

Based on the CT brain, the most common location for the abscess is the frontal region in 24 patients (47.1%). The other sites of abscess were in parietal (29.4%), temporal (13.7%), and occipital regions (9.8%). Out of 51 cases, 23 patients (45.1%) had undergone burr hole aspiration as their first surgical treatment. Among these, 11 patients required re-surgery for residual abscess. Eight underwent second burr hole aspiration and three underwent craniotomy excision. The other 28 patients (54.9%) had undergone craniotomy and excision of the abscess. One of the patients required second craniotomy excision due to recurrence of the abscess.

Only 38 patients (74.5%) had culture and sensitivity results available. Out of these, pus taken during the surgery was sterile in 22 patients (57.9%) and organisms were isolated in only 16 cases (42.1%). The most common organism seen is *Streptococcus* sp. (43.7%) followed by *Staphylococcus* sp. (25%).

Repeat brain CT was performed for all patients within one week after surgery to assess the residual volume of the abscess. Twenty-two patients (43.1%) had no residual abscess on brain CT. There were 6 patients (11.8%) who had significant residual abscesses. All of these were from the burr hole aspiration group and required second surgery within one week of the first surgery. The other 23 patients (45.1%) had

minimal residual abscesses. However, 5 of these patients required a second surgery after one week due to expanding abscesses. One was from the craniotomy excision group and the rest were from the burr hole aspiration group.

Three patients died within one week after the first surgery (surgical mortality rate of 5.9%). Two were from the craniotomy group. Both of these patients presented with MRS grade 4. They had multiple co-morbid illnesses, namely uncontrolled diabetes, hypertension and heart disease. Brain CT showed large abscess (>5 cm) with significant midline shift and oedema. Craniotomy and evacuation were performed in an attempt to save the patients lives; however, they died a few days after the surgery despite aggressive medical and surgical therapy. The other patient in the burr hole group who died was a 62-year-old lady who experienced myocardial infarction after surgery. At 3-month follow-up, there were another 2 patients from the burr hole group who died due to sepsis and severe cyanotic heart disease. The total survival rate at 3 months was 46 patients (90.2%). Functional status of the patients was graded with MRS. Post-operative assessment of the patients revealed that 27 patients (52.9%) showed improvement in their MRS grades within a week after the first surgery. Improvement of neurological status was found to be greater in the patients who underwent craniotomy (71.4%) as compared with the burr hole group (30.4%). However, at 3-month follow up, neurological improvement was seen in 85.7% of patients from the craniotomy group and 82.6% from the burr hole group.

The majority of patients who underwent craniotomy excision showed satisfactory clearance of the abscess in brain CT (89.3%) but only 10 patients (43.5%) in the burr hole group displayed satisfactory clearance. This led to 11 out of 23 patients (47.8%) in the burr hole group requiring a second surgery, whereas in the craniotomy group only 1 patient (3.6%) underwent another surgery. This showed craniotomy and excision had a significantly better clearance as compared to burr hole aspiration ($P < 0.001$) as well as a lower rate of re-surgery ($P < 0.001$).

In this study, 27 patients (52.9%) showed significant improvement of neurological status within a week following surgery. Twenty out of 28 patients (71.4%) in the craniotomy group had significant improvement in their neurological status, which was higher than in the burr hole group (7 out of 23 patients, 30.4%). There was significant association between the two surgical methods and improvement of neurological status at one week ($P = 0.004$). Patients who

had undergone craniotomy and excision had earlier improvement in their neurological status compared to those who underwent burr hole and aspiration. However, at the end of 3 months after the surgery, a total of 39 patients (76.5%) already showed significant improvement in neurological status: twenty-two out of 28 patients (78.6%) in the craniotomy group and 17 out of 23 patients from the burr hole group (73.9%). There was no significant difference in the improvement of neurological status between the two surgical methods at 3-months follow-up (P -value = 0.70).

Among 28 patients who underwent craniotomy excision as their first surgical method, 2 patients (7.1%) died. In the other group, 3 (13.0%) out of 23 patients who underwent burr hole aspiration died. We found no statistically significant difference in the survival of the patients who were treated surgically either with craniotomy excision or burr hole aspiration (P -value = 0.65).

Discussion

The best method for treating cerebral abscess is still difficult to determine. Nonsurgical treatment with antibiotics alone is the least invasive. Heineman et al. were the first to suggest that brain abscesses might be successfully treated only with antibiotics (4). Rosenblum also reported a series of 67 cases managed and cured by antibiotics alone (5). However, antibiotics alone are usually insufficient in a large and well-capsulated abscess. Rousseaux reported a series of 15 out of 31 cases which were successfully treated by antibiotics alone but all were less than 2.5 cm (6). In view of this, cases with abscess <2.5 cm were excluded from this study. Another problem with management without surgical intervention is failure to determine culture and determine the sensitivity of the organism. Therefore, multiple broad-spectrum antibiotics had to be used to address all possible organisms. This is clearly a major disadvantage of nonsurgical treatment.

The two main surgical methods of treatment include burr hole aspiration and craniotomy excision of the abscess. The best approach remains controversial. Argument has persisted over the use of burr-hole aspiration versus craniotomy excision. Different authors have reported contradictory results.

As mentioned earlier, excellent outcomes have been reported in patients managed by burr hole aspiration (7,8, 9–12, 13). The aspiration approach offers a number of advantages: avoidance of general anaesthesia, access to

multiple lesions without an increase in surgical complexity, and an ability to decompress lesions in eloquent areas as well as deep-seated locations. However, most of the series that show favourable results for burr hole aspiration are performed under CT-guided or image-guided stereotaxic aspiration. In Malaysia these facilities are not widely available and hence aspiration was performed when deemed appropriate based on measurements on contrasted brain CT film. However, in this study only superficial abscesses were studied; localisation of the abscess is not technically difficult, even for free-hand aspiration.

Some authors of recent studies have advocated craniotomy excision in the management of brain abscess. This surgical recommendation was based on their observation that despite satisfactory localisation, these abscesses were inadequately evacuated by burr hole aspiration. More cases treated with burr hole aspiration as compared to craniotomy required second or more surgeries. Complete evacuation of the abscess reduces the mass effect better and allows for better antibiotic penetration.

Males (64.6%) were more commonly affected than females (35.4%), at a ratio of 1.8:1. Jafri reported a similar finding in his series of 60 patients; he found that 66.7% of those affected were male, at a ratio of 2:1 (14). We only included patients aged more than 12 years old. The mean age was 36.6 years old. After 12 years of age, physiological status is similar to that of an adult and hence the surgical risk is also similar to that of the adult age group. Therefore only patients older than 12 years were included in this study. This minimised the bias in terms of age group with regard to the decision to pursue a certain method of surgery. In the adult age group, the majority of the patients are in their second or third decades of life. This result is comparable with most of the published series on brain abscess.

Altered sensorium is the most common presentation in our series (82.4%). However, the majority of patients have a Glasgow Coma Scale of 13–14 (59.2%). Other symptoms presented included fever (66.7%), headache (62.7%), vomiting (39.2%), focal neurological deficit (33.3) and seizure (17.6). Similar findings were seen in published local data (14).

The decision to use a certain type of surgical methods in our unit was based on clinical and radiological findings, as well as neurosurgeon preference. Out of 51 patients included in this study, 23 patients underwent burr-hole aspiration as their primary surgery, representing 45.1% of cases. Another 28 patients (54.9%) had

undergone craniotomy excision of abscess as their first surgical treatment. Previously burr hole and drainage was usually the surgical method of choice and craniotomy was only advocated for cases of refractory or residual abscess; however, the current trend in our centres favours craniotomy excision as first surgical treatment as long as the abscess is superficial and the patient is fit for major surgery (Figure 1).

In terms of neurological status, we found that 71.4% of the patients from the craniotomy excision group showed improvement as measured by MRS within a week. In the burr hole aspiration group only 30.4% showed improvement ($P=0.004$). Patients who underwent craniotomy excision of abscess had earlier and better neurological improvement as compared to those who underwent burr hole aspiration. The reason for this is craniotomy allows total or more complete evacuation of the abscess with the capsule and the brain is adequately decompressed, which improves neuronal function. However, at 3 months follow-up, 76.5% and 73.9% of cases from the craniotomy and burr hole groups,

respectively, already exhibited improvements in their neurological function. Statistical analysis revealed a p-value of 0.70 and hence no significant difference between the two groups in neurological function at 3-month follow-up (Table 1).

Surgical method was also found to be statistically significant for the clearance of abscess on brain CT ($P < 0.001$) (Table 1). Patients who underwent craniotomy have been noted to have a better abscess clearance on the CT scan. The advantage of craniotomy over the burr hole procedure is that it allows direct visualisation of the abscess and complete removal of the capsule. The stage of the abscess seen on the CT scan is also particularly important to determine the mode of surgery. In the cerebritis stage the capsule is not well formed and it is difficult to excise the abscess. Most authors advocated medical treatment with or without burr hole aspiration during this stage. Therefore only stage 3 or 4 abscesses (Britt staging) were included in our study.

In terms of re-surgery, more patients in the burr hole group had to undergo another operation in this study. There was a significant association

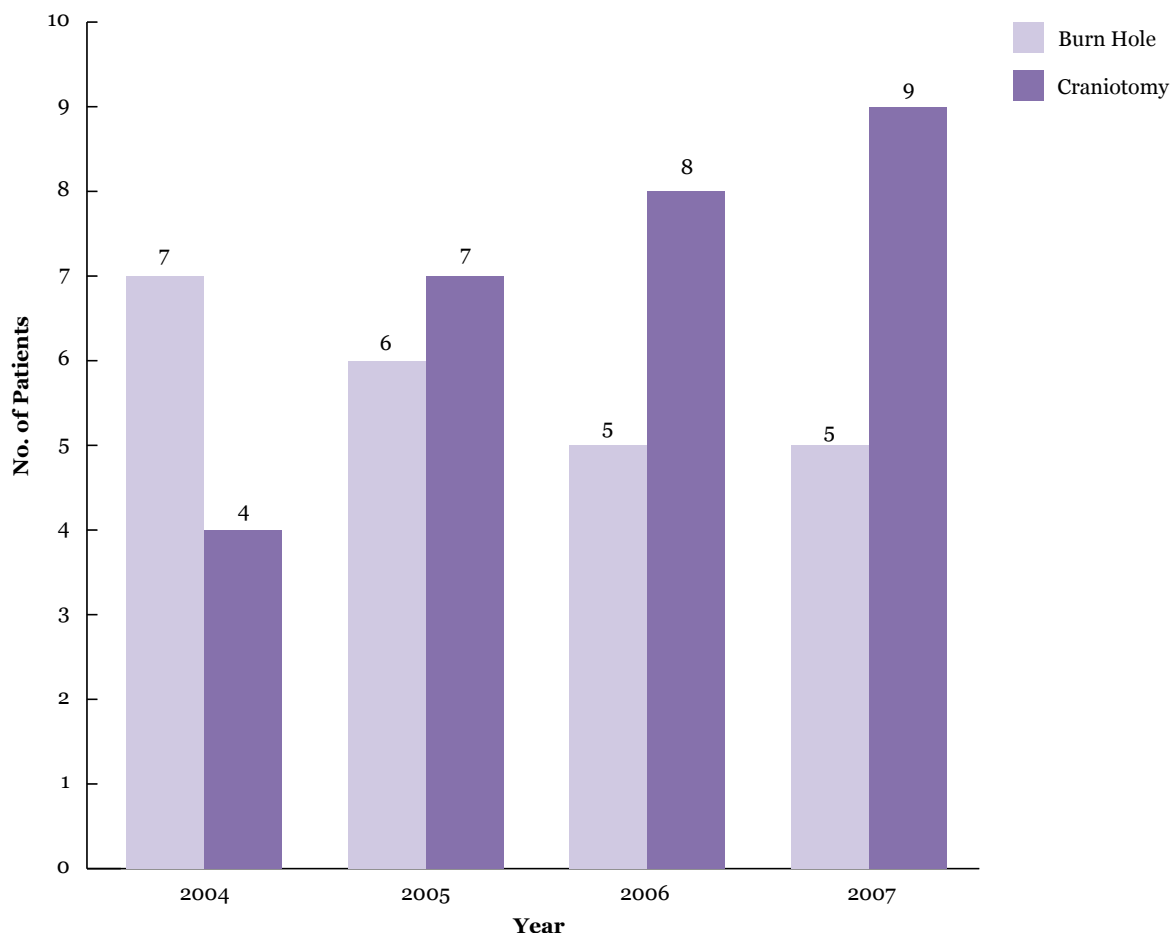


Figure 1: Mode of first surgery for SCA from 2004-2007

Table 1: Association between surgical method and outcome

Outcome	Surgical Methods, n (%)		χ^2 stat (df)	P value
	Craniotomy Excision	Burr Hole Aspiration		
Improvement of neurological status at one week				
Yes	20 (39.2)	7 (13.7)	8.518 (1)	0.004 ^a
No	8 (15.7)	16 (31.4)		
Improvement of neurological status at three months				
Yes	22 (43.1)	17 (33.3)	0.152 (1)	0.696 ^a
No	6 (11.7)	6 (11.7)		
Radiological clearance				
Satisfactory	25 (49.0)	10 (19.6)	12.307 (1)	<0.001 ^a
Not satisfactory	3 (5.9)	13 (25.5)		
Repeat surgery				
Yes	1 (2.0)	11 (21.6)	13.744 (1)	<0.001 ^a
No	27 (52.9)	12 (23.5)		
Survival				
Alive	26 (51.0)	20 (39.2)	-	0.647 ^b
Death	2 (3.9)	3 (5.9)		
Morbidity				
Independent	23 (50.0)	17 (37.0)	-	>0.95 ^b
Dependent	3 (6.5)	3 (6.5)		

^a Pearson χ^2 test applied^b Fisher exact test applied

between surgical method used and re-surgery ($P < 0.001$). Patients in the burr hole group were noted to have a higher rate of re-surgery as compared to the craniotomy group. Re-surgery was closely related to the amount of residual abscess and the clinical response of the patients to medical treatment. The rate of re-surgery is proportionate to the amount of residual abscess remaining after the first surgery. Recurrence of pus collection can be attributed to ongoing seeding of pathogens from the primary source if it was not treated effectively. This is particularly true in some cases related to otorhinogenic causes and removal of the primary source by an otolaryngologist may be necessary.

