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EDITORIAL

It's Time for Doctors to Speak Out on Climate Change

Graham McAll
Devonshire Green Medical Centre, United Kingdom

There is no doubt now. Climate change is the biggest threat to human health this century (1). Initially it is the poor who are suffering most, but even wealthy nations are not escaping the consequences. The air we breathe, the water we drink, the weather we experience, and even the depth and acidity of the oceans are changing. Climate change is increasing the incidence of weather-related disasters and acting as an amplifier for many diseases. Action to reduce anthropogenic green house gases (GHG) is urgent, especially because the full effects of the present levels have yet to work their way fully through the global system. Even if we reduce GHG levels now we will still experience considerable global temperature rises, but if we fail to act then we face global climatic catastrophe. Carbon dioxide is the most important green house gas and latest figures from the Mauna Loa observatory in Hawaii (2) confirm that the global CO_2 level continues its inexorable rise.

The heat gain in the 20th century was 0.76 °C and is now accelerating. The International Panel on Climate Change (IPCC) reported in 2007 that they were unable to predict the effect of glacial and polar ice melt on the sea level rise (3). With this proviso the IPCC warned that a sea level rise of 18–59 cm could be expected by 2100 by thermal expansion of the oceans. The expected rise for 2008 had been 1.8 mm, but actual measurement showed a rise of 3.1 mm, so in March 2009 the prediction of sea level rise was revised to 28–79 cm by 2100 (4). Even this scenario seems optimistic. The observations on temperature, ice melt and sea level rise have been consistently at the high end of the predicting models. A sea-level rise of 1 m in the Bay of Bengal would put 17% of the coastal land of Bangladesh underwater, creating many millions of climate refugees (5).

According to Munich Re, the multinational insurance company, the number of great weather-related disasters increased from an average of less than two a year in 1950 to more than six in 2007 (6). Increasingly powerful storms and typhoons wreak havoc. In wealthy countries the effect is not as catastrophic initially as in poorer countries. Compare for example Hurricane Ike in September 2008 with Cyclone Nargis in the same year. The death toll from Ike was 194 dead and 43 missing, but from Cyclone Nargis the final death toll was approximately 140 000 with 2.5 million made homeless. Whilst no one storm can be specifically blamed on climate change the increasing frequency and severity of storms can be. If it is the carbon-emitting nations who have caused the problem, it is the poor who are bearing the brunt of the consequences and are suffering now. Increasingly, sudden floods and mudslides are taking a huge toll, especially in poorer areas. The loss of fresh water sources is becoming a major problem for coastal dwellers because of the salination and depletion of aquifers; and for the millions who rely on glacial melt waters as glaciers dwindle.

Previous progress in reducing global malnutrition has gone into reverse in the last year. According to the Food and Agriculture Organisation of the United Nations (FAO) in 2007 about 800 million people had calorie-deficient diets. In June the projected number exceeded 1 billion (7). Whilst the rise in food price has been partially attributed to the switch to bio-fuels in the USA and unstable oil prices, another major component has been unpredictable weather such as the drought in Australia. Continuing growth in the world's human population (1.5 million people each week) is another pressure on the global carbon footprint and food supplies.

Human beings are steadily displacing other species with our voracious appetite for limited resources. Species extinctions are running at about 1 000–10 000 times the natural background rate (8). Much of our pharmacological knowledge is derived from other animal and plant species. The rapid destruction of species-rich rainforest for cropping not only releases more carbon dioxide; it has been described as the equivalent of burning our best pharmacological library after only reading a few of the books.

There is some reduction from cold deaths in temperate countries as temperatures rise, but this is outweighed by heat wave deaths. Heat islands—

the phenomenon of localized areas of extreme heat due to the surface characteristics of the built environment in cities—tend to worsen air pollution by the addition of the dangers of ground level ozone to airborne particulate matter as experienced in haze conditions. Particulate matter and ozone are associated with increases in mortality and admissions from respiratory, cardiovascular, cerebrovascular and allergic diseases. Vector-borne and infectious diseases will alter their range. Malaria, dengue and Chikungunya are among those that will extend their frequency and range as temperatures increase. Malaysia recorded 24 543 cases of dengue in the first six months of 2009 with 62 deaths (9). It is known that Stegomyia aegypti is very sensitive to humidity, temperature and cloud cover and it is suggested that by 2080 about 6 billion people in the world will be exposed to risk of dengue compared with 3.5 billion if the climate had remained unchanged (10).

Doctors must not remain silent. The medical profession is a trusted bridge between science and humanity and so doctors have a key role in communicating the dangers of climate change and the urgency of action to both patients and politicians. There are four main areas to address: mitigation, adaptation, education and research. A first and simple act is to read and sign the pledge at http://www.climateandhealth.org/. This will give the politicians meeting at the United Nations Climate Change Conference ('COP15') in Copenhagen in December 2009 the support for the challenging decisions they face.

The medical profession should be leading mitigation at personal, corporate and community levels. The personal example involves adopting lower carbon lifestyles. Generally the medical profession is well paid and has choices that may not be available to others in eco-friendly living. Secondly doctors should help our hospitals, clinics and communities identify carbon reduction strategies. Much investment is offset by savings in energy consumption and expensive waste management. There is already a great body of shared experience from across the world available on the internet.

As climate changes threaten, we need to consider what adaptive strategies in health care will be needed. Education inside and outside the health community is urgent, and this will include the continued empowerment of women with education and access to good contraception. There is a need to engage in our faith communities whose critical role is encouraging commitment to the stewardship of God's creation for our neighbours and future generations. Finally, as ever, more research is needed. The World Health Organisation has clear priorities for research into climate change, (11) and certainly our knowledge of the health effects is still in its infancy.

It would be an irony if the medical profession contributed to a major deterioration in the health of the global community by its own carbon emissions and inactivity in the face of this global challenge.

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ORIGINAL ARTICLE

Identification of Dengue-specific B-Cell Epitopes by Phage-display Random Peptide Library

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Abstract

Background: **Dengue is the most important human viral disease transmitted by arthropod vectors. The availability of random peptide libraries (RPL) displayed on phage has provided a powerful tool for selecting sequences that mimic epitopes from microorganisms that are useful for diagnostic and vaccine development purposes. In this paper, we describe peptides that resemble the antigenic structure of B-cell epitopes of dengue virus identified from a phage-peptide library using human sera containing polyclonal antibodies against dengue virus.**

Materials and Methods: **Eighteen phage clones were isolated from the phage-display peptide library, J404, by affinity selection using human antisera against dengue virus type 3. These clones were tested for reactivity by ELISA with a panel of hyperimmune ascitic fluids (HAFs) containing antibodies either against all four dengue serotypes, West Nile virus (WNV) or Eastern equine encephalitis virus (EEEV) with control ascitic fluid (NAF) used as a negative control.**

Results: **Eight clones were recognized by HAFs against the four dengue serotypes, of which four significantly inhibited binding of anti-dengue antibodies to the virus. Two peptides with similar sequences to regions of NS3 and NS4B non-structural dengue virus proteins were identified.**

Conclusion: **Our results suggest that these peptides could be used for the development of diagnostic tools for the detection of dengue virus infection and for a potential vaccine against this pathogen.**

Keywords: *medical sciences, virology, dengue, epitopes*

Introduction

Dengue is the most important human viral disease transmitted by arthropod vectors. Annually, it is estimated that 100 million cases of dengue fever (DF) occur in tropical and subtropical regions, of which 500 000 result in dengue haemorrhagic fever (DHF) and 25 000 cases result in death. DF and DHF are caused by the four dengue viruses, DEN 1, 2, 3, and 4, which are closely related antigenically. Dengue virus belongs to the Flaviviridae family whose members are enveloped, positive-sense, single-stranded RNA viruses, such as those that cause Yellow fever, Japanese encephalitis, West Nile fever and hepatitis C (1). The flaviviral genome is translated as a single polypeptide that is post-translationally processed by cleavage into three structural proteins (C, M, and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (2). The E protein is considered to be the immunodominant protein (3). C-prM and prM proteins are able to induce an immune response and long lasting antibodies (4). The presence of antibodies against some non-structural proteins has also been demonstrated (5–9).

Prevention and control of DF and DHF has become more urgent with their expanding geographic distribution and increased disease incidence (10). Active laboratory-based surveillance and effective use of vaccines should be

components of disease prevention programs (11). Dengue diagnosis based on antibody identification has emerged as the most practical approach (1). Most methods of antibody detection rely on the use of whole dengue virus antigens produced in tissue culture or in suckling mouse brain. The use of such material is expensive and production costs associated with virus cultivation are generally high (12). Commercial kits are available for serological dengue diagnosis, but they still need careful evaluation. Although dengue diagnosis has improved, better tools are still needed for early, rapid, specific, sensitive and inexpensive diagnosis (13). One of the major difficulties associated with the development of a dengue virus vaccine is attributed to observations that most cases of DHF occur in individuals experiencing a secondary viral infection by a different dengue virus serotype, which therefore requires a safe and effective tetravalent vaccine (14). The absence of a suitable animal model, poor understanding of the pathogenesis of the disease, poor financial support and several other problems need to be solved before effective and safe dengue vaccines become available (13).

The availability of RPL displayed on bacteriophage has provided a powerful tool for selecting peptide sequences that mimic epitopes of infectious agents (15). Peptides mimicking epitopes of dengue virus proteins present in an RPL could be an alternative source of antigens for the development of diagnostic assays, and selection of peptides mimicking immunologically relevant B- and T-cell epitopes of dengue virus could be useful for disease prevention. B-cell epitopes of dengue proteins have been previously identified using mouse monoclonal antibodies (16–19). In the present work using human polyclonal antibodies against dengue virus, we report the identification of peptides capable of mimicking antigenic determinants of dengue virus non-structural proteins that could be useful in the development of a diagnostic kit or a potential antigen for vaccine production.

Materials and Methods

Human sera

The serum samples used in the study were obtained from the collection of the Arbovirus Laboratory, Department of Virology, "Pedro Kourí" Tropical Medicine Institute, Havana City, Cuba. All of the sera were tested for dengue virus-specific IgM and/or IgG antibodies (20) and by plaque reduction neutralization test (PRNT) (21). A panel of 21 sera was used, including 8 negative sera for IgM and IgG antibodies to dengue virus and 13 positive sera of dengue infection with DEN 1 (n=1), DEN 3 (n=11), and DEN 4 (n=1). All of the serum samples were classified as primary infection and showed IgG antibodies

Affinity selection: Reactivity of phage clones with hyperimmune ascitic fluids (HAFs) and a dengue anti-complex monoclonal antibody (H3/6).

The methodology used to identify dengue virus epitopes using polyclonal antisera is essentially similar to that described by Larralde et al. (22). The J404 bacteriophage-display peptide library (PDPL) (kindly donated by Dr. Jim Burritt, Montana State University, USA) (23), human serum samples positive for dengue virus type 3 antibodies and sera collected from healthy donors (negative controls) were used.

Clones derived from the affinity selection were immune-screened by slot blot with three positive sera against dengue virus type 3 and three negative sera as follows: serial dilutions of the phage sample were performed in LB broth and 100 µL of each dilution was mixed with melted soft agar, followed by the addition of TG1 Escherichia coli cells in stationary phase. This mixture was poured onto a solid LB agar plate followed by an overnight incubation at 37 °C. Isolated clones were picked using a Pasteur pipette, transferred to tubes containing 1 mL of LB broth and incubated overnight at 37 °C with gentle mixing. The supernatant was then transferred into a new tube and centrifuged at 6000 g for 30 min at 4 °C. Supernatants from phage clones and M13K07 (negative control) were titred and their concentrations were adjusted to $7.5x10^7$ pfu/mL. Fifty microlitres of each sample was applied onto a nitrocellulose membrane in a slot blot apparatus. The membranes were blocked with PBS containing non-fat dry milk (PBSNM) for 2 h at room temperature (RT) with four buffer changes. Three positive sera against dengue virus type 3 and three negative sera were pre-adsorbed with TG1 Escherichia coli extract and UV-inactivated M13K07 phage for 2 h at RT. The pre-adsorbed sera were added to the nitrocellulose discs

and incubated overnight at 4 °C with gentle mixing, followed by 10 washes with PBS/0.1% NP40. The washed membranes were incubated with alkaline phosphatase-conjugated goat anti-human IgG (Sigma, 1:5000 in PBSNM) for 4 h at 4 °C, washed and developed in NBT/BCIP chromogen for 2–5 min.