Three months morbidity among survivors has no significant statistical association with method of surgery in this study ($P > 0.95$). Patients with SCA had equal probability of having permanent disability or post-infective seizures later in life regardless of their primary surgical method. As stated in the literature, other prognostic factors

were level of consciousness upon admission, immune deficiency, co-morbid illness and deep-seated abscess (15).

In a Russian series with 110 patients who underwent surgical treatment for brain abscess, they found that craniotomy and excision of the abscess was the most effective management. Sixty-three patients who underwent craniotomy excision had a favourable outcome as compared to the burr hole group (16). The advantages of the craniotomy excision were complete removal of the abscess with its capsule. Blind aspiration of the abscess renders it difficult to estimate the adequacy of the evacuation; furthermore, the capsule might collapse partially and prevent further aspiration and leave a residual abscess after surgery. This factor probably contributed to the slower improvement in neurological function in patients who underwent burr hole aspiration. Another risk is damage to the friable hyperaemic capsule, which causes bleeding.

Conclusion

The findings from this study suggest that craniotomy and excision is probably the better surgical method in the treatment of SCA. Compared to burr hole aspiration, craniotomy and excision has been shown to improve neurological status more quickly, with better abscess clearance as well as a reduced rate of re-surgery. However, this is not a prospective randomised series, so the results need to be verified through further studies.

Further study will be required to assess the cost effectiveness, intensive care needs, and possibility of short-term antibiotic usage as compared to burr hole aspiration in view of earlier neurological improvement.

There were some limitations in this study. The main limitation was the retrospective non-randomised nature of the study. There were also different surgeons and two hospitals involved. Small sample size with 35% dropout (27/78) was another limitation. Only 51 patients were enrolled in this study due to incomplete data, missing case notes or exclusion criteria.

Author s contributions

Conception and design, data analysis and interpretation, data collection and assembly: WMT

Provision of study material or patients: JSA

Final approval of the article: MSMH

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Prevalence and Sources of Stress among Universiti Sains Malaysia Medical Students

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Abstract

Background: Being in medical school has always been regarded as highly stressful. Excessive stress causes physical and mental health problems. Persistent stress can impair students' academic achievement and personal or professional development. The aim of this study is to explore the nature of stress among medical students by determining the prevalence, sources and pattern of stress and the factors affecting it.

Methods: We chose a cross-sectional study design utilizing validated questionnaires, the 12 items General Health Questionnaire (GHQ-12) and Medical Student Stressor Questionnaire (MSSQ), to evaluate stress levels and stressors. School and ethical committee clearance were obtained prior to the study. Data were analysed using SPSS version 12.

Results: Of the medical students who were administered the questionnaire, 761 (72%) respondents participated in this study. The prevalence of stress among the medical students was 29.6%. The top 10 stressors were academic-related. Prevalence of stress for the first, second, third, fourth and fifth year students was 26.3%, 36.5%, 31.4%, 35.3% and 21.9%, respectively. Year of study was the only significant factor affecting stress among medical students (P -value < 0.05).

Conclusions: The prevalence of stress among medical students in USM is high. Academic-related problems were the major stressor among medical students. Year of study was the factor most significantly associated with medical students' stress. There was a bimodal pattern of the stress level throughout the year of study.

Keywords: medical students, mental health, stress, medical sciences

Introduction

Tertiary medical training has always been regarded as being highly stressful. Many studies have described the stressors of medical training and the associated negative consequences on the mental and physical health of medical students (1–10).

Stress is defined as the body's non-specific response to demands made upon it, or to disturbing events in the environment (11–12). It is not just a stimulus or a response but rather, it is a process by which we perceive and cope with environmental threats and challenges (13). Personal and environmental events that cause stress are referred to as stressors (14). In short, stress includes the emotional disturbances or changes caused by stressors. Linn & Zeppa (15)

have suggested that some stress in medical school training is needed for learning. Stress that facilitates learning is called 'favourable stress' and stress that suppresses learning is called 'unfavourable stress'. Depending upon their cultural backgrounds, personal traits, experience and coping skills, medical students may perceive the same stressors differently.

An optimal level of stress, referred to earlier as 'favourable stress', can enhance learning (16). However, excessive stress can lead to physical and mental health problems (17). It can reduce students' self-esteem (16,18) and may affect academic achievement and personal or professional development. Studies in the United States have suggested that the practice of medicine entails certain risks to the mental health of qualified medical students (19), and numerous studies have revealed high rates of psychological

morbidity in medical students at various stages of their training (1,3–5,20). Other studies among medical students have found that stress is associated with anxiety and depression (21–22), interpersonal conflict (23), sleep disturbances (24), and poor academic or clinical performance (15). Stress was also found to decrease attention, reduce concentration, impinge on decision-making, and reduce students' abilities to establish good relationships with patients (21). As a consequence, students have reported feelings of inadequacy and dissatisfaction with clinical practice in the future. This may affect the lives of patients and the health of a community. Moreover, stress has also been linked to medical student suicide (25), drug abuse (26–27), and alcohol use (28). A study conducted in the United Kingdom reported that over one-third of medical students suffered from emotional disturbances as measured by the General Health Questionnaire (GHQ) (3–5). A study conducted in a Malaysian university reported that 41.9% of medical students had emotional disorders based on the GHQ (9).

The objective of this study was to determine the prevalence, sources and predictors of stress among USM medical students. We reasoned that this information would be useful to establish a database on the extent of the problem. Notably, an understanding of these factors could help in the planning of measures to reduce stress.

Materials and Methods

We carried out a cross-sectional study of 1058 medical students enrolled in the School of Medical Sciences (SMS), Universiti Sains Malaysia (USM), during the 2008/2009 academic session. Data were collected using a questionnaire comprised of two parts: (i) sociodemographic questions and (ii) questions designed to elicit information about the sources and levels of stress. We collected sociodemographic information including: gender, year of study, race, grades in subjects such as English, Malaysian language, Physics, Additional Mathematics, and Biology, entry qualifications, religion and involvement with co-curriculum activities. Some details were required in the co-curriculum section to enable scoring and categorizing into active and inactive groups. We chose these variables based upon prior studies illustrating their association with stress.

One of the most widely used tools to measure stress levels is the 12-item General Health Questionnaire (GHQ-12). Various studies have demonstrated reliability GHQ-12 coefficients ranging from 0.78 to 0.95. The items on the GHQ-12 represent 12 manifestations of stress, and

respondents were asked to rate the presence of each of these manifestations in themselves during the recent week preceding the study period. Subjects respond to each question by choosing from four typical responses: 'not at all', 'no more than usual', 'rather more than usual' and 'much more than usual'. A binary scoring method is used to evaluate responses. This method assigns a score of zero to the two least symptomatic answers and a score of one to the two most symptomatic answers; thus, responses can only be scored as zero or one. 'Caseness' was defined as a total questionnaire score of 4 or more (29–30).

In this study, a similar questionnaire was used to measure stress levels and a newly developed instrument, the Medical Students Stressor Questionnaire (MSSQ), was used to identify sources of stress. The items on MSSQ represent 40 events that have been reported to be possible sources of stress in medical students. Respondents were asked to rate each event in themselves during the recent weeks by choosing from five responses: 'causing no stress at all', 'causing mild stress', 'causing moderate stress', 'causing high stress' and 'causing severe stress'. The MSSQ is scored by assigning a value of zero to four for each of the respective responses. For example, a response of 'causing no stress at all' would be scored as zero and a response of 'causing severe stress' scored as four. In order to test the validity and reliability of both instruments in a medical student population and to determine the appropriate GHQ-12 score for 'caseness', both questionnaires were piloted to 141 newly graduated medical students of the 2007/2008 academic session. From the pilot data, we calculated Cronbach's alpha values for the GHQ-12 and MSSQ of 0.85 and 0.95, respectively. The sensitivity and specificity of the GHQ-12 at the cut-off point of 4 were 81.3% and 75.3%, respectively. The positive predictive value was 62.9%, comparable to the Goldberg findings (29–30). The pilot study showed that both questionnaires were valid and could reliably measure stress levels and identify stressors among medical students. Respondents with a score of 4 or greater on the GHQ-12 were considered to be under significant unfavourable stress, defined as 'caseness' in this study.

Data collection was performed two months after the start of the 2008/2009 academic session. We chose this period to avoid the stressful examination period, which could potentially introduce measurement bias. Thus, we reasoned that the level measured was representative of the natural level of stress in medical students. The questionnaires were semi-structured, self-administered questionnaires which were

distributed to the medical students during face-to-face sessions in a lecture hall separately according to the year of study. The students were told to follow the instructions. The process of filling in the questionnaire took about 15 minutes to complete and they were to be returned on the same day. Verbal consent was obtained from all participants. Completion of the questionnaires was voluntary and would not affect their progression on the medical course. Clearance was obtained from the school and ethical committee prior to the start of the study.

Data were analysed using Statistical Package for Social Sciences (SPSS) version 12. All data collection forms were given serial numbers. Data were entered, checked for data entry errors, explored and cleaned. Data were interpreted using an alpha (α) set at 0.05 and confidence interval of 95%. Descriptive statistics were used for the analysis of the demographic data, the students' stress prevalence based on the GHQ-12 score and the stressor items. Assumptions were made before running statistical tests. Binary Logistic Regression was applied to determine the predictors of stress.

Results

A total of 761 (72%) out of 1058 medical students responded, 474 (62.3%) of which were female students. All years of study were approximately equally represented: 213 students (28%) from year one, 104 students (13.7%) from year two, 159 students (20.9%) from year three, 139 (18.3%) from year four and 146 (19.2%) from year five. With regards to ethnicity, 459 (60.4%) were Malay, 266 (35%) were Chinese, 33 (4.3%) were Indian and 3 (0.3%) were self-reported as other. Several religions were represented in the sample: 462 (60.7%) were Muslim, 206 (27.1%) were Buddhist, 53 (7%) were Christian, 29 (3.8%) were Hindu and 11 (1.4%) were reported as other. Most students (79.1%) were from the matriculation programme. The majority of them (73.2%) have excellent academic results (their qualification far exceeds the stipulated entry qualification which is at least B in all subjects) and co-curriculum backgrounds prior to their entry into medical school.

Figure 1 shows that the overall prevalence of stress (GHQ score of 4 as the cut-off point) among the students was 29.6%. The prevalence

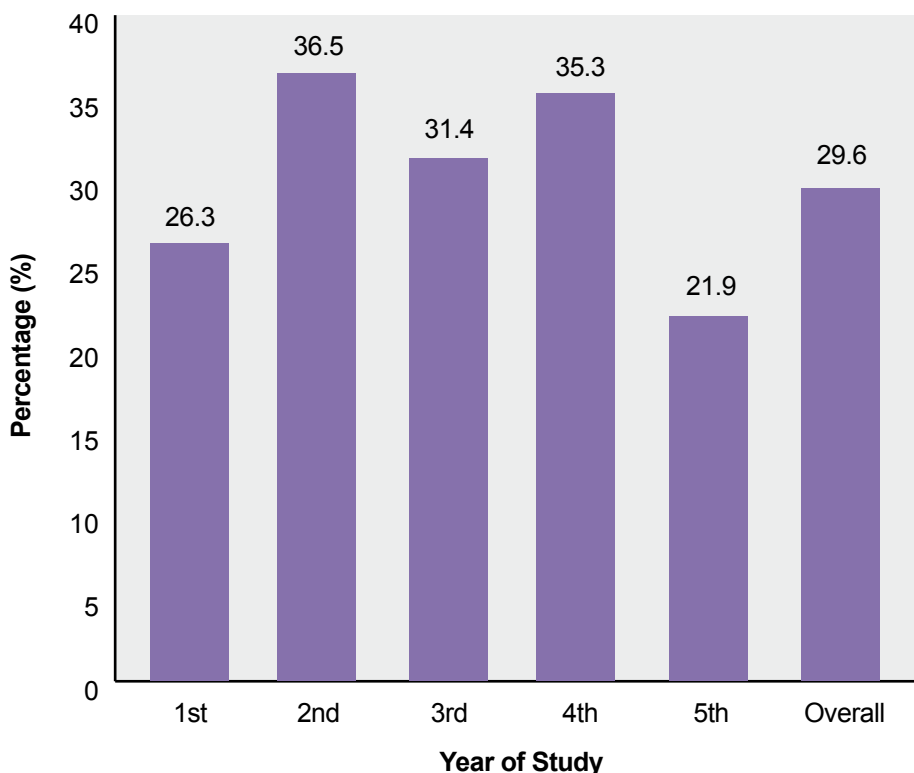


Figure 1: Prevalence of stress among medical students in School of Medical Sciences, Universiti Sains Malaysia according to year of study.

of stress for first, second, third, fourth and fifth year students were 26.3%, 36.5 %, 31.4%, 35.3% and 21.9%, respectively. We observed the highest prevalence of stress among second and fourth year students. The lowest prevalence of stress was observed among the first and fifth year students. The stress prevalence among third year students was at an intermediate level between the highest and the lowest levels. Table 1 shows the rank of each stressor based on the degree of stress perceived by the students. All of the top 10 stressors were basically academic-related stressors.

Binary Logistic regression (Forward Stepwise Method) was applied to determine the predictors of stress among medical students. The only significant predictor of stress was year of study ($X^2 = 10.16$, $P\text{-value} = 0.038$). Indeed, 19 percent of the stress level among medical students was influenced by year of study (Nagelkerke $R^2 = 0.19$). This study indicates that the main predictor influencing the stress level of medical students was year of study. Gender, race, religion, academic achievement, extracurricular achievement and qualification entry were not predictors of stress among medical students.