To confirm their specific reactivity with dengue virus antibodies, the selected phage clones were evaluated with HAF either against the four dengue serotypes, West Nile virus (WNV) or Eastern equine encephalitis virus (EEEV), and a control ascitic fluid (NAF) using an indirect ELISA. Briefly, multi-well plates (Nunc Maxisorp F8, Life Technologies Limited, Paisley, UK) were coated with 100 µL of anti-M13 monoclonal antibody (Amersham Pharmacia Biotech, UK) (10 µg/mL in 50 mM $NaHCO_3$, pH 9.6). Plates were incubated overnight at 4 °C, washed three times with PBS/0.05 % Tween 20 (v/v) (PBS-T) and blocked with PBS-T/5 % non-fat dry milk (w/v) for 1 h at 37 °C. Phage clones and wild-type phage (as controls) were added (100 µL/well) and incubated for 4 h at RT. Plates were washed three times with PBS-T and test serum was added (1/100, pre-adsorbed with TG1 E. coli extract and UV-inactivated M13K07 phage, for 4 h at RT). Plates were washed four times with PBS-T, incubated for 4 h at 37 °C with 100 µL/well of goat anti-human IgG/alkaline phosphatase conjugate (Sigma-Aldrich, UK) diluted 1:5000. They were then washed and developed with p-nitrophenyl phosphate substrate. The absorbance at 405 nm was recorded by an automated ELISA reader (Dynex Technologies, UK). For each serum sample, the average results from two independent experiments were evaluated. Values were considered positive when the ratio of absorbance of phage clones over absorbance of phage M13K07 (wild-type control) (P/N) was >2 and was more than twice the NAF. Phage clones with a P/N ratio of >2 in relation to NAF were discarded due to nonspecific reactions. Data were further analysed statistically by principal component analysis, cluster analysis and exploratory data analysis.

The ability of phage clones to be recognized by H3/6, a dengue anti-complex monoclonal antibody (25), was evaluated by the following ELISA: multi-well plates (Nunc Maxisorp F8, Life Technologies Limited, Paisley, UK) were coated with 10 µg/mL of H3/6 monoclonal antibody. Plates were incubated overnight at 4 °C, washed three times with PBS-T and blocked with PBS-T/5 % non-fat dry milk (w/v) for 1 h at 37 °C. Phage clones and wild-type phage (as controls) were added (100 µL/well) and incubated for 4 h at RT. Plates were washed four times with PBS-T, incubated for 4 h at 37 °C with 100 µL/well of goat anti-human IgG/alkaline phosphatase conjugate (Sigma Aldrich, UK) diluted 1:5000. The plates were then washed and developed with p-nitrophenyl phosphate substrate. The absorbance at 405 nm was recorded by an automated ELISA reader (Dynex Technologies, UK). Phage clones generated with the dengue anti-complex monoclonal antibody H3/6 (unpublished data) were used as positive control. Values were considered positive when the ratio of absorbance of phage clones over absorbance of phage M13K07 (wild-type control) (P/N) was >2.

Competitive inhibition assay

The ability of peptides displayed in the phage clones to compete with dengue virus for binding to antibodies present in the sera from dengue patients was evaluated by an inhibition ELISA (20). Sera positive for antibodies against DEN 1, 3 and 4 and negative sera were tested with and without pre-incubation with phage clones and M13K07 (109 phage particles). The percent inhibition of anti-dengue virus antibodies by the phage clones was estimated:

$$\%\ inhibition = 1 - \frac{\text{O.D serum sample without absorption by phages}}{\text{O.D serum sample with absorption by phages}} \times 100$$

DNA sequencing and similarity search

Selected phages were used to infect exponentially growing TG1 Escherichia coli cells. Infected cells were grown overnight in LB agar plates containing kanamycin (Sigma Aldrich, UK) at 75 µg/mL. Single colonies were picked and grown in LB broth containing kanamycin at the same concentration as above, and phage DNA was purified (QIAprep Spin Miniprep Kit, Qiagen, USA). The phage DNA was sequenced using a geneIII-specific primer, which anneals to 50 nucleotides from the 27-mer insert, as described Burrit et al. (26). Amino acid sequences were deduced using the GENERUNNER program. The phage-displayed peptide sequences were ran against the proteomes of the four dengue serotypes using the stand-alone BLAST program (27).

Results

Affinity selection: Reactivity of phage clones with hyperimmune ascitic fluids (HAFs) and a dengue anti-complex monoclonal antibody

Eighty-four phage clones were obtained after affinity selection of the RPL with a human serum sample containing a high titre of anti-dengue virus antibodies. Supernatants of the 84 isolated phages were tested by immunodot assay and ELISA, against three positive sera and also against three sera from non-infected individuals, resulting in the selection of 18 phage clones. These clones did not react with the negative sera. The reactivities of these 18 phage clones with different HAFs, as measured by ELISA, are shown in Table 1. Clones Ph2, Ph15, Ph24, Ph34, Ph35, Ph37, Ph79, and Ph84 showed the strongest antibody binding against serotype 2 and serotype 3. Clones Ph8, Ph26 and Ph64 were excluded because they reacted with NAF, suggesting a nonspecific reaction. The statistical analysis allowed the segregation of the phage clones into two clusters. Cluster 1 is comprised of the phage clones Ph2, Ph24, Ph34, Ph37, Ph79, and Ph84 and Cluster 2 is comprised of clones Ph15, Ph16, Ph26, Ph27, Ph27, Ph35, and Ph64 (Fig. 1A). The best recognition was obtained with HAF against dengue virus 3. Differences in the recognition of phage clones included in both clusters were not found by the HAF against WNV, EEEV, and the NAF negative control (Fig. 1B). None of the phage clones were recognized by the H3/6 monoclonal antibody (data not shown).

Competitive inhibition assay

The reaction of the eight previously selected phage clones with anti-dengue virus type 3 antibodies is shown in Table 2 as the percent inhibition of binding of anti-dengue 3 to dengue virus compared with the unabsorbed sera. Clones Ph2, Ph15, Ph35, and Ph37 inhibited the binding of anti-dengue 3 antibodies to the virus. The same clones were also evaluated with antisera against

Table 1: ELISA reactivity of HAFs to phage clones

Phage clone	HAF						
	D1	**D2**	**D3**	**D4**	**WN**	**EEE**	**NAF**
Ph2	1.23	3.00	3.36	0.88	0.61	1.20	1.28
Ph4	0.61	1.37	1.53	0.43	0.94	1.14	1.09
Ph5	0.59	1.15	1.32	0.50	1.15	1.30	1.11
Ph6	0.72	1.54	1.58	0.49	0.67	1.14	1.16
Ph8 [a]	1.70	5.80	6.56	1.95	2.05	1.31	2.08
Ph15	1.18	2.32	2.76	0.90	1.03	1.04	1.00
Ph16	1.15	1.43	1.28	0.47	0.97	1.29	1.03
Ph24	1.42	2.78	3.92	0.93	1.42	1.37	1.73
Ph26 [a]	1.09	1.23	2.07	0.80	1.89	1.40	2.08
Ph27	1.14	1.62	1.76	0.57	1.49	1.39	1.24
Ph34	1.31	4.10	5.75	1.37	1.42	1.09	1.55
Ph35	1.31	2.42	3.21	0.78	1.34	1.31	1.48
Ph37	1.24	2.82	3.91	0.84	1.21	1.36	1.85
Ph64 [a]	1.22	2.29	2.99	0.78	1.32	1.35	2.23
Ph78	1.22	2.26	2.69	0.70	1.16	1.63	1.68
Ph79	2.69	3.10	5.17	2.56	1.21	1.15	1.70
Ph84	1.57	3.46	4.30	1.48	1.81	1.38	1.71

Results are expressed as the ratio of absorbance of phage clones over absorbance of wild-type phage (P/N). Values were considered positive when (P/N) >2 and differed by more than twice the NAF value. Shaded cells indicate positive results.

[a] Discarded by reactivity with NAF

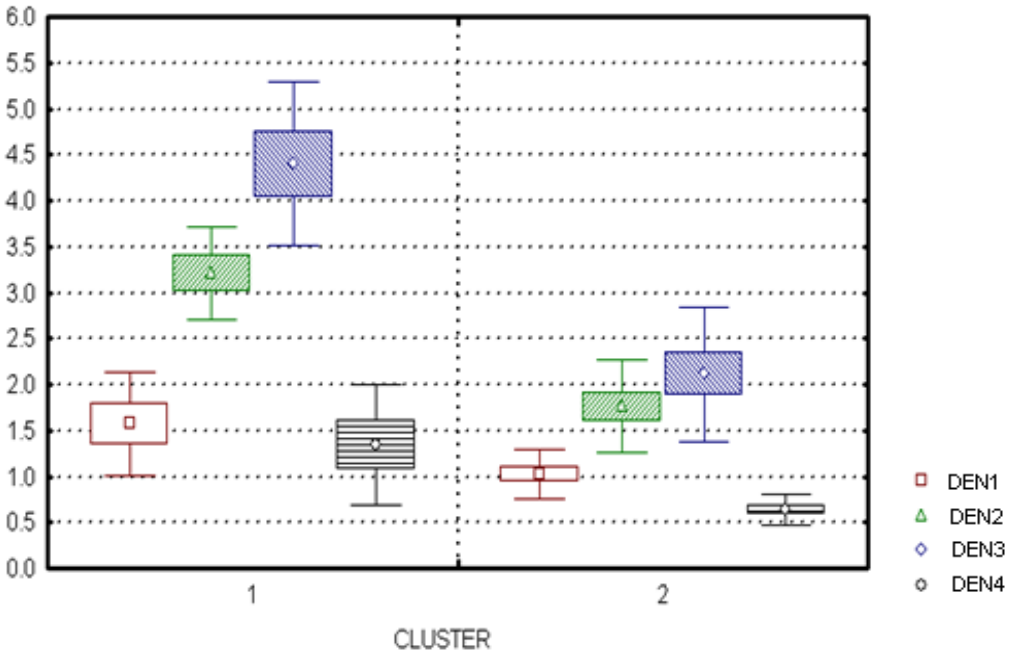

Figure 1A: Reactivity of phage clones by HAFs against DEN serotypes 1 to 4. Cluster 1 (Ph2, Ph24, Ph34, Ph37, Ph79, and Ph84) and Cluster 2 (Ph4, Ph5, Ph6, Ph15, Ph16, Ph26, Ph27, Ph35, and Ph64)

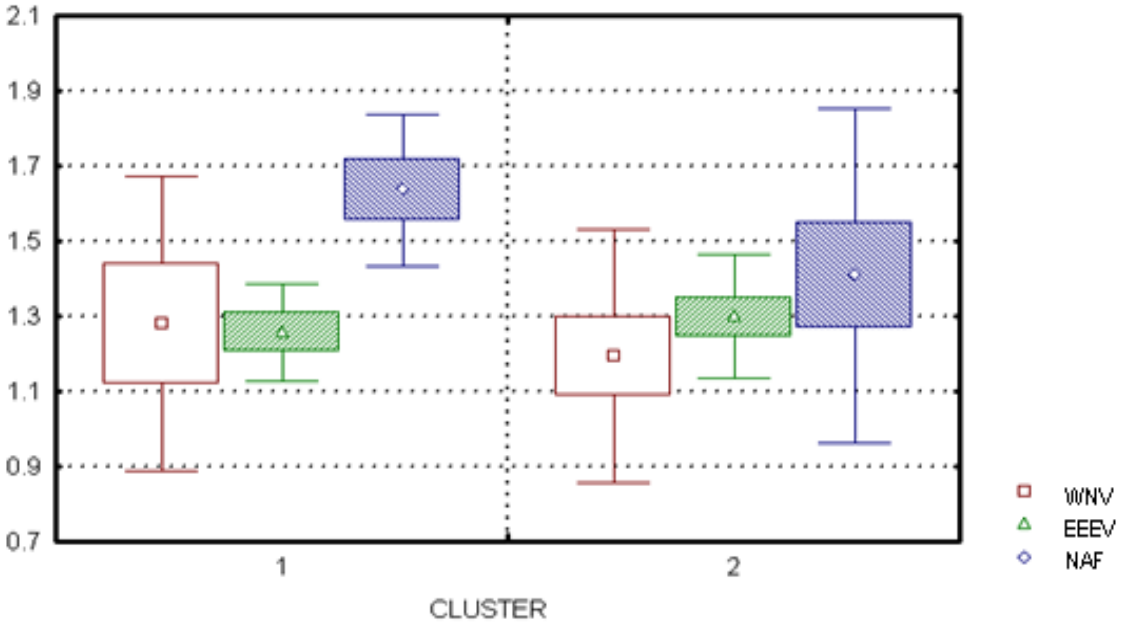

Figure 1B: Reactivity of phage clones by HAFs against WNV, EEEV and NAF.