Discussion

The relatively high response rate in this study (approximately 72%) is similar to the 70%-80% response rate obtained by other studies (3,31). This is perhaps an indication of the strength of students' feelings and their perceived need for a medical education curriculum that minimizes their stress during the course of medical studies. Medical programmes have always been regarded as a popular choice for tertiary education (9). Only those who have excellent academic achievement can be successful in the course. Therefore, the medical programme may be even more competitive and stressful for students who are accepted (6).

Based on previous studies, stress prevalence among medical students ranges from 30% to 50% (1–6,9–10,20). This level of stress is high in comparison to that of the general population (3) and that of students in other courses of study (1,6). It is noteworthy that excessive exposure to stress causes physical and mental problems (17), and therefore it is important to detect stressed students earlier in order to prevent deleterious

Table 1: Stressors (identified by the Medical Student Stressor Questionnaire) ranked by mean degree of stress perceived by medical students

Rank	Items	*Degree of stress Mean (SD)
Causing moderate to high stress		
1	Tests/examinations	2.63 (1.00)
2	Large amount of contents to be learnt	2.39 (1.04)
3	Lack of time to review what have been learnt	2.27 (1.08)
4	Getting poor marks	2.09 (1.22)
5	Need to do well (self-expectation)	2.06 (1.19)
6	Not enough medical skill practice	2.03 (1.16)
7	Falling behind in reading schedule	2.02 (1.13)
Causing mild to moderate stress		
8	Heavy workload	1.91 (1.11)
9	Having difficulty understanding the content	1.89 (1.11)
10	Unable to answer the teachers' questions	1.87 (1.13)
11	Learning context – full of competition	1.64 (1.15)
12	Need to do well (imposed by others)	1.53 (1.18)
13	Quota system in examinations	1.50 (1.25)
14	Feeling of incompetence	1.43 (1.18)
15	Poor motivation to learn	1.43 (1.29)
16	Participation in class presentation	1.41 (1.13)

17	Inappropriate assignments	1.33 (1.25)
18	Uncertainty of what is expected of me	1.26 (1.22)
19	Lack of time for family and friends	1.24 (1.22)
20	Teacher – lack of teaching skills	1.23 (1.18)
21	Unjustified grading process	1.21 (1.15)
22	Participation in class discussion	1.21 (1.10)
23	Lack of guidance from teacher(s)	1.15 (1.15)
24	Frequent interruption of work by others	1.12 (1.17)
25	Not enough study material	1.12 (1.12)
26	Unable to answer questions from patients	1.10 (1.12)
27	Conflicts with other students	1.07 (1.14)
28	Lack of recognition for work done	1.06 (1.13)
29	Facing illness or death of the patients	1.05 (1.16)
Causing nil to mild stress		
30	Not enough feedback from teacher(s)	0.92 (1.08)
31	Family responsibilities	0.92 (1.16)
32	Verbal or physical abuse by teacher(s)	0.87 (1.18)
33	Conflict with personnel(s)	0.86 (1.11)
34	Verbal or physical abuse by other student(s)	0.76 (1.10)
35	Verbal or physical abuse by personnel(s)	0.75 (1.11)
36	Conflict with teacher(s)	0.75 (1.10)
37	Parental wish for you to study medicine	0.57 (0.98)
38	Unwillingness to study medicine	0.56 (1.05)
39	Working with computers	0.54 (0.93)
40	Talking to patients about personal problems	0.50 (0.90)

* Degree of stress classification: 0 - 1.00 is 'causing nil to mild stress', 1.01 – 2.00 is 'causing mild to moderate stress', 2.01 – 3.00 is 'causing moderate to high stress' and 3.01 – 4.00 is 'causing high to severe stress'

long-term effects of stress on the students (1,3–4,9).

The prevalence of stress among medical students in the SMS, USM (29.6%), as measured by the GHQ-12, was lower in comparison to that reported in other studies among medical or non-medical students using the same questionnaire (1,3,5–6,20). For example, the prevalence of stress in Singapore law students and medical students was 47.2% and 57%, respectively (6). One possible reason for the lower prevalence of stress is that, since its inception, the school has incorporated personal and professional development elements into its curriculum where relevant inputs such as ethics, communication skills, professionalism and leadership could be imparted to students at various places in the time table (32). This observation is in keeping with the General Professional Education of Physician (GPEP) Report of the Association of American

Medical Colleges (AAMC), which recommends enhancing the personal development of students to help them cope with the stress of tertiary education. However, even though the prevalence is lower in comparison to other studies, it remains high compared to the general population in the UK (less than 10% as reported by Firth in 1986). A comparison of the prevalence to the Malaysian population could not be made since data reflecting the stress prevalence in the Malaysian population were not available. We recommend that a study be undertaken to examine the prevalence of stress among the general population of Malaysia in order to obtain the baseline data.

It should be noted that a stress prevalence of 29.6%, as recorded by SMS, USM, is much lower in comparison to the results of other studies. For example, prevalences of 41.9% and 46.2% were measured in a Malaysian government medical school and in a Malaysian private medical school,

respectively (9,10), both determined by the GHQ. We recommend that a multi-centre study be carried out to establish the baseline prevalence of stress among Malaysian medical students as well as to investigate this matter further.

In this study, we found a lower stress prevalence in both first and final year students (26.3% and 21.9%, respectively) in comparison to students in other years of study (prevalences of 36.5%, 31.4%, and 35.3 for second, third, and fourth year students, respectively). One possible reason for the low stress prevalence in final year students is that they have developed skills to manage their studies and therefore are better able to cope with stress, in comparison to students in other years of study. Moreover, the first year students had just entered the course 2 months prior and may have still been experiencing the stages of novelty and euphoria. In addition, during this time period, they had yet to face difficult subjects because most of the subjects studied during the first 3 months are subjects that the students have learned during their matriculation and STPM.

This present study also showed that the highest prevalence of stress among USM medical students was among second and fourth year students. This was an interesting finding because both of these groups were in the early stage of phase two and phase three, respectively. Since each phase requires a different learning approaches, a possible reason for the high stress prevalence could be the impact of the transitional and adaptation periods due to the new phases of study (6). That is, the students in their second and fourth year may experience more stress compared to other years of study because they are struggling to adjust their learning approaches according to the new phase requirements. Nevertheless, because this is a cross-sectional study that provides only a snapshot of the stress prevalence, causality could not be definitively confirmed. It is recommended that a longitudinal study be performed to investigate the real pattern and trend of stress among medical students.

One important finding of this study is that more attention be given to medical students during transitional periods: notably first, second and fourth years. At the same time, the third and final year medical students should not be neglected. One potential intervention programme that could be implemented to reduce stress levels of second and fourth year students is a structured orientation programme that addresses issues such as expectations for each phase, how the students are going to be evaluated, how to cope with study in each phase and how to get through each phase smoothly.

As expected, the top ten stressors (based on scores given by the medical students) were related to academic matters. The top ten stressors were tests and examinations, the large quantity of contents to be learned, lack of time to review what has been learned, poor marks, a desire to do well (self-expectation), insufficient skill in medical practice, falling behind in reading schedule, heavy workload, difficulty understanding the content, and inability to answer teachers' questions. Seven of the stressors were rated as causing moderate to high stress, and the other three stressors were rated as causing mild to moderate stress. This is in keeping with findings from other studies (3,5,8,33–34). The overall pattern of stressors in this medical school is similar to other medical schools (i.e., most of the top ten stressors were related to academic matters). However, the frequency (rank) of some stressors may be significantly different from studies done elsewhere (33–34).

In this study, the only significant factor impacting stress prevalence was the year of study. Other factors such as gender, race, religion, co-curriculum involvement, and academic achievement before entry, English, Physics and Biology results did not contribute to stress among medical students. This suggests that medical students' stress levels are significantly influenced by the year of study. This is in keeping with findings from other studies (2,10). However, Guthrie et al. (4) found that there was no significant association between stress level and year of study; however, they did report that the best predictor of psychological morbidity in the final year is the GHQ-12 score in the first year. This finding suggested that future intervention programmes in SMS, USM should be focused on the year of study.

In conclusion, the prevalence of stress among medical students in SMS, USM is high. There was a bimodal pattern of stress prevalence throughout the year of study. Academic-related problems were the major stressors among medical students. Year of study was the best predictor of a medical student's stress level.

Author s contributions

Conception and design, data analysis and interpretation, drafting of the article: MSBY, AFAR, MJY

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A Study on the Magnitude and the Effectiveness of the Observation Ward of Hospital Universiti Sains Malaysia

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Abstract

Background: The observation ward (OW) allows patients to be reassessed and monitored before deciding either to admit or to discharge them. This is a six-month descriptive cross-sectional study conducted in the observation ward of the Emergency Department (ED) of Hospital Universiti Sains Malaysia, Kelantan. The objective of this study was to examine the demographic characteristics and clinical profiles of adult observed patients and to determine the effectiveness of OW management.

Methods: Patients were selected randomly by convenience sampling. One hundred and twenty-four patients were included in the study. The mean age was 40.3 ± 18.5 years (95% CI: 37.2 to 43.8).

Results: Among the common clinical problems were abdominal discomfort (23%), diarrhoea and vomiting (13%) and fever (13%). Reasons for OW admission included diagnostic uncertainty (63%) and short course of treatment (33%). The mean length of stay was 4.1 ± 1.8 hours (95% CI=3.8 to 4.4 hours). Most of the patients (85%) were discharged.

Conclusions: The OW of HUSM is effective in managing adult patients as determined by the hospitalisation rate and the length of stay.

Keywords: observation ward, adult patients, length of admission and discharge, medical sciences

Introduction

The concept of observation medicine has attracted significant attention in the published literature since the Nuffield Provincial Hospital Trust Review of Short Stay Units published their report in 1960. They made a remarkable statement by saying "short stay observation beds were essential for good casualty departments" (1).

In 1988, the American College of Emergency Physicians (ACEP) published the first article on Observation Ward Medicine, entitled "Guidelines on Management of Observation Units" (2). A year later, the British Association of Accident and Emergency Medicine (BAEM) published their guidelines on management of observation wards (3). BAEM emphasised the importance of the observation ward (OW) for patient management and recommended one short stay bed for every 5,000 attendances (4). The advantages of OWs include providing continuous patient management and better definition of patient diagnoses, reducing hospital costs and preventing inappropriate patient disposition (2,5,6).

The study was conducted to examine the demographic characteristics and clinical profiles of adult observed patients and to determine the effectiveness of OW management. We hypothesise that the management of adult patients in OWs of HUSM is efficient and effective.

From the available data, the magnitude of observed adult cases, the strengths and the weaknesses of the OW of HUSM can be determined and thus contribute to the improvement of total patient care. As there was no descriptive analysis for OWs in Malaysian hospitals, the results of this study can serve to establish a database for information on patients that really need OW admission. This knowledge will hopefully reduce the morbidity and mortality rate and ultimately improve patient quality of life.

Materials and Methods

Kelantan is located at the northern part of the east coast of Peninsular Malaysia. Kota Bharu is the capital city of Kelantan with a population of 398 835. There are two major hospitals in

Kota Bharu. Hospital Universiti Sains Malaysia (HUSM) is a teaching hospital under the Ministry of Higher Education, whereas Hospital Raja Perempuan Zainab II is a public hospital under the Ministry of Health. HUSM is also recognised as the regional tertiary referral centre for the east coast region of Peninsular Malaysia. The OW of Emergency Department (ED) of HUSM was started in 2000 with a lot of deficiencies, mainly due to lack of manpower. At present, it provides services for patients who require less than 24 hours of inpatient care. It has eight beds with portable monitors and resuscitation equipment. It was placed under the supervision of emergency physicians.

This is a descriptive cross-sectional study. It was conducted in the observation ward of the Emergency Department, HUSM Kubang Kerian, Kelantan. All of the data were collected from the admission book of the OW from January until June 2004. Patient data or variables, including name, registration number, age, sex, address, diagnosis upon admission, time of admission and discharge, reason of admission, and final disposition (admitted as an inpatient or discharged), were recorded into the designated data collection sheet. Patients were divided into two groups: paediatric (0 to 12 years old) and adult (more than 12 years old), as these are the age categories being used in Malaysia. Transit cases such as pneumonia, heart failure, and unstable angina were excluded.

Data were analysed using the Statistical Package for Social Sciences statistical software (SPSS) 11.0 for Windows. Numerical data were expressed as the mean, median, mode, and standard deviation. Categorical data were expressed as frequency and relative frequency. A 95% confidence interval (CI) was used for

continuous variables, and the chi-square test or one-way ANOVA test was used for univariate analysis of dependent categorical data. Statistical tests were two-sided, and significance was accepted at P -value < 0.05 .

Results

A total of 124 adult patients entered the study, mainly Malays (95.2%) and females (73%). The mean age of the patients was 40.3 ± 18.5 years old (Table 1).

In this study, there were three main clinical problems: abdominal discomfort, vomiting and diarrhoea, and fever. The percentages of patients who had abdominal discomfort, vomiting and diarrhoea, and fever were 23.4%, 12.9% and 12.9%, respectively (Table 2).

Sixty-three percent of the study population were admitted and observed for diagnostic evaluation, and another 33% were admitted for a short course of treatment (Table 3). Most of the patients with the above clinical problems were hospitalised after a few hours of observation. The percentages of patients admitted with abdominal discomfort, vomiting and diarrhoea, and fever were 90%, 75%, and 75%, respectively.