Table 2: Inhibition of binding of anti-dengue 3 antibodies to dengue virus by phage clones

Phage clones	Inhibition (%)[a]		
	Positive sera DEN 3		
	Serum1	Serum 2	Serum 3
Ph2	21.73	4.55	9.86
Ph15	6.37	4.08	7.98
Ph24	1.34	1.01	0
Ph34	1.17	0.67	3.2
Ph35	4.24	8.99	3.58
Ph37	16.61	13.80	9.36
Ph79	-8.90	-13.79	0.81
Ph84	-5.57	-9.92	-2.54
M13	0.84	-14.02	-8.52

[a]Inhibition of binding was calculated as: % inhibition = 1–(O.D. without serum sample absorption by phages/O.D. with serum sample absorption by phages) x 100. M13 = wild-type phage M13K07. Phage clones with the highest percent inhibition of binding of antibodies to the virus were selected for the next experiment.

DEN 1, 3, and 4 (Table 3). Each of the clones inhibited each anti-serotype by approximately 13 to 46 %. Negative percent of the inhibition of binding of anti-dengue antibodies to dengue virus by phage clones were considered negative.

DNA sequencing and similarity search

The deduced amino acid sequences of clones Ph2, Ph15, Ph35, and Ph37 have a range of similarity from 50% to 70% with regions of the NS3 and NS4B dengue proteins of the four dengue serotypes. Figures 2A and 2B show the comparison of these peptides with NS3 and NS4B proteins of DEN serotype 3. The BLAST results were similar for all dengue serotypes. The peptide sequence, FERVPGEVT, was found in Ph2, Ph15, and Ph35 and exhibited several amino acids at the same position as the NS4B protein in residues 164-172 (dengue 1, 2 and 3), and 161-168 (dengue 4). Peptide RRALPPVSS from Ph37 showed a high similarity with two regions of the NS3 protein of the four dengue serotypes in regions corresponding to residues 425-432 and 537-544.

Discussion

Recent studies have shown that phage-displayed peptides selected using antibodies raised against pathological antigens can be important tools for both diagnosis and disease prevention (28-36). This approach has previously been used to identify serotype-specific epitopes of dengue virus using mouse monoclonal antibodies (16-19). In this work, peptides that resemble the antigenic structure of B-cell epitopes of dengue virus were identified from a phage-peptide library using human polyclonal antisera from patients who had recovered from dengue virus infection. Eighteen phage clones were isolated by the following procedure: affinity selection of the random peptide library with a positive serum containing a high titre of anti-dengue antibodies; screening by slot blot with a panel of antisera (three positive and three negative sera); ELISA using three positive and three negative sera. Assessing the reactivities of these 18 phage clones with different HAFs by ELISA facilitated the selection of eight dengue virus-specific phagotopes. The fact that they reacted only with HAFs against dengue and did not react with HAFs against WNV, EEEV, or NAF suggests that they do not share epitopes with these arboviruses. Clones Ph8, Ph26, and Ph64 were rejected based on their reactivity with other HAFs, so as to minimise the possibility of enriching for "false positive" clones which may display unrelated target peptides.

Table 3: Inhibition of binding of anti-dengue antibodies to dengue virus by phage clones

Phage clones	Inhibition (%)[a]				
	Positive sera			Negative sera	
	DEN 1	DEN 3	DEN 4	M30	M37
Ph2	39.0	27.08	13.3	1.033	1.069
Ph15	36.9	33.12	13.8	-7.20	-9.0
Ph35	46.01	35.5	35.9	2.04	8.81
Ph37	44.06	32.9	25	0.13	0.757
M13	1.05	1.80	1.08	0.59	0.23

[a]The inhibition of binding of anti-dengue antibodies to dengue virus is expressed as the percent inhibition compared to M13 (wild-type phage M13K07)

(A)

```
>YP_001531175|NS4B
          Length = 248

 Score = 12.7 bits (21), Expect = 4.9
 Identities = 4/8 (50%), Positives = 6/8 (75%), Gaps = 0/7 (0%)

Query: 1   FERVPGEV 8
           FE+  G+V
Sbjct: 164 FEKQLGQV 171
```

(B)

```
>YP_001531172|NS3
          Length = 619

 Score = 14.2 bits (26),  Expect = 1.6
 Identities = 5/7 (71%), Positives = 5/7 (71%), Gaps = 0/7 (0%)

Query  1     RRALPPV  7
             RR L PV
Sbjct  426   RRCLKPV  432


 Score = 10.0 bits (16),  Expect = 30
 Identities = 5/8 (62%), Positives = 5/8 (62%), Gaps = 2/8 (25%)

Query  1     RRA-LPPV  7
             RR  LP V
Sbjct  538   RRGDLP-V  544
```

Figure 2: Deduced amino acid sequences of mimotopes by BLAST search against the dengue virus serotype 3 proteome. (A) Pairwise alignment of peptide FERVPGEVT displayed on Ph2, 15 and 35 with NS4B protein. (B) Pairwise alignment of peptide RRALPPVSS displayed on Ph37 with NS3 protein. The BLAST results were similar for all dengue serotypes

Phage panning is a very dynamic process that is influenced by affinity, avidity, the nature of target and the combined impact of multiple experimental parameters (29). The serological diagnosis of dengue virus infection is complicated by the existence of cross-reactive antigenic determinants shared by all four dengue serotypes and some other flaviviruses (38). The absence of cross-reactivity between HAFs against WNV and the selected phage clones makes these phage-peptides very attractive for diagnostic purposes. The use of anti-dengue 3 sera in the selection process could explain the optimal recognition of phage clones included in both clusters by HAFs against dengue 3. H3/6 has been characterized as a dengue anti-complex monoclonal antibody specific to the E protein that is non-reactive with other flaviviruses (25). The fact that none of the phage clones was recognized by this monoclonal antibody suggests that they do not display peptides mimicking the epitope of the E protein recognized by this monoclonal antibody.

Competition ELISAs with the original antigen are necessary to ensure that the phage clones are specific for the antigen binding site of the antibody (29). Inhibition of the reaction of the human sera positive for dengue virus antibodies after absorption with the phage clones supports the hypothesis that the peptides mimic dengue virus epitopes and block the reaction of serum antibodies with the virus. Differences in absorption of the antibodies by the different phage clones can be explained by differences in the concentrations of antibodies against the corresponding epitope and the affinity of the antibodies for the mimotope. Only four phage clones were able to compete with the virus for binding to dengue virus antibodies. Peptides exposed on these clones could mimic specific dengue mimotopes. Competitive assays are particularly useful in cases in which a large panel of sera containing antibodies of the studied entity is not available or when it is not possible to sequence all of the selected clones.

Two peptides mimicking B-cell epitopes of the NS3 and NS4B non-structural proteins of the four dengue virus serotypes were identified. Three phage clones (Ph2, Ph15, and Ph35) displayed peptides with the same amino acid sequence (FERVPGEVT). This peptide shares partial homology with the NS4B dengue protein. Although NS4B has not been previously reported as one of the principal proteins involved in dengue virus antibody responses, consistent antibody responses to NS4B were recently found in a study of 100 sera samples from dengue patients that were tested against recombinant NS4B by ELISA (9). Phage clone Ph37 displays a peptide that is similar to two regions of the NS3 protein of the four serotypes. This peptide shares five residues with the amino acid region 537–547. The NS3 amino acid region 537–547 is highly conserved with at least 80% identity between a total of 44 strains from the four serotypes (39). In the same study, this sequence was not shared with 64 other flaviviruses, suggesting that this sequence is dengue virus-specific, which corroborated the results obtained for reactivity with HAFs. It has been proposed that this peptide could possibly function in cell attachment (39). The peptide expressed on clone Ph37 also exhibited similarity with five residues in the NS3 region (amino acids 421–481). This sequence has been reported as a strong inducer of T-cell responses in dengue virus-infected patients (40). Although the NS3 protein induces a strong T-cell response, and a preponderance of T-cell epitopes have been identified (41), the functional significance of antibody responses against this protein remains to be elucidated (5–9). Further studies should be performed to determine the participation of the selected peptides in T-cell responses. There have been several reports of the identification of B-cell epitopes of dengue virus using serotype-specific monoclonal antibodies of dengue virus (16–19). In our work, two peptides were selected using serum samples of confirmed dengue patients, suggesting this method could be used to develop a reagent for the diagnosis of dengue patients.

During a primary infection, individuals develop IgM after 5–6 days and IgG antibodies after 7–10 days. During a secondary infection, high levels of IgG are detectable even during the acute phase and they rise considerably over the next two weeks. IgM levels are lower and, in some cases, absent during secondary infection. The presence of IgM antibodies suggests a recent infection, although they are still present after 2–3 months. High titres of IgG are a criterion of secondary infection (13). The ability of the phage-displayed peptides to bind to IgG antibodies from dengue patients could be potentially useful to discriminate between primary and secondary infection.

Several studies have been conducted on antibody responses to non-structural proteins (9). A comparison of the amino acid sequences of the selected clones showed similarity with NS3 and NS4B proteins of dengue virus. Further investigations are needed to evaluate the immunogenicity of these peptides as experimental anti-dengue subunit vaccines. Synthetic peptide vaccines are relatively cheap, safe to produce, and heat stable. The antibody dependent enhancement (ADE) hypothesis emphasizes the importance of the immune response in the development of DHF/

Dengue Shock Syndrome (DSS). Therefore it is necessary to determine if antibodies against these peptides can enhance dengue virus infection and study its possible role in the immune-amplification phenomenon.

In the present study, two B-cell epitopes of dengue virus were identified using a phage-display peptide library and polyclonal anti-dengue virus antibodies. Our results suggest that these two peptides are immunologically important and could be used for the development of diagnostic systems and a potential vaccine against this pathogen.

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Author's contributions

Conception and design: NA
Data analysis and interpretation: NA, AA, FC, JCR, EMP
Data collection and assembly , drafting of the article: NA, AA
Critical revision of the article: FC, MP, DIS, EMP, A.Acosta
Provision of study materials or patients: FC, YV, MP
Statistical expertise: LI
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ORIGINAL ARTICLE

A Study of Learning Environments in the Kulliyyah (Faculty) of Nursing, International Islamic University Malaysia

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Abstract

Background: **In a nursing programme, the main objective is to produce nursing graduates who can provide comprehensive care and treatment to the community. A good approach to the systematic design of a learning environment can lead to positive outcomes for graduates. The learning environment is more than student-teacher interaction, teaching and learning activities. Good physical structures and facilities provided by the university are important, too. Furthermore, the university must also be concerned about meeting students' psychosocial and emotional needs. The aim of this study is to measure the learning environment by administering the Dundee Ready Educational Environment Measure (DREEM) questionnaire to students across the four years of the Bachelor of Nursing programme at the Faculty of Nursing, IIUM, and to identify areas for change that may contribute to a more meaningful student learning experience.**

Methods: **The DREEM questionnaire was administered to 105 Bachelor of Nursing students at IIUM.**

Results: **The total mean score on the 50-item DREEM inventory was 120.12 out of a maximum of 200. Student perceptions of learning and their teachers, their academic self, social self and their perception of the atmosphere were all positive. Eight items with low mean scores (less than two) on the DREEM questionnaire were identified as requiring remediation.**

Conclusion: **The implications include the need to create and maintain a supportive environment, in addition to designing and implementing interventions to remedy unsatisfactory elements of the learning environment if effective and successful teaching and learning are to be realised. Thus, specific remedial steps to improve the student learning environment of the Faculty of Nursing, IIUM are described.**

Keywords: *learning environment, curriculum, nursing and DREEM, health sciences*

Introduction

The learning environment is not limited to student-teacher interaction, teaching and learning activities, but also includes having good physical structures and facilities provided by the university (1). The university has to be concerned about students' psychosocial and emotional needs as well. By providing all these features, the university has the potential to offer a productive learning environment. Studying the learning environment is important in improving the quality of an educational programme (2). Many universities use a basic approach to determine students' needs by viewing students as main stakeholders in their own education (3).

In nursing education, teachers have paid particular attention to student perceptions of the learning environment (4). Moreover, students' perceptions of the learning environment should be studied over time. This is because of changes in student-body composition and the teacher population. Sometimes new innovative educational approaches can also give rise to different student perceptions.

The concept of the learning environment

Learning environment issues in higher education can be viewed through many perspectives. Each school has its own understanding about its learning environment. However, the concept of the learning environment must come from someone who is an expert in the education field. This is because historically, the learning environment is derived from educational practise. Therefore, in order to implement a good and appropriate learning environment, we need to understand the concept of the learning environment and implement it in our school appropriately. The concept of learning has been well-recognised in the educational literature but is a relatively new concept in nursing education (5–7).