In this study, the mean length of stay was 4.12 ± 1.78 hours; (95% CI=3.8–4.4). Mild head injury patients were observed for quite a long period of time. Their mean length of stay was 9.67 ± 1.0 hours. The other two clinical problems that resulted in long stays were chest pain and headache syndrome. The length of stays of these patients was 5.5 ± 0.4 and 5.4 ± 1.9 hours, respectively (Table 4). There was no association between types of clinical problems and length of stay (one-way ANOVA, $P < 0.05$). About 85% of

Table 1: Clinical characteristics and outcomes of adult patients in the observation ward

Clinical Characteristics and Outcomes	
Mean age (years)	40.3 ± 18.5 (95% CI: 37.2–43.8)
Sex	
Male	51 (41.1%)
Female	73 (58.9%)
Race	
Malay	95.2%
Others	4.8%
Outcome	
Discharged	105 (84.7%)
Admitted	19 (15.3%)

Table 2: List of clinical problems and their frequencies

Clinical problem	n (%)
Abdominal discomfort/pain	29 (23.4)
Non-specific chest pain	5 (4)
Renal colic	5 (4)
Fever	16 (12.9)
Asthma/hyperventilation	5 (4)
Headache syndrome	4 (3.2)
Dizziness/vertigo	3 (2.4)
Pain management post injury	2 (1.6)
Mild head injury	3 (2.4)
Hypertension	2 (1.6)
Allergy	2 (1.6)
Upper respiratory tract infection (URTI)	9 (7.3)
Musculoskeletal pain (backache/contusion)	4 (3.2)
Vomiting and diarrhoea	16 (12.9)
Others	19 (15.3)

Table 3: Indications and frequencies of OW admissions according to clinical problems

Clinical problem	Diagnosis n (%)	Treatment n (%)	Other* n (%)	Total n (%)
Abdominal discomfort/pain	28 (22.6)	1 (0.8)	-	29 (23.4)
Non-specific chest pain	5 (4.0)	-	-	5 (4.0)
Renal colic	5 (4.0)	-	-	5 (4.0)
Fever	13 (10.5)	-	3 (2.4)	16 (12.9)
Asthma/ hyperventilation	-	5 (4.0)	-	5 (4.0)
Headache syndrome	4 (3.2)	-	-	4 (2.4)
Dizziness/vertigo	-	3 (2.4)	-	3 (2.4)
Pain management post injury	-	2 (1.6)	-	2 (1.6)
Mild head injury	-	3 (2.4)	-	3 (2.4)
Hypertension	-	2 (1.6)	-	2 (1.6)
Allergy	-	2 (1.6)	-	2 (1.6)
URTI	9 (7.3)	-	-	9 (7.3)
Musculoskeletal pain	1 (0.8)	3 (2.4)	-	4 (3.2)
Vomiting and diarrhoea	-	16 (12.9)	-	16 (12.9)
Upper gastrointestinal bleed	1(0.8)	-	-	1 (0.8)
Others	13 (10.5)	4 (3.2)	1 (0.8)	18 (14.5)
Total (%)	79 (63.7)	41 (33.1)	4 (3.2)	124 (100)

* Awaiting review of laboratory results or psychosocial needs

Table 4: Clinical problems and length of stay

Clinical problem	Mean ± SD (hour)	95% CI
Abdominal discomfort/pain	4.6 ± 1.5	4.0 – 5.1
Non-specific chest pain	5.4 ± 0.4	4.8 – 6.0
Renal colic	3.6 ± 0.9	2.6 – 4.7
Fever	3.5 ± 1.1	2.9 – 4.0
Asthma/ hyperventilation	4.9 ± 2.4	1.9 – 7.8
Headache syndrome	5.4 ± 1.9	2.4 – 8.3
Dizziness/vertigo	3.1 ± 1.6	- 1.1 – 7.2
Pain management post injury	4.0 ± 2.1	3.8 -5.9
Mild head injury	9.7 ± 1.0	7.1 – 12.2
Hypertension	3.5 ± 0.7	- 2.8 – 9.8
Allergy	4.3 ± 1.8	- 11.6 – 20.1
URTI	3.4 ± 1.0	2.6 – 4.1
Musculoskeletal pain	4.9 ± 2.1	1.5 – 8.2
Vomiting and diarrhoea	4.0 ± 1.9	3.0 – 5.0
Upper gastrointestinal bleed ^a	4.0	n/a
Others	2.9 ± 1.2	2.3 – 3.5

^a Data from one case

the study patients were discharged home with advice and medications (Table 1). However, there was no association between the clinical problems and the outcomes (admission and discharge) (Chi-square test, P -value=0.9).

Discussion

Emergency Medicine (EM) practices in HUSM evolved dramatically after the introduction of the postgraduate program of EM in 1998. A concept of “our patient” was introduced in the daily practice. Patients were managed according to the current standard of practice with a definite criterion for discharge or admission. As a result, patients needed to be observed for longer times until the team was satisfied with the management.

In our observation ward, the majority of patients were adult Malays. This is consistent with the Kelantan population composition in which Malays were the majority (7). Two-thirds of the adult study population were female. Their mean age was 40.3 ± 18.5 years (95% CI=37.2–43.8). The narrow confidence interval indicates that the sample size was adequate for inferential statistical evaluation, and this result was clinically significant. The demography of patients seen in the ED or OW varies according to the society and location of the hospital.

In this study, the main clinical problem requiring OW admission was abdominal pain or discomfort (23%), due to diagnostic uncertainty. This finding is quite similar to a Singaporean study (8). However, the admission rate of abdominal pain was higher (45.1%). Abdominal pain was one of the diagnostic challenges to the emergency physicians (EP) as aetiology varies widely among populations, and patients frequently present with ‘non-classical’ signs and symptoms, which challenges the doctor’s ability to arrive at a definitive diagnosis (9). The diagnosis and decision for ward admission or discharge can be safely made after a few hours of observation. Minor therapy such as pain management, correction of dehydration with intravenous infusions or anti-emetic for vomiting may also be prescribed during this period while waiting for investigation results. Perhaps patients’ satisfaction towards ED management is improved. Most of them were admitted into the common ward. Their mean length of stay in our OW was 4.6 ± 1.5 hours (95% CI = 4.1–5.0 hours). In contrast, about 80% of these patients were observed for six hours or less at Singapore General Hospital (8).

The second clinical problem was vomiting and diarrhoea (13%). Inability to take fluids orally and electrolyte imbalance were the main reasons for admission. Patients were discharged

once hydration improved and they were able to tolerate fluids orally. Most of them (75%) needed admission for further management. Their mean length of stay was 4.0 ± 1.9 hours (95% CI = 3.0–5.0 hours). In Singapore (8), cardiac-related chest pain contributed to about 19% of admitted cases and was the second common clinical problem after abdominal pain. The mean length of stay of these patients was 4.8 ± 8.6 hours. We do not have adequate facilities and trained staff to monitor this group of patients. In this study, another 13% of admitted cases consisted of patients with fever, and they usually stay for about three hours. In Singapore (8), the third cause of admission was fever (9.3%), and patients usually stayed for about two hours.

Four mild head injury patients (3%) were observed for at least nine hours (95% CI = 7.1–12.2 hours). This percentage of admitted cases was almost similar with the Singaporean study (2.4%), but the length of stay of those patients was about five to six hours (8). By principle, we were not supposed to admit mild head injury patients in the OW. Reasons included lack of staff and inadequate monitoring system in the OW. However, sometimes the beds in the ward were fully occupied; therefore, the OW was the next option. Few papers in the literature have commented on the appropriateness and the safety of the OW in managing head injury patients (10).

Most of the admitted patients could be discharged. Only 15.3% of them required hospitalisation. This finding was not much different from the Singaporean study (19%) and the Indian study (21%) (8). Indications for ward admission are according to the recent available criteria and physician suggestions. Our references are from a book written by Leonard R. Fank entitled *Admission and Discharge Decisions in Emergency Medicine* (11). In the future, these criteria should be validated in the context of the Malaysia perspective.

The standard length of stay depends on the purpose or the function of the OW (i.e., assessment unit or observation ward). Cooke et al. defined an assessment unit as an area where emergency patients are assessed and initial management is undertaken by inpatient hospital teams. Patients are only in this area while early assessments are being made, for example, up to 12 hours, and then they are moved to another ward. Cooke et al. defined the observation ward as an area where patients can be observed or have early investigation/management within the A&E department. Patients are admitted to this area with an expectation of discharge within 24 hours (12). Bentman et al. used a mean length of stay

cut-off point of less than 18 hours to determine the efficacy in their study (13–16). Lack of staff, especially during the night shift, is a major deficiency in our ED. The on-call physicians have to make a decision on a patient's disposition before the night shift. The OW should be managed or staffed by senior personnel or EPs (17,18).

In this study, the mean length of stay for adult patients was 4.12 ± 1.78 hours (95% CI = 3.8–4.4 hours). As a comparison, the mean length of stay stated in the Singaporean and Indian studies were 5.6 and 7.7 hours, respectively. By looking at the present data, probably a mean length of stay less than four hours seems to be efficacious, though further justification needs to be made in terms of number of staffs and the adequacy of OW medical facilities. We need further prospective studies to determine the effectiveness and efficiency of the OW.

In the Malaysian context, the OW was managed either by the emergency department specialist or inpatient specialist team. This practice may influence the orientation of OW existence and is the subject of a conflict of interest. EP have a greater role in developing this unique ward in their departments. However, a few factors need to be emphasised to ensure the OWs run effectively and efficiently. Vital components that need to be improved include clear definition or criteria of OW admission and discharge, ability to maintain the flow of patients through the ward, access to regular senior consultations, good diagnostic facilities and access to external agencies for discharge planning.

The OW at HUSM offers a few advantages. It improves patient care flow, avoids unnecessary admission and improves satisfaction. It allows the health care provider to re-evaluate a patient's diagnosis and treatment. Consultants are more content in conducting bedside teaching in OWs. Postgraduate students also have an opportunity to review the patients frequently and help in data collection for the dissertation topics.

Conclusion

The OW of HUSM is effective in managing adult patients as determined by hospitalisation rate and the length of stay. A protocol prior to admission to the OW at HUSM should be done for common diagnoses to improve the general performance of OWs. There is a lot of room for improvement to develop an ideal OW, either for HUSM in particular or the Malaysian Public Hospital in general. Further evaluation or study on administration and clinical work within this ward needs to be conducted and analysed to achieve a similar standard throughout the country.

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Author s contributions

All authors have contributed equally to the conception and design of the study, and drafting the article.

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Angioarchitecture of Brain Arteriovenous Malformations and the Risk of Bleeding: An Analysis of Patients in Northeastern Malaysia

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Abstract

Background: Central nervous system arteriovenous malformation (AVM) is a vascular malformation of the brain and involves entanglement of veins and arteries without an intervening capillary bed. Affecting predominantly young male patients, AVM presents with different clinical manifestations namely headache, seizures, neurological deficit and intracranial haemorrhage. The patients who present acutely with intracranial bleeding have a significant morbidity and mortality. The aim is to study the angioarchitecture of brain AVM (BAVM) and determine the risk factors for intracranial bleeding. Ultimately, the goal of the study is to look for the association between volume of haematoma and architecture of BAVM.

Methods: A cross-sectional study of 58 patients was conducted at the Hospital Universiti Sains Malaysia. Data were collected over a period of seven years (2000 to 2007) to look for the association between the angioarchitecture of brain arteriovenous malformations (BAVM), haemodynamics and the natural history and risk of intracranial haemorrhage.

Results: BAVM was predominantly found in young male patients in 65.5%. Small nidal size (P-value=0.004), deep location (P-value=0.003) and deep venous drainage (P-value=0.006) were found to be significant factors contributing to intracranial haemorrhage. All patients with coexisting intranidal or prenidial aneurysms presented with intracranial haematoma.

Conclusion: The angioarchitecture of BAVM like nidal size, deep location and deep venous drainage can predict the risk of intracranial bleeding and can help in the management of high risk patients without any delay. Small sized and deep seated lesions have a diffuse type of intracranial bleed which eventually need more attention to the managing team as diffuse haematoma indicates more insult to brain.

Keywords: angioarchitecture, brain arteriovenous malformation, intracranial haemorrhage, stroke, neurosciences, neuroradiology

Introduction

Brain arteriovenous malformation (BAVM) is a vascular malformation in the supratentorial and infratentorial compartments of the brain (1). It consists of a tangle of veins and arteries without an intervening capillary bed. It predominantly affects young male patients and presents with different clinical manifestations, such as headaches, seizures, neurological deficits and intracranial haemorrhage. The patients who present acutely with intracranial bleeding have significant morbidity and mortality (2). The purpose of this study was to identify the risk factors for intracranial bleeding associated with

BAVM in patients referred for angiography and management from the Hospital in the North and North East of Malaysia. This study also enabled us to examine the association between the haematoma volume and the angiographic architecture of brain arteriovenous malformations.

Materials and Methods

This was a cross-sectional study of inpatients at the Department of Radiology, Hospital Universiti Sains Malaysia (HUSM), collected from the year 2000 to 2007. A total of 58 patients were included, after excluding patients with vein of Galen malformation, dural arteriovenous fistula and brain haemangiomas. The demographic

features and the first clinical manifestations that brought patients to the hospital were evaluated by patient interviews or were recorded from case notes.

Intraarterial digital subtraction angiography (IADSA) was performed via femoral artery puncture and selective four- or six-vessel cerebral catheterisation. The imaging system used was manufactured by Advantage GE Medical Systems. Routine views were taken, including: a) AP and lateral views for the internal carotid artery run; b) Towne's and lateral views for the vertebral artery run; and c) additional views such as oblique and cross compression, whenever necessary. Non-contrast computed tomography (CT) scanning was performed with a helical multislice scanner (Lightspeed, GE Medical systems) with a slice thickness of 3.5 mm from the base of the skull through the posterior fossa, followed by 7.5 mm contiguous axial sections to the vertex, with a KVP of 120 and an MA of 200. Pre-treatment CT scans and MR images were used.

The nidal size of the lesion was measured on a cerebral angiogram in both the antero-posterior and lateral views, but the maximum linear diameter in any plane was considered for this study. When the calibration was not marked on the images, the diameter of the genu of the petrous portion of the internal carotid artery (5 mm) was used as a reference for sizing a nidus, either using callipers or a customised scale on paper (2–3). Venous drainage, feeding-artery aneurysms and location were further evaluated using cerebral angiograms and CT scans or magnetic resonance imaging (MRI). Nidal size was classified per Spetzler Martin's grade (4).

Arterial feeders were divided into two categories: superficial supply and deep supply. The superficial supply categorisation included cortical branches of the anterior, middle, and posterior cerebral arteries (ACA, MCA and PCA). The deep supply categorisation included perforating branches, choroidal arteries, and posterior fossa arteries. Mixed supply from both the superficial and deep arteries was considered to be deep supply. The location was grouped under two main categories: superficial and deep. The superficial areas were the temporal, frontal, parietal and occipital lobes. Deep-seated BAVM was a lesion that was situated at the basal ganglia, corpus callosum, thalamus or cerebellum.

Venous drainage was divided into two subgroups: superficial and deep. Superficial drainage was considered present if all the drainage from the BAVM was through the cortical venous system and the cerebellar hemispheric veins. The venous pattern was considered deep if any or all of the drainage was through the deep

cerebral veins, such as the internal cerebral vein, the basal veins, the precentral cerebral vein or in the venous sinuses. Aneurysms were categorised as either present or absent.

The patients who solely presented with intracranial haemorrhage were analysed and the type and pattern of haemorrhage was recorded from the CT scan images. Patterns of haemorrhage were further divided into focal and diffuse where focal meant intraparenchymal haematoma (IPH) only, whereas diffuse included intraventricular (IVH), subarachnoid or intraparenchymal haematomas. Patients who presented with solely subarachnoid haemorrhage (SAH) were further graded according to the Fisher score (5), and any association between the angioarchitecture of BAVM was analysed using McNemar's test.

Statistical analysis was performed using SPSS for Windows (version 12.01) software. The association between the angioarchitecture of BAVM and intracranial haemorrhage was analysed using multiple logistic regression (backward model). The objective was to evaluate the association between the angioarchitecture of BAVM and patterns of haematoma using Pearson's chi-square and Fisher's exact tests.

Results

Patient ages ranged from 5 to 61 years. The mean age and standard deviation were 26.7 years ($SD \pm 12.96$). The median age was 23.50 years. A preponderance of males was noted in this study; the sample population consisted of 38 (65.5%) males and 20 (34.5%) females. Additionally, out of the 40 (69%) patients who presented with intracranial haemorrhage, 27 (67.5%) were males and 13 (32.5%) were females. Among the 58 patients, 82.8% were Malays, 8.6% were Chinese, 5.2% were Indians and 3.4% were Siamese. Sixty-nine percent of the patients arrived at the emergency department with a clinical presentation of intracranial haemorrhage and were investigated using non-contrast CT scanning. Nineteen percent of the patients presented with seizures, and these patients were evaluated by contrasted CT or MRI or both.

In total, 8.6% of patients presented with headache and 3.4% with neurological deficit. These patients were also evaluated using contrasted CT, MRI or both. The BAVM patients, who presented with intracranial haematomas, had different types of bleeding: a total of 29.3% presented with no bleeding; 18 patients (31%) arrived with solely intraparenchymal haemorrhage; 17 patients (29.3%) had intraparenchymal bleeding and, at the same time, intraventricular bleeding;

three patients (5.2%) had both subarachnoid and intraventricular bleeding; two patients (3.4%) had subarachnoid and intraparenchymal haemorrhage; and one patient (1.7%) had all three types of bleeding: intraparenchymal, intraventricular and subarachnoid haematomas. A total of six patients who presented with subarachnoid haemorrhage were further graded based on their CT Fisher scores, and all were found to have a score of four, which suggests that SAH was extended either intraparenchymally, intraventricularly, or both.

A multivariate model was constructed using multiple logistic regression to further test for significance (Table 1). Small size of nidus (P-value=0.004) and deep lesions (P-value=0.003) were significant predictors of intracranial bleed. Venous drainage failed to show any significance in the multivariate model, even though was significant at the univariate level (P-value=0.858), in relation to intracranial haemorrhage. No association between angioarchitectural factors and patterns of haematoma were found at the univariate level. Six patients presented solely with subarachnoid haemorrhage, and all of them had a score of four. No significant relationship was found between size of nidus and the other angioarchitectural factors (venous drainage, site of lesion, and draining veins) in the Fisher scores of four patients, using McNemar's test.

Discussion

This study revealed that in the sample population, haemorrhage was the main clinical event and accounted for 69.0% cases at the initial presentation. This observation may indicate that acute onsets of symptoms are quite easily

diagnosed as cases of BAVM, but unfortunately other clinical manifestations, such as seizures and headaches, may be missed or misdiagnosed. The remaining 31% presented with other clinical manifestations. For the 58 patients, the age range was 3 to 61 years and the mean age was 26.67 (SD ± 12.96) years; this shows that the population harbouring BAVM was relatively young, compared to Western populations (6). We also observed a higher preponderance of male patients than female patients, with a ratio of 1.9:1. Malays (82.8%) were found to be at the highest risk, however, this result is biased because the population consists more of Malays. There are a variety of haemorrhage types represented; solely intraparenchymal bleed (31%) followed by a combination of intraventricular bleeding and intraparenchymal haematoma (29.3%). No patients presented with only subarachnoid haemorrhage, but many presented with a combination with either intraparenchymal or intraventricular bleeding. Six patients had subarachnoid haemorrhages, and all had Fisher scores of four. Only one patient had diffuse bleed with subarachnoid, intraparenchymal haematoma and intraventricular bleeding at the same time

Small nidal size was found to be an independent predictor for intracranial haemorrhage in both univariate (P-value=0.000) and multivariate models (OR=19.8, P-value=0.004, 95 %CI=2.7–142.9). Additionally, 64.9% of patients had nidal size of less than or equal to 3 cm, of which 86.5% presented with intracranial bleed. This association of small size with intracranial bleeding is in accordance with many studies. The risk factors for intracranial bleeding have been researched as early as 1980 by Guidetti and Delitala followed by Graf et al. in 1983, Crawford et al. in 1986, and Stapf et al. in 2006 (7–10).

Table 1: Results of a multivariate analysis to determine the association between the angioarchitecture of BAVM and intracranial bleeding

Variable	n	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Size of nidus					
<3 cm	20	0.08	0.000	19.8 (2.7-142.9)	0.004
3-6 cm	37	(0.0-0.3)			
Venous drainage					
Superficial	26	5.40	0.007	0.79 (0.06-10.3)	0.858
Deep	32	(1.6-18.4)			
Location					
Superficial	28	18.7	0.000	0.01 (0.0-0.2)	0.003
Deep	30	(3.7-94.1)			

Deep venous drainage was a significant factor at the univariate level in relation to intracranial haemorrhage (P-value=0.007); however, it failed to show any significance at the multivariate level. This goes against most of the studies in which venous drainage was an independent factor in causing intracranial haemorrhage (9–11). This may be due to the small number of patients in our study.

The morphologies of the draining veins were not assessed in detail, because they have been recorded in two previous studies carried out by Miyasaka in 1992 and Nataf et al. in 1997 (12,13). The morphology of the venous drainage is a very important factor in determining intracranial haemorrhage because it contributes to the haemodynamics of the lesion.

Deep location was an independent risk factor for intracranial haemorrhage in both the univariate and multivariate models (OR=0.01, P-value<0.05, 95% CI=0.0–0.2) in our study. Overall, 51.7% of BAVM had a deep location, of which 93.3% had a haemorrhagic presentation, which is consistent with major studies (6,11). We found that feeding arteries were not a significant factor for intracranial bleeding, (P-value>0.05, OR 0.01, 95% CI) which was consistent with the results of Stefani et al. in 2000 (12).

In this study, 70.8% of patients with superficial and 67.6% of patients with deep supply presented with intracranial bleeding. Most of the lesions had a mixed supply from both the superficial and deep arteries, and, as mentioned above, they were considered to be deep supply arterial feeders. Therefore, we can postulate that mixed arterial supply can reduce the intranidal pressure within the lesion and, subsequently, these lesions have less of a tendency to bleed (14).

All patients who had aneurysm coexisting with brain arteriovenous malformation had intracranial haematoma, which is significant clinically. However, due to a small sample size of six patients harbouring aneurysms, it was not found to be a statistically significant predictor of intracranial haemorrhage. This result is different than those of most other studies (15,16). However, the presence of aneurysms was clinically significant, as 100% of BAVM cases with aneurysm had intracranial haemorrhage. The prevalence of coexisting aneurysms was 8.6%. Only five patients out of 58 had aneurysms; all of them presented with haemorrhage. Four patients had intranidal and one patient had prenidial aneurysmal dilatation. The size of the nidus, location, venous drainage, arterial feeders and the presence of aneurysms were not significant

factors (P-value>0.05) influencing the patterns of intracranial haematoma.

The patients presenting with subarachnoid haemorrhage had a Fisher score of four. They were analysed using McNemar's test to examine the association between size and other angioarchitectural factors such as venous drainage, location of the lesion and arterial feeders, but no factors were found to be significant, with a P-value>0.05.

Conclusion

From our study, we can conclude that young male patients with a mean age of 26.6 years were found to be more prone to BAVM. Most patients (69%) presented with intracranial haemorrhage, followed by seizures (19%), headaches (8.6%), and neurological deficits (3.4%). The patients who presented with intracranial haemorrhage and/or intraparenchymal haematoma constituted the most common type of bleeding.

The angioarchitectural factors, namely, small nidal size, deep seated lesions and deep seated venous drainage, are predictive of the risk of intracranial bleeding. Coexisting aneurysms are a clinically significant factor predicting intracranial bleeding. Small nidal size is 2.7-times more likely to be related to bleeding than large nidal size, and deeply located BAVM is 0.2 times more likely to involve bleeding.

Radiologists or neuroradiologists who diagnose BAVM must note that certain angioarchitectural factors, such as small nidal size, deep seating lesions and deep venous drainage, increase the risk of intracranial haemorrhage. These patients will need to be referred either to neurointerventional radiologists, neurosurgeons, neurologists or radiosurgeons, as a multidisciplinary approach is required for appropriate management.

Author s contributions

SK and MSA contributed equally to the conception and design, data collection, analysis and interpretation, drafting of the article and revision. Statistical expertise: NNN

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Abstract

Phonophobia and hyperacusis are two separate but closely related symptoms that are often mistakenly used in clinical practice as the same entity. Here we present a case report to highlight the distinguishing features of both and discuss the steps of management in these conditions. It is vital for the attending doctors to recognise hyperacusis and phonophobia as different entities to manage them successfully.

Keywords: hyperacusis, phonophobia, medical sciences

Introduction

Phonophobia is defined as a persistent, abnormal, and unwarranted fear of sound. Often, these are normal environmental sounds (e.g., traffic, kitchen sounds, doors closing, or even loud speech) that cannot under any circumstances be damaging. Phonophobia may also be related to, caused by, or confused with hyperacusis, which is an abnormally strong reaction to sound, occurring within the auditory pathways, in levels that would not trouble a normal individual (1).

Case Report

A 12-year-old girl was referred to the Ear, Nose and Throat (ENT) clinic with reported acute, electrifying, intensified noise sensations in both ears when hearing sudden loud sounds. The symptom started after a history of exposure to the sudden loud sound of fire-crackers at a Chinese New Year celebration a few months earlier. Since then, she began experiencing abnormally intensified sounds followed by unpleasant buzzing noises every time she was exposed to normal intensity sounds. For example, the sound of balloon popping or the rustle of a plastic bag were almost unbearable to her, to a point where she developed palpitations, shivering, excessive sweating and crying. She denied other otological symptoms and has never been operated on in the ear before. Her condition gradually worsened such that she only wanted to spend her time in a quiet room and was no longer attending social functions in school.

Her parents denied that she experienced any psychiatric comorbidities, and she was developmentally normal until this event. It was very difficult to get a thorough history from the distressed girl, so we proceeded with the investigations to rule out causes of hyperacusis. A thorough ENT clinical examination, including otological and neurological assessments, showed normal findings. She subsequently underwent audiological tests that included pure tone audiometry, the stapedius reflex and the auditory evoked potential, which also showed no abnormality. Magnetic resonance imaging (MRI) of her skull revealed no lesions in the brain, pons or the auditory pathway.

She was then referred to a psychiatrist whom later, after a thorough psychiatric evaluation, diagnosed the girl with phonophobia based on the DSM-IV criteria for specific phobia (2). She had two weekly therapy sessions which included psycho-education for both parents and patient, relaxation exercises and graded exposure behavioural therapy. Psycho-education allows the patient to ventilate her problems, and the parents to cope with anger and frustration and subsequently participate in the child's behaviour intervention. Relaxation techniques involved breathing exercises and progressive muscle relaxations. Graded exposure desensitisation started with the least provoking stimulus at first, for example drawing a smiling balloon and then drawing a bursting balloon. After the child was comfortable with this, the stimulus was then increased to bursting inflated balloons in the clinic and at home with parents acting as a co-

therapist. Each successful session was rewarded accordingly. The child showed tremendous improvement in her symptoms after 3 months of therapy. Gradually, the child was brought to public places (e.g., a restaurant) and finally was brought again to watch a fireworks show, with no resulting complications after 6 months of therapy.

Discussion

Hyperacusis and phonophobia are two subjective phenomena that sometimes are indistinguishable, as their descriptions very much rely on information from the patient. The definition of both can also be confusing, and in many medical publications, the terms hyperacusis and phonophobia have been used in the same context. The definition of hyperacusis put forth by Jastreboff and Hazell has been widely accepted (1). They stated that hyperacusis is an abnormal sound sensitivity arising from within the auditory system, either peripheral or central. This may explain why there should be some abnormality in the audiological examinations or investigations noted with true hyperacusis (3). However, they went on to suggest that decreased sound tolerance consists not only of hyperacusis; it also consists of a fear of sound known as phonophobia or a strong dislike of sound called misophonia. Jastreboff and Hazell describe a patient with misophonia or phonophobia as having abnormally strong reactions of the limbic and autonomic nervous systems but do not involve a significant activation of the auditory system, as hyperacusis does. Phonophobia, to them, is an extreme form of misophonia. Based on this description, misophonia and phonophobia can therefore arise from hyperacusis and may not be totally different entities after all.

True phonophobia, or sometimes termed 'ligyrophobia' is a psychiatric disorder where there is usually no or minimal abnormality in the peripheral or central neuro-audiological pathways. Here certain learning or conditioning processes lead to the development of specific reactions and avoidance patterns to certain acoustic stimuli (1). Phonophobia is also used within the neurological literature to describe sound intolerance in migraine headaches, and this can add to further confusion in its own real definition.