Bloom (5) described the educational or learning environment concept as "the conditions, forces, and external stimuli which challenge on the individual. These forces may be physical, social, as well as intellectual forces and conditions". He conceived a range of environments from the most immediate social interactions to the more remote cultural and institutional forces. He regarded the environment as providing a network of "forces and factors which surround, engulf, and play on the individual". Therefore, it can be said that the learning environment is an interactive network of forces within the teaching and learning activities that influence students' learning outcomes. Specifically, in nursing education, the learning environment has to be integrated between theory and clinical practise in order to obtain balanced learning outcomes (6–8).

The DREEM instrument is able to assess both components—theory and clinical practise. It also includes all aspects involving teaching and learning in both the medical or health professional schools that are synonymous with the clinical environment. Although the learning environment is a subtle and intangible concept, considerable progress has been made over the last quarter of the twentieth century in its conceptualisation. The development of assessment inventories enables student perceptions of the learning environment to be quantified and compared, either longitudinally within a single health care institution or between institutions (9).

A British study clearly recognised the existence of a learning environment and identified several areas of importance in the characterisation of that environment. Organisational and attitudinal characteristics were major predictors of the learning environment. Organisational issues identified included: the ward routine, patient care, the structuring of teaching, and the matching of clinical and classroom procedures (curriculum). A ward attitude that recognises and values the students as learners provides a superior learning environment (8). Therefore, ward staff are the most influential participants, apart from the students themselves, in the learning environment. They are the gate keepers and guides to learning opportunities, and the students' most consistent link between the educational and workplace demands of the learning environment (10).

Kulliyyah (Faculty) of Nursing, IIUM

The Kulliyyah of Nursing, the most recently established of the International Islamic University Malaysia (IIUM) kulliyyahs, admitted its first class of undergraduate degree programme students in June, 2004. The curriculum of the nursing kulliyyah at IIUM, as in all nursing schools in Malaysia, is still a mix of innovative and conventional practises that have been in existence for more than a decade. Although the nursing programme has changed from a hospital-based to a university-based education, the teaching styles remain the same. The main approach in teaching and learning activities is teacher-centred, in which information is provided via lecture to a large number of students, and the students fully depend on the information gathered in their lectures. In tutorial and practical sessions, students participate more actively but still expect their teachers to continue providing information. Interestingly, most of the nursing schools in Malaysia are now introducing some innovative approaches in their programmes, such as problem-based learning through subject-oriented practise. However, the goals of these approaches are difficult to achieve due to subject-based practises in the curriculum. For instance, problem-based learning is only effective if it is used with a multidisciplinary approach that is integrated into the curriculum (11).

As one of the newest faculties at IIUM, the Kulliyyah of Nursing aims to produce highly competent nursing graduates by introducing sophisticated teaching and learning environments. Hence, this study aims to determine nursing students' perceptions of the learning environment in their undergraduate nursing programme and identify areas for change. The objective is to use this information to critically evaluate the learning environment, with a view to enhancing the learning experience, after four years of running the programme. Therefore, the findings of this study will be used as baseline information for the curriculum review committee to inform changes to the current curriculum that will improve the quality of student life on campus, including

areas such as social atmosphere and effective administration. Moreover, the study findings may assist in developing guidelines to help teachers improve their teaching skills in relation to students' perceptions.

As at the commencement of the 2007/2008 academic year, the focus of the Kulliyyah's teaching activities are on the conduct of Years One, Two, Three and Four of its four-year undergraduate programme, which leads to the award of the Bachelor of Nursing (Honours) degree. This programme has been designed to prepare nurses for entry-level professional practise and, at the same time, provide a strong basis for postgraduate study. The programme is four years long and incorporates a substantial amount of guided clinical practice in hospitals and health care settings as well as a range of campus-based theoretical and laboratory-based teaching and learning activities. The objectives of this study are:

- to identify the overall score of nursing students' for the learning environment of the IIUM nursing programme
- to identify any differences between mean scores on the learning environment survey across the various years of the nursing programme

Materials and methods

This research used a quantitative, cross-sectional survey design. All nursing students from years one to four (n = 107) were eligible to participate as study respondents. The study took place at the Kulliyyah of Nursing, IIUM. The researchers sought ethical approval from the Kulliyyah of Nursing, IIUM and the Centre of Medical Education, Dundee University. The questionnaire was distributed each year of the Bachelor of Nursing programme. Participants provided their consent prior the completion of the questionnaire, after reading a summary of information regarding the purpose of the survey, and their confidentiality and anonymity were assured on at the front page. The total time required to answer the 50-item questionnaire was estimated at approximately 20 minutes. Participant return the completed questionnaire in the sealed box provided.

Instrument

The Dundee Ready Education Measure (DREEM) is an internationally validated, non-culturally specific inventory that provides medical and health profession educators with a diagnostic tool to measure the state of their school's learning and teaching climate (2). It can produce global readings and diagnostic analyses of an undergraduate learning environment in medical schools and other health profession institutes. It allows quality assurance comparisons between courses and even between components of a particular course. The items in DREEM are of such a nature that it is the environment of the entire curriculum is being assessed.

Roff et al. (12) developed the 50-item DREEM using a standard methodology utilising grounded theory and a Delphi panel of nearly 100 health profession educators from around the world, with validation by over 1 000 students in countries as diverse as Scotland, Argentina, Bangladesh and Ethiopia. Participants were asked to measure and 'diagnose' the undergraduate learning environments for the health professions. The instrument was designed to be a non-culturally specific instrument and was used in several settings including the Middle East, Oman, Thailand, Nepal, Nigeria, United Kingdom, Canada, Ireland, Indonesia, Malaysia, Norway, Sweden, Venezuela, the West Indies, Sri Lanka, and Yemen (13).

DREEM was used as an instrument to measure students' perceptions of their learning environment and allowed quality assurance comparisons between years as well as within the theoretical and clinical components of a particular programme. The response options for items on the DREEM inventory are: 4 for Strongly Agree (SA), 3 for Agree (A), 2 for Uncertain (U), 1 for Strongly Disagree (SD). However, nine of the 50 items (numbers 4, 8, 9, 17, 25, 35, 39, 48, and 50) are negative statements and therefore reverse coding is required. The 50 DREEM items add up to a maximum score of 200, which would be an 'ideal learning environment'. A score of 0 is the minimum and would be a worrying result for any medical or health institution. The instrument contains five domains, which are as follows (12):

1. Student perception of learning (SPoL) – 12 items / maximum score = 48
2. Student perception of teaching (SPoT) – 11 items / maximum score = 44
3. Student academic self-perception (SASP) – 8 items / maximum score = 32
4. Student perception of atmosphere (SPoA) – 12 items / maximum score = 48
5. Student social self-perception (SSSP) – 7 items / maximum score = 28

SPSS (version 12.0.1) was used to analyse the data in this study. Data were coded, entered, checked for data entry errors, explored and cleaned. The researcher used alphas of 0.05 and confident intervals of 95%. Frequencies for each items score were tabulated, and any missing records verified.