A study to estimate the prevalence of hyperacusis and phonophobia among school-aged children concluded that their prevalence was around 10 percent of the population (4). Clinically, hyperacusis can be caused by lesions in the peripheral or central auditory system

(3,5). Myasthenia gravis, Bell's palsy, Ramsey Hunt Syndrome, Meniere syndrome, noise-induced hearing loss and other sensorineural auditory disorders are known peripheral causes of hyperacusis. Central causes can be from migraine headaches, depression, head injury, William's syndrome, multiple sclerosis, transient ischaemic attack, Lyme disease, Addison's disease and stimulant drug dependency.

Patients with hyperacusis or phonophobia may first seek treatment in the general practitioner's clinic or general outpatient clinics, and these doctors usually then refer the patient to specialty clinics (e.g., the ENT, psychiatry or neurology) or the general physician's clinic according to the suspected diagnosis. Thus, taking the medical history is vital at the first consultation for correct referral to the specialty clinic. However, the distinction between hyperacusis or true phonophobia often cannot be made simply from the history, especially in children. Thus, the patient should be investigated at least to rule out causes of hyperacusis. Objective audiological assessments are among the tests that can be performed, including the acoustic reflexes and the auditory evoked potentials, together with MRIs to rule out peripheral and central causes within the auditory system (4,5,6). However, there should be some caution when it comes to testing hyperacusis patients with any procedures that involve loud sounds (i.e., the acoustic reflexes and the auditory evoke potential) because these tests may aggravate the sound intolerance, especially in children (5). In our case, we ordered these tests only after careful consideration and explanation to the patient and the parents of its potential drawbacks. When all the otological and audiological signs and investigations are negative, we must always remember to look for other related components of hyperacusis (i.e., the neurologic, endocrinologic and psychiatric causes). Blood investigations may be ordered to rule out underlying endocrinological causes, but only upon clinical suspicion from the history and physical examination, and they should not be routinely performed. MRI is expensive and not widely available, but it is useful to rule out certain central causes of hyperacusis. However, it again should not be a routinely performed test here.

Like all fears and phobias, phonophobia is created by the unconscious mind as a protective mechanism. According to DSM-IV classification, specific phobias like phonophobia are characterised by clinically significant anxiety provoked by exposure to a specific feared object or situation, leading to avoidance behaviour (2). At some point in the past, there was likely an event

linking loud noises and emotional trauma, and a detailed history of the event is often required. As with all other phobias, treatment of phonophobia may involve behavioural, cognitive and drug therapies. Phonophobia is a treatable psychiatric condition, often with a good prognosis. Despite successful treatment in our case, we would like to reiterate that it was not a proof that phonophobia and hyperacusis are distinct entities at all times. In practice, most people with hypersensitivity to environmental sound have both hyperacusis and phonophobia together in varying proportions. In treating these conditions, it is important to diagnose which condition is present and which is dominant. Baguley and Andersson, in their latest book on hyperacusis, suggest that “addressing hyperacusis must always involve the classical auditory system and also systems of emotion and behaviour—and as such is both physiological and psychological at the same time” (7). In many cases, their statement is valid.

In conclusion, phonophobia and hyperacusis are parts of sound intolerance phenomena with different involvements of audiological, emotional and behavioural components. Phonophobia is a treatable psychiatric disorder, and the majority of patients may first present to out-patient clinics or general practitioners. Thus, the attending doctors should be able to recognise the features of phonophobia and hyperacusis to successfully manage both conditions.

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Author s contributions

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An Unexpected Cause of Hoarseness of Voice in a Healthy Teenager

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Abstract

Laryngeal amyloidosis is a rare cause of stridor in a healthy young adult. We report a case of localised laryngeal amyloidosis, including our MRI findings, which included a necrotic centre that has not previously been described. This case also highlights the need for a high index of clinical suspicion to achieve the correct histopathological interpretation.

Keywords: medical sciences, hoarseness, stridor, laryngeal, amyloidosis

Introduction

Primary amyloidosis is an unusual entity, occurring without any pre-existing primary disease. Isolated laryngeal amyloidosis is even more uncommon, accounting for less than 1% of all benign laryngeal tumours. Only two hundred such cases are reported in the literature. Descriptions of the MRI appearance of primary laryngeal amyloidosis are scarce in the literature, and the presence of a necrotic centre has not previously been described.

Case Report

RM, an 18-year-old Malay boy, presented with hoarseness of voice for a duration of one year prior to presentation. It was also associated with stridor, dysphagia, and intermittent fever. Indirect laryngoscopy revealed a polypoid mass arising from the left side of the hypopharynx and oropharynx. The lesion was excised by laser knife surgery guided by laryngoscopy under general anaesthesia. The histopathological examination results were interpreted as respiratory papillomatosis.

The patient remained asymptomatic for a year before similar symptoms recurred. During the second presentation, an MRI was done, revealing lobulated submucosal lesions involving the posterior wall of the right oropharynx, right aryepiglottic fold, vallecula, and paralaryngeal spaces bilaterally down to the hypopharynx at the level of false cord. The lesions were isointense

to the muscle on T1WI and slightly hyperintense compared to the surrounding muscle on T2WI (Figure 1). Following contrast administration, there was avid but patchy enhancement of these lesions (Figure 2). There was a cystic area in the right pyriform fossa that did not show enhancement. The appearance of the non enhancing cystic paralaryngeal lesion most likely represents a necrotic centre (Figure 3). True cord and subglottic larynx were normal. Based on MRI analysis, the probable diagnosis of recurrent juvenile papillomatosis in the right oro- and hypopharynx was made which has caused localised narrowing of the laryngeal vestibule.

A chest X-ray done during the second presentation did not show any evidence of luminal narrowing involving the tracheobronchial tree.

The initial diagnosis of laryngeal papillomatosis was doubted by the primary managing team, as the age of presentation was atypical. The pathologist reviewed the slides from the original biopsy sample, which showed the presence of amorphous eosinophilic material in the stroma that was positive for amyloid after Congo red staining, consistent with a diagnosis of amyloidosis.

Discussion

Amyloid is derived from the Greek words amylo, meaning "starch", and eidos, meaning "resemblance". The clinical presentation encompasses a wide spectrum, ranging from a potentially lethal condition or merely an

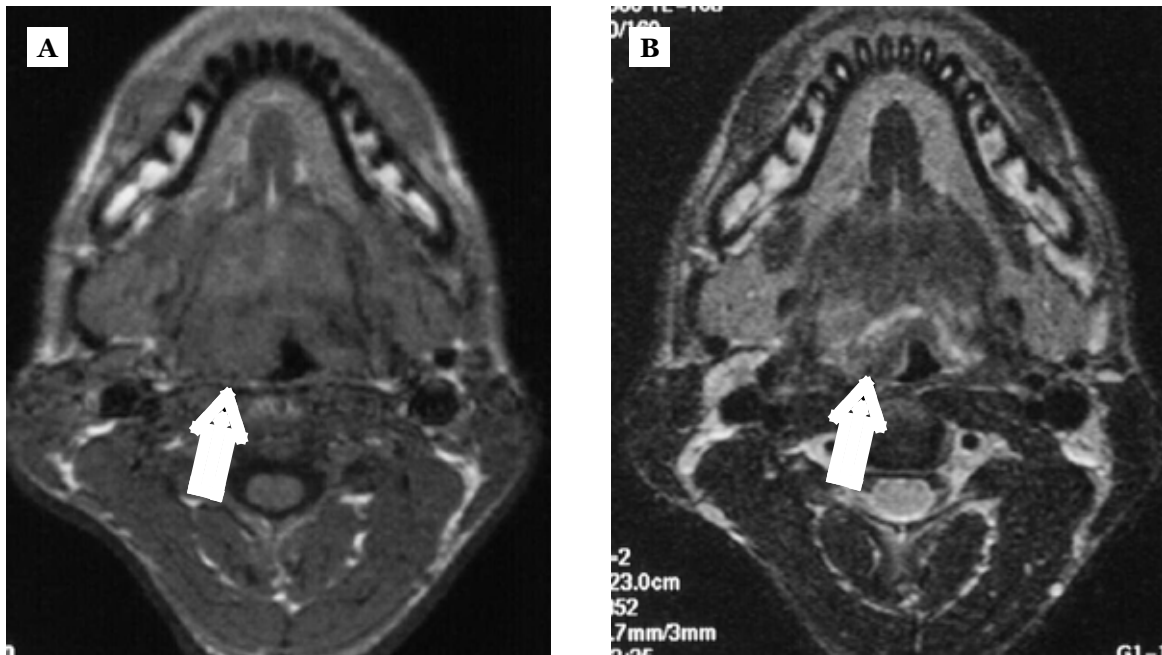


Figure 1: Axial images showing a submucosal lesion involving predominantly the right aryepiglottic fold, which is isointense on T1WI (A) and has intermediate signal intensity on T2WI (B).

incidental finding. The symptoms depend on the site affected and the magnitude of the amyloid deposition (1). Amyloid is composed of pathological proteinaceous material deposited in between cells of various tissues. It can occur in variety of clinical conditions (1). Consequently, amyloidosis should be regarded not as a single disease but as a group of diseases that exhibit tissue deposition of protein that displays a similar histological appearance (1). Under light microscopy with standard tissue staining, amyloid deposits will appear as an amorphous, hyaline, eosinophilic extracellular material. The material may appear to be encroaching on or producing pressure effects on the adjacent cells (1).

Amyloidosis can be categorised based on its biochemical-clinical manifestation (1). In this classification scheme, amyloidosis is divided into systemic amyloidosis and localised amyloidosis. Clinically, systemic amyloidosis can be subclassified as a primary or secondary lesion (1). Primary amyloidosis is associated with immunocyte dyscrasia, whereas secondary amyloidosis is associated with chronic inflammation or tissue destruction (1). Localised amyloidosis is limited to a single organ without involvement of other sites. This case is an example of localised amyloidosis occurring at the larynx. No amyloid-associated disease was detected in this patient.

The respiratory tract may be affected diffusely or focally from the larynx to the smallest bronchioles (1). In the larynx, amyloidosis may appear as a deposition of acellular eosinophilic material infiltrating the connective tissue stroma (in a haematoxylin- and eosin-stained section) and forming a nodular lesion. With increasing amount of amyloid deposition, pressure effect exerted may render the seromucinous glands to disappear while the covering epithelium remains intact (2). Frequently, mononuclear inflammatory cells can be seen at the periphery of the amyloid material. This may correspond to a localised form of immunocyte-derived amyloid (1).

The diagnosis ultimately depends on identification of this proteinaceous material in appropriate biopsy specimens (1). The amyloid deposits may be confused with other hyaline material, such as collagen or fibrin (1). Histological diagnosis of amyloidosis is best supported by Congo red immunochemical staining, which imparts a pink or red colour to amyloid deposits under ordinary light and produces a green birefringence under crossed polarised light. This appearance is shared by all types of amyloid material due to the cross- β -pleated configuration of the amyloid fibrils (1). In the present case, the histopathological evaluation during the first presentation may have missed the amyloid material in view of the low clinical suspicion of amyloidosis and scanty presence of

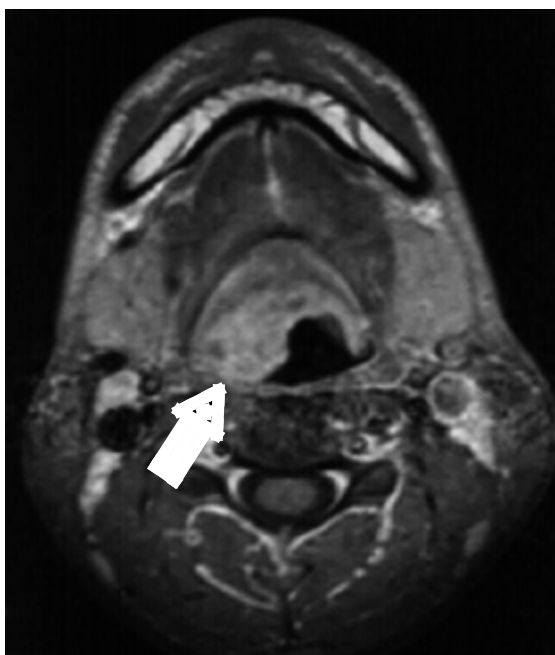


Figure 2: Axial T1WI with gadolinium showing avid but patchy enhancement of the lesions involving the aryepiglottic folds.

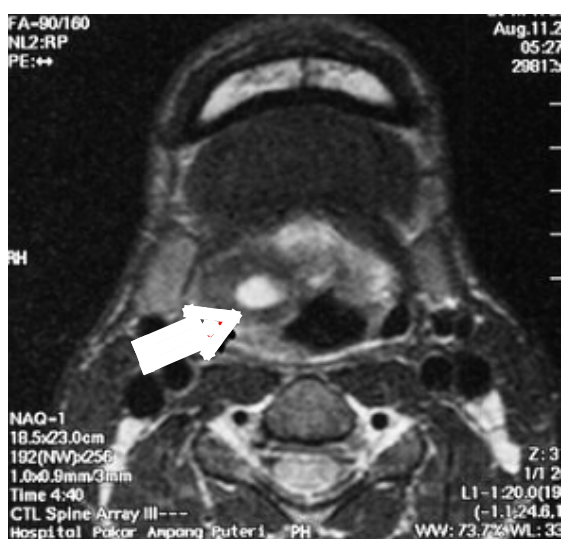


Figure 3: T2WI showing the focal area of high signal intensity within the lesion in the right paralaryngeal space; this is likely to represent necrotic tissue.

amyloid material. As amyloid deposition in the upper respiratory tract is generally submucosal in nature, it may form a polypoid lesion. On histopathological examination, the polypoid lesion caused by amyloid deposition is lined by stratified squamous epithelium, resembling the epithelial lining seen in polyps due to papillomatosis.

Laryngeal amyloidosis was first documented in 1875 as reported by Fernandes et al. (3). It is rare, accounting for less than 1% of all benign laryngeal tumours. Only over two hundred cases have been reported in the literature. Laryngeal amyloidosis occurs most commonly in the fifth decade of life with male predominance (4,6). In laryngeal amyloidosis, disease is usually localised to the larynx, and the aetiology is usually primary (4). The ventricles and false vocal folds are affected most frequently (4,5).

Few descriptions are available in the literature regarding the MRI features of laryngeal amyloidosis (4). To our knowledge, there are also no previous reports of laryngeal amyloidosis with necrotic centre. On T2-weighted images (T2WIs), the lesion may appear to have a slightly higher signal than the surrounding muscles, as seen in this case, but it may also appear hypointense relative to the surrounding muscles (4). On T1WI, lesions are similar in intensity to the peripheral muscles, showing marked contrast enhancement (4,6). Therefore, imaging is non-specific, and its role is mainly to evaluate the extent of the disease and to rule out other differential diagnoses (6).

The therapy of choice is local excision (i.e., CO₂ laser resection) (4). Amyloidosis is a benign process. Nonetheless, it can be progressive or can recur after treatment. Regular follow-up with MRI is thus recommended, as its recurrent nature may require repeated surgical interventions (7).

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Endoscopic-assisted Enucleation of Radicular Cysts — A Case Report

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Abstract

The standard management for the majority of benign jaw cysts is enucleation, marsupialisation, curettage and decompression. Enucleation has the advantage that the whole specimen is sent for microscopic evaluation so that more sinister pathological processes (i.e. squamous cell carcinoma) may not be missed. In a large cystic lesion, enucleation is still possible, but technical difficulties might be encountered. In such instances, inevitable damage can occur to the surrounding structures. We report a case of a large radicular cyst of the maxilla that was enucleated via endoscopic assistance through the Caldwell Luc approach.

Keywords: jaw cyst, endoscope, enucleation, Caldwell Luc, medical sciences

Introduction

Epithelial jaw cysts are the most common cause of benign swelling of the jaw and can be further divided into inflammatory and developmental types. Radicular cysts are the most common among the inflammatory types and occur solely at the apices of non-vital teeth as a reactive process, especially in adults. They form as a result of the stimulation of the odontogenic epithelium (rests of Malassez) in the vicinity of the root tip, by the necrotic pulp, and the contents of the root canal system. Different forms of treatment of jaw cysts have been described, such as enucleation, curettage, decompression, marsupialisation and resection with or without jaw continuity. However, in large cysts that extend into the maxilla, difficulties may be encountered due to the limited exposure and access for the enucleation unless a generous incision is made. In this situation, a rigid endoscope used in a Caldwell Luc procedure may facilitate the enucleation of the cyst.

Here, we report a case of a large radicular cyst that displaced the floor of the maxillary sinus superiorly and was enucleated via endoscopic assistance via the Caldwell Luc approach.

Case Report

A 26-year-old female presented with persistent frontal headaches that had lasted for four months associated with left-sided facial fullness and pain, rhinorrhoea, itchiness, post-nasal drip, and alternating nasal blockage. She was initially treated for allergy rhinitis with steroid nasal spray and showed some response. However, the frontal headache persisted along with the left facial fullness and pain. There was no significant past medical history. Upon examination, there was a mild swelling on the left side of her face, with obliteration of the nasolabial and nasomaxillary groove but with normal-looking overlying skin. Anterior rhinoscopy revealed a slight bulging of the floor of the left nostril, and it appeared to be soft in consistency upon palpation using a nasal septum elevator. Examination of the middle third of the left nostril by rigid 0-degree endoscopy revealed a medialised uncinate process, and no mass or pus was observed in the middle meatus. There were no enlarged regional lymph nodes. All cranial nerves were intact. The occipito-mental view of her sinus X-ray revealed only haziness of her left maxillary sinus area. A CT scan of the paranasal sinus revealed a well-defined expansile, non-enhancing, homogenous soft tissue mass occupying the whole left maxillary sinus, massively affecting the surrounding



Figure 1: CT scan picture illustrating a cystic mass displacing the floor of maxillary sinus (arrow) giving a double wall appearance

walls and exhibiting a double wall appearance superiorly (Figure 1). The mass was arising from the alveolar process of the left maxilla without the presence of the impacted tooth within. Based on the patient's history, physical examination and CT scan findings, we concluded that she had a benign jaw cyst. Excision of the cyst was planned and intraoperatively under general anaesthesia, a sublabial incision was employed after local anaesthesia was administered at the upper left gingivobuccal sulcus. Initially, enucleation was performed under direct visualisation, but as the cyst extended superiorly, pushing the floor of the maxillary sinus until it approached the roof of the maxillary sinus, further enucleation was hampered by poor visibility and illumination. From this point onward, enucleation was carried out with the assistance of a rigid (0-degree) endoscope, which was held with the most dominant hand while the other hand performed the enucleation. The cyst was noted to have been attached firmly to the root of the erupted left upper canine, which was subsequently extracted. The patient's postoperative period was uneventful, and she was discharged on the second postoperative day. Postoperative histopathological examination reported the mass as a radicular cyst.

Discussion

Endoscopy is the visual examination of the inside part of a body cavity, structure or hollow organ. The word endoscopy comes from the Greek words 'endo,' meaning 'inside,' and 'skopein,' meaning 'to examine.' (1). One of the advantages of an endoscopic technique is the avoidance of extensive tissue damage during the operation, thus minimising blood loss and reducing postoperative morbidity. There are many options in the management of benign jaw cysts, such as enucleation, curettage, decompression, marsupialisation, and resection with or without jaw continuity. However, enucleation has the advantage that the whole specimen can be sent for a complete histological evaluation. This is recommended to ensure that a more sinister pathological lesion is not missed, such as squamous cell carcinoma (2). In smaller-sized cysts, enucleation can be accomplished without many problems. However, in some instances, the cyst can be very big and can occupy the entire maxillary sinus, making complete removal difficult unless a generous incision is made either sublabially or via a lateral rhinotomy incision. This approach is overly aggressive for such a benign lesion. In this situation, the assistance from a rigid nasoendoscope (4.0-mm, 0-degree

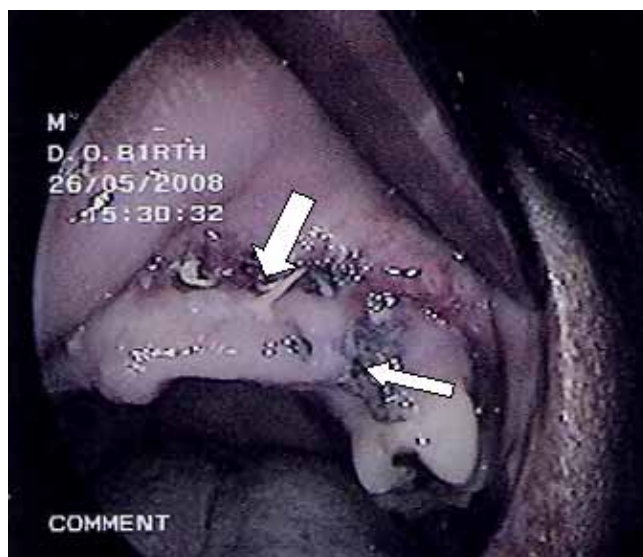


Figure 2: Sublabial incision scar (thick arrow) and site of extracted left canine (thin arrow)

Hopkins endoscope) is helpful in guiding the enucleation of the cyst safely without affecting the surrounding tissues. A suction elevator was used to separate the cyst from the surrounding bone, as the surgical field was slightly bloody. This technique not only reduces the size of the incision required, but it also offers a superior visualisation of the difficult corners and angles around the posterior and superior aspects of the lesion. Furthermore, it provides good illumination and a clear and magnified visualisation of the operating field, and thus it results in a more conservative surgery with precise enucleation. Furthermore, with the presence of important structures nearby, such as the orbital apex, infra-orbital nerve and internal maxillary artery, meticulous enucleation is necessary and can be safely performed via endoscopic assistance.

There is very little literature describing the use of an endoscope for the removal of large benign jaw cysts transorally, although many surgeons have used an endoscope to extract the impacted tooth transnasally. Micozkadioglu and Erkan reported a case in which they removed a dentigerous cyst and extracted the tooth transnasally (3). Similarly, Di Pasquale and Shermetoro used the same technique in their patient (4). Suarez-Cunqueiro et al. described a case in which they used an endoscope to facilitate the enucleation of a jaw cyst (1). However, in that case, the cyst arose from the right lower third molar region, as compared to our case, which involved the maxilla.

In our case, the benign cyst pushed the floor of the left maxillary sinus and further displaced it superiorly to meet the roof of the maxillary sinus, thus exhibiting a double wall appearance on the coronal CT scan. Our initial plan was to remove the cyst via a sublabial approach. However, we encountered difficulties when approaching the superior and posterior aspect of the cyst wall. From this point onward, enucleation was carried out with the assistance of a rigid endoscope, which clearly outlined the difficult corners and provided good illumination and visualisation to the surgeon for further precise enucleation. Jaw cysts are commonly managed by the oromaxillofacial team, but in certain circumstances the presentation is not as straightforward as in our case, and referral to the otorhinolaryngology (ORL) unit was required. Handling of a rigid endoscope is a routine practice in the ORL clinic as well as in the operating room. Therefore, in cases with large cystic lesions, a combined approach between the oromaxillofacial and ORL teams is imperative to provide the most effective treatment for the patient. The decision to extract the tooth was probably unjustified in this case, after it was reviewed and discussed retrospectively with the oromaxillofacial team. Root treatment could probably have been done, and the tooth could have been saved from unnecessary extraction.

In conclusion, endoscopic-assisted enucleation of benign jaw cysts is a useful technique for large cysts because it provides superior intraoperative illumination, magnification and visualisation. This technique provides the surgeon

with an alternative approach for the removal of large jaw cysts. It reduces postoperative morbidity and avoids unnecessary tissue damage (the size of our sublabial incision was ~ 1.5 cm (Figure 2), and the size of the cyst was ~ 2.0 x 3.5 cm). A combined approach between maxillofacial and ORL teams is recommended in isolated cases of large cyst for the maximum benefit to the patients.

Author s contributions

Conception and design: KA

Data analysis and interpretation: SAK

Drafting of the article: AA

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Scalene Myofascial Pain Syndrome Mimicking Cervical Disc Prolapse: A Report of Two Cases

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Abstract

Scalene myofascial pain syndrome is a regional pain syndrome wherein pain originates over the neck area and radiates down to the arm. This condition may present as primary or secondary to underlying cervical pathology. Although scalene myofascial pain syndrome is a well known medical entity, it is often misdiagnosed as being some other neck pain associated with radiculopathy, such as cervical disc prolapse, cervical spinal stenosis and thoracic outlet syndrome. Because scalene myofascial pain syndrome mimics cervical radiculopathy, this condition often leads to mismanagement, which can, in turn, result in persistent pain and suffering. In the worst-case scenarios, patients may be subjected to unjustifiable surgical intervention. Because the clinical findings in scalene myofascial pain syndrome are “pathognomonic”, clinicians should be aware of ways to recognize this disorder and be able to differentiate it from other conditions that present with neck pain and radiculopathy. We present two cases of unilateral scalene myofascial pain syndrome that significantly impaired the patients’ functioning and quality of life. This case report serves to create awareness about the existence of the syndrome and to highlight the potential morbidity due to clinical misdiagnosis.

Keywords: cervical radiculopathy, myofascial pain syndrome, pain radiation, Scalene muscle, trigger point, neurosciences

Introduction

Myofascial Pain Syndrome (MPS) is a medical term used to describe chronic regional pain syndrome that presents with hyperirritable spots called trigger points (TPs) and/or tender spots (TSs) that arise from taut bands (TB) in the skeletal muscle. This chronic pain syndrome is often accompanied by a bizarre referred pain pattern that is specific to the muscle involved (1). Functionally, MPS causes the muscle to become weak and stiff, leading to reductions in range of movement. Thus, MPS is known as a major cause of morbidity, with a significant impact on daily activity, function and quality of life (1-6). Myofascial pain is treatable but is often under-treated due to lack of awareness among clinicians (3).

Scalene myofascial pain is a relatively common myofascial pain syndrome; however, it is commonly under-diagnosed or misdiagnosed as being some other neck pain-associated radiculopathy (2,3,4). The most preferred diagnoses among clinicians are cervical disc herniation/prolapse, cervical stenosis and

thoracic outlet syndrome (TOS), as most of these conditions are associated with neck pain and pain radiation to the arm (3,4). In other situations, the neurological symptom associated with scalene myofascial pain syndrome may either present with referred pain to the distal arm mimicking other well known causes of neuropathies, such as Carpal Tunnel Syndrome and peripheral polyneuropathy (2,4,5). These situations often lead to mismanagement and contribute to persistent pain and extra suffering (4,7). Because the clinical findings in scalene myofascial pain syndrome are pathognomonic, clinicians are expected to be able to make the diagnosis clinically in order to carry out effective management. These case reports serve to create awareness about the existence of the condition and to emphasize the relative ease of making the correct diagnosis, which can lead to successful treatments.

Case Report

Case 1

A 50-year-old Chinese woman presented to the orthopaedic clinic with neck pain associated with radiating pain and numbness over the radial distribution of her left hand. These symptoms persisted for three months without progression of neurological symptoms. She was a healthy person without any medical problems. Upon evaluation by the orthopaedic team, she was diagnosed with cervical spondylosis, presented with multiple cervical facet joint arthritis along with C6, C7 posterior cervical disc prolapse, which was confirmed by MRI. There was also minimal evidence of co-existing 6th nerve root impingement on her left side. Cervical X-rays showed no evidence of an accessory cervical rib, distorted clavicle bone fracture or elongated transverse process of C7. She was scheduled for several courses of cervical traction, in addition to being given a soft collar to prevent her from engaging in neck extension. Oral medications consisting of etoricoxib 60 mg daily (OD), gabapentin 300 mg three times a day (TDS), baclofen 10 mg TDS and neurobion 1 tablet twice a day (BD) were commenced. She was referred to the pain clinic because the pain persisted following the treatments, and she refused surgery as proposed by the orthopaedic surgeon. Cervical epidural steroid injection was also recommended by the managing team and she agreed.