Statistical assumptions were tested prior to running the analyses, and all variables were found to satisfy the assumptions for the normal distribution, homogeneity of variance and independence of observations.

Participants

The response rate among the Bachelor of Nursing students at IIUM was 98.13%; 105 out of 107 students returned the completed survey forms. Eighteen (17.10%) were males and 87 (82.90%) were females. Ages ranged from 19 to 23 years, with a mean age of 21.18 (SD = 1.01) years. Year One students represented the largest cohort, making up (45.70%) of respondents. This was followed by Year Two (22.90%) and Year Three (20.00%) respondents. The lowest number of respondents was from the Year Four nursing students (11.40%), representing the first batch of nursing students to commence study at IIUM, in 2004 (Table 1). All the respondents underwent matriculation at the IIUM foundation centre prior to enrolling in the nursing bachelor program and were staying together in the same hostel accommodation provided by IIUM on campus.

Results

Total DREEM score for Bachelor of Nursing, IIUM

Table 1 shows the overall mean DREEM scores for IIUM Bachelor of Nursing respondents. The mean total score was 120.12 out of 200 for the 50 items, and this total score was in the range for 'positive' (rather than 'negative') learning environments. Eight items had mean scores of less than two, with an average of one to two items in each domain. The highest mean score was 3.18 (item 2), and the lowest mean score was 1.56 (item 12). Only three items had a real positive perception, from the respondents' point of view. A total of 39 items had aspects of the learning environment climate that could be enhanced.

Total of each domain score for the Bachelor of Nursing, IIUM

Table 2 illustrates the total mean scores for each of the five domains in the DREEM inventory. The total mean score for domain 1 was 28.54 out of 48.00. The highest score was 31.43, from Year One. The overall total score for this domain represents a 'positive' perception of the learning environment. For domain 2, the maximum attainable score was

Table 1: Single item mean scores for learning environment of the IIUM nursing students in each year, and overall scores.

Item	Year One (n=48)	Year Two (n=24)	Year Three (n=21)	Year Four (n=12)	Overall (n=105)
Students' perception of learning (SPoL)					
1. I am encouraged to participate in class	2.94	2.92	2.90	3.08	2.94
7. The teaching is often stimulating	3.05	2.25	2.48	2.42	2.69*
13. The teaching is student-centred	2.29	1.71	1.57	1.67	1.94*
16. The teacher is sufficiently concerned about developing my competence	2.85	2.08	1.86	1.92	2.37*
20. The teaching well-focused	2.60	2.08	1.90	1.92	2.27*
22. The teacher is sufficiently concerned about developing my confidence	2.81	2.08	1.71	1.92	2.32*
24. The teaching is put to good use	2.98	2.37	2.19	2.25	2.60*
25. The teaching is over-emphasised, compared with factual learning	1.92	1.83	2.14	1.83	1.93
38. I am clear about the learning objectives of the course	2.65	2.63	2.43	2.42	2.57
44. The teaching strategies encourage me to be an active learner	2.69	2.04	2.14	2.08	2.36*
47. Long-term learning is emphasised over short-term learning	2.58	2.83	2.71	2.17	2.62
48. The teaching is too teacher-centred	2.08	1.96	1.76	1.50	2.00

Students' perception of teaching (SPoT)					
2. The teachers are knowledgeable	3.77	2.50	2.86	2.75	3.18*
6. The teachers are patient with patients	3.11	2.37	2.67	2.33	2.77*
8. The teachers ridicule the students	3.19	2.29	2.33	2.17	2.70*
9. The teachers are authoritarian	1.50	1.79	1.57	1.50	1.58
18. The teachers have good communication skills with patients	3.04	2.17	2.81	2.25	2.70*
29. The teachers are good at providing feedback to students	2.92	1.79	1.57	2.17	2.30*
32. The teachers provide constructive criticism here	2.63	2.21	2.24	2.50	2.44
37. The teachers are approachable	2.96	2.46	2.48	2.50	2.70*
39. The teachers get angry in class	3.08	1.92	1.76	2.08	2.44*
40. The teachers are well-prepared for their classes	3.06	2.13	2.38	2.67	2.67*
50. The students irritate the teachers	2.71	2.75	2.67	2.25	2.66
Student academic self -perception (SSAP)					
5. Learning strategies which worked for me before continue to work for me now	2.21	1.83	2.14	2.50	2.14
10. I am confident about passing this year	2.94	2.75	3.10	2.58	2.89
21. I feel I am being well-prepared for my profession	2.56	1.87	1.52	1.58	2.09*
26. Last year's work has been a good preparation for this year's work	2.29	2.25	1.52	1.92	2.09*
31. I have learned a lot about empathy in my profession	3.12	3.17	3.33	2.50	3.10*
41. My problem-solving skills are being well-developed here	2.60	2.29	2.19	2.17	2.40
45. Much of what I have to learn seems relevant to a career in nursing	3.21	2.88	2.86	2.83	3.02
27. I am able to memorise all I need	1.90	1.62	1.48	1.42	1.70
Students' perception of atmosphere (SPoA)					
12. This kulliyyah is scheduled well	2.46	1.13	0.48	0.75	1.56*
17. Cheating is a problem in the kulliyyah	2.19	3.04	1.90	2.58	2.37*
23. The atmosphere is relaxed during lectures	2.77	2.13	2.24	1.92	2.42*
30. There are opportunities for me to develop interpersonal skills	3.23	2.96	2.67	2.50	2.97*
33. I feel comfortable in class, socially	2.94	2.79	2.67	2.17	2.76*
34. The atmosphere is relaxed during teaching sessions and tutorials	2.83	2.29	2.38	1.92	2.51*
35. I find the experiences disappointing	2.58	2.13	2.14	2.00	2.32
36. I am able to concentrate well	2.10	1.96	1.81	2.00	2.00
42. The enjoyment outweighs the stress of studying nursing	2.46	2.17	2.57	1.50	2.30*
43. The atmosphere motivates