In the pain clinic, the patient was re-evaluated and was found to have cervical facet joint tenderness bilaterally over the C2, C3 and C3, C4 level, in addition to pain and stiffness during both lateral flexion and extension of her neck. Neck flexion, however, did not aggravate her pain. Her left shoulder range of movement showed limited internal rotation due to pain. Tendon reflexes in the biceps (C5), supinator (C5, C6) and triceps (C7) were normal. Spurling's Test was negative for both sides of the neck. On further examination, she was found to have scattered TPs around her neck and shoulder arising from the left scalene, upper trapezius and supraspinatus muscles. She also displayed evidence of a classical 'jump sign' during digital compression over those muscles. The scalene TPs were typically reproducible during repeated digital compression with concomitant referred pain into the left hand side. The Scalene Cramp Test and Scalene Relief Test were positive. There were no trigger points found on the serratus anterior and pectoralis minor muscles. A diagnosis of secondary MPS of the left scalene anterior muscles, upper trapezius

and supraspinatus was made. There was no sign of dilatation of the subcutaneous collateral veins, oedema or cyanosis of the hands and fingers on the affected side to suggest subclavian vein thrombosis.

In the pain clinic, the patient was given a trigger point injection of 1 mL of 0.5% bupivacaine over the trapezius and supraspinatus muscles in a fan-shaped manner. TP injection of the anterior scalene muscle was performed in the operating room under nerve stimulator and fluoroscopy guidance. She received immediate pain relief following these TP injections; for long-term pain relief, she was scheduled for several courses of active stretching exercise and heat therapy by a physiotherapist. Amitriptyline 25mg ON and baclofen 10mg TDS were added to her treatment regiment. Her symptoms were dramatically relieved during the next visit to the pain clinic.

Case 2

A 36-year-old Thai woman came to the orthopaedic clinic with complaints of chronic right-sided neck pain with referred pain down to her right hand over the past four months. Initially, the pain started around the interscapular region and later extended to the posterior part of the neck and right shoulder. On further questioning, she admitted to having pain that radiated down to the radial side of her right hand with numbness over the fingers. She had neither any underlying medical problems nor a history of neck trauma. She worked as a clerk, which routinely required her to be at a desk for prolonged periods of time (i.e., throughout office hours).

On physical examination, she had good posture with no structural asymmetry. Extension, flexion and rotation of the neck were within the normal range. Palpation revealed tenderness over the right upper trapezius muscle. There were neither motor nor sensory deficits over the upper limbs. Tendon reflexes in the biceps (C5), supinator (C5, C6) and triceps (C7) were normal. Spurling's Test was negative for both sides of the neck. Cervical X-rays showed no evidence of accessory cervical rib, distorted clavicle bone fracture or elongated transverse process of C7. MRI revealed neither evidence of cervical spondylosis nor disc prolapse. A diagnosis of muscle strain of trapezius muscle was made. The patient was prescribed celecoxib 200mg BD, tramadol 50mg TDS and neurobion 1 tablet BD. The physiotherapist prescribed a few courses of deep heat therapy with shortwave diathermy. Active stretching and behavioural modification at her work place were also instituted. She was referred to the pain clinic as her pain had become

refractory and her Visual Analogue Pain Score (VAS) remained at 7/10.

In the pain clinic, she was found to have reproducible TPs over her right upper trapezius and right scalene muscles. Gentle digital pressure over the right scalene anterior muscle simply produced the 'jump sign' with referred pain to the radial distribution of her right hand side. The Scalene Cramp Test and the Scalene Relief Test were found to be positive. There were no trigger points found on the serratus anterior and pectoralis minor muscles. Diagnoses of MPS of the right scalene anterior and upper trapezius muscles were made. Nevertheless, there were no signs of subclavian vein thrombosis, such as dilatation of subcutaneous veins, oedema or cyanosis of the hands and fingers, and she was subjected to a few courses of scalene and upper trapezius active muscle stretching by a corresponding physiotherapist, in addition to shortwave diathermy heat treatment. With regard to pharmacological treatment, she was given amitriptyline 10 mg daily and eperison sodium 50 mg BD. Her symptoms improved gradually within one month, as she had been re-evaluated during follow up to the pain clinic.

Discussion

Cervical disc prolapse or cervical stenosis is often the primary concern when making a clinical diagnosis for a patient with neck pain and radiculopathy. Although TOS (including scalene muscle disorder) is an established clinical entity, scalene MPS is seldom included in the differential when making the diagnosis. Muscle pain in the neck, shoulder and arm caused by MPS often resembles cervical radiculopathy. The types of MPS that resemble cervical radiculopathy are those caused by MPS of pectoralis minor, scalene and serratus anterior, which need to be ruled out individually when assessing patients with symptoms of neck pain and "cervical radiculopathy" (4,5). For instance, MPS of the pectoralis minor causes neck and shoulder pain, which may radiate along the arm, simulating C7, C8 radiculopathy. Arm abduction often may add a neurovascular syndrome to pain due to the compression of the axillary artery and brachial plexus close to its insertion at the coracoid process. Serratus anterior usually causes pain in the chest under the axilla and sometimes causes dyspnea, especially during deep breathing. The pain may radiate down to the ulnar part of the arm, simulating C7, C8 radiculopathy (1,5).

MPS of scalene usually presents with unilateral neck and shoulder pain associated with

typical referred pain in the radial distribution of the affected arm/hand, simulating C6 radicular pain (Figure 1)(4). When the referred pain is due to MPS of the scalene muscle, the referred pain and numbness can be due to brachial plexus irritation as a result of direct compression between two scalene muscles (3,5). This phenomenon justifies the established fact that MPS of the scalene muscle is one of the causes of TOS. Therefore, it is prudent for clinicians to be able to distinguish the cause of "cervical radiculopathy", whether it is purely from MPS of the scalene (compression syndrome) or from a genuine cervical disc prolapse with nerve root impingement. In other words, one should be able to precisely differentiate whether the pain is 'radicular' or 'muscular' in origin or both (3,4).

The aetiology of MPS of the scalene muscle can be primary or secondary to other medical problems known as precipitating and perpetuating factors. Chronic muscle overuse, poor posture and repetitive microtrauma are the leading causes for the primary aetiology of this condition (1,6). This is clearly seen in case two, as the patient's desk job resulted in prolonged time at her work station, which resulted in the overuse of certain groups of muscles leading to MPS of the supraspinatus, upper trapezius and scalene muscles. Secondary MPS of scalene muscle is known to be associated with other medical problems such as osteoarthritis, trauma, complex regional pain syndrome (CRPS) and various systemic medical illnesses (1,5). It is not uncommon for scalene MPS to present as secondary to cervical spine diseases, such as cervical stenosis, disc prolapse, facet joint arthritis and post whiplash injury (1,5). As illustrated in case 1, the MPS of the scalene was secondary to facet joint arthropathy and cervical disc prolapse. In an extreme situation, the "radiculopathy" symptom can be a result either of secondary MPS of the scalene muscle or from the coexisting cervical disc prolapse with nerve root impingement. In this situation, one should be able to find the main pain generator that gives rise to the cervical "radiculopathy". Is it MPS of the scalene or cervical disc prolapse with nerve root impingement that is giving rise to the symptom of cervical radiculopathy?

As MPS of the scalene mimics cervical disc prolapse, the actual diagnosis of neck pain with radiculopathy can be misleading. For instance, in Case 1, MPS of the scalene muscle presented as the main pain generator in the presence of coexisting facet joint arthropathy and cervical disc prolapse; the significance of the former was not given due to recognition, while the diagnosis of cervical disc prolapse was preferred as it was consistent with the MRI findings. Unknowingly,

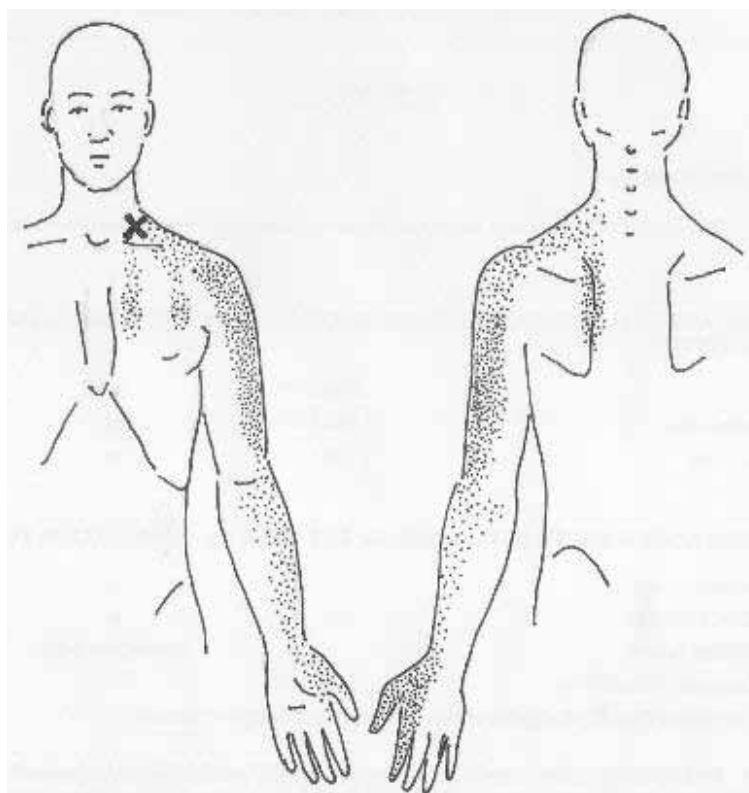


Figure 1: Location of pain and referred pain pattern in scalene MPS

the false positive from the MRI report had been cited, even though evidence of nerve root impingement from the MRI finding was trivial. After all, cervical disc prolapse/stenosis is often the more sought-after diagnosis. In addition, abnormal imaging findings are frequently found among asymptomatic individuals and may not necessarily be the cause of the pain (8). As a result, patients may be subjected to unnecessary surgery if the pain persists following conservative therapy failure (7). Therefore, it is prudent to identify and rule-in other possible causes of neck pain with ‘radiculopathy’ instead of ruling out cervical disc prolapse/stenosis as the first provisional diagnosis. With regard to this issue, TOS, including myofascial pain syndrome around the neck and shoulder, is the most sensible differential diagnosis to be entertained (2,3).

TOS may present as one of three different types, arterial, venous or neurogenic; each of these can be easily identified clinically. Neurogenic TOS is the most common, comprising over 90% of all TOS. Symptoms include extremity paraesthesia, pain and weakness as well as neck pain due to brachial plexus compression (1,3). The most common cause of neurogenic TOS originates from the scalene muscle. The scalene muscle could have been injured and scarred from

a previous injury (whiplash injury), development of tight congenital band or simply scalene MPS (3). Other causes of TOS that need to be ruled out include cervical rib syndrome, subclavian vein thrombosis, congenital band of scalene muscle, distorted clavicle bone fracture and an elongated transverse process of C7 (2,3,4).

Clinical diagnosis and management of MPS of scalene

Diagnosis of MPS of scalene is often considered after diagnosis of cervical disc prolapse has been ruled out. Diagnosis of cervical disc prolapse is often made from the typical history of neck pain that is made worse on neck flexion associated with cervical radiculopathy. This finding should be supported with a positive Spurling’s test during physical examination, in addition to significant evidence from MRI findings (10). Both of our cases were inconsistent with cervical disc prolapse, as the Spurling’s test was unremarkable. Once cervical disc prolapse is excluded, diagnosis of TOS-origin neck pain (including scalene) can then be evaluated. In our cases, the diagnosis was initially performed by a few provocation/relieving tests.

The Elevated Arm Stress Test is a sensitive screening test in TOS and, if positive, is suggestive

for TOS in origin. The test is done by asking the patient to elevate his/her arm with a flexed elbow to shoulder level for three minutes. This test is considered positive if the patient complains of an uncomfortable feeling, including pain and paraesthesia along the arm after less than three minutes (9). In order to determine if the scalene muscle is responsible, the above test should be followed by the Scalene Cramp Test and the Scalene Relief Test, which are pathognomonic for scalene MPS. A positive Scalene Cramp Test is appreciated when neck pain and radiculopathy are aggravated by placing the patient's chin over the ipsilateral supraclavicular groove for 60 seconds. Neck pain with radiculopathy or a tingling sensation on the lateral aspect of the hand is expected to be reproducible, as the anterior scalene muscle being compressed irritates the brachial plexus (9). This pain can be inhibited by performing the Scalene Relief Test, wherein the clinician asks the patient to bring his or her forearm up to the forehead and to rotate the shoulder forward on the symptomatic side. The cessation of pain and tingling sensation experienced during this manoeuvre is perceived as a positive Scalene Relief Test (9).

The principal management of MPS is performed by trigger point elimination, which corrects the perpetuating factors. Eradication of trigger points can be performed in combination with trigger point injection, stretching exercises, massage, deep heat therapy and oral medications (1,5). Active stretching exercises are the most fundamental of all, as they allow patients to be independent and to actively participate in the long-term management of their chronic pain (1). Pharmacologic treatment of patients with chronic musculoskeletal pain includes analgesia and medications to induce sleep and to relax the muscles. Antidepressants, narcotic analgesics, neuroleptics and non steroidal anti-inflammatory agents are often prescribed for these patients (1,5). Predisposing and perpetuating factors in chronic overuse or stress injuries of the muscles must be eliminated as they will increase the efficacy of other modalities and speed the process of recovery. Known perpetuating factors include biochemical, mechanical, metabolic, physiological, psychological and infectious factors. Such an evaluation is strongly indicated if appropriate treatment provides little or no pain relief from MPS. In primary MPS, correction of posture, an ergonomic human-machine system (Case 2) and structural realignment are of paramount importance in order for the positive effects to last beyond the treatment (1,5).

Conclusion

Myofascial pain syndrome of the scalene muscle may present with neck pain and cervical radiculopathy, which has been frequently underdiagnosed. A lack of awareness among physicians may lead to misdiagnosis and thus to inappropriate management.

Author s contributions

Conception and design, data analysis and interpretation, drafting of the article: NAJ
Critical revision of the article: NAJ, MSA
Provision of study materials or patients: MSA
Administrative, technical or logistic support: MA

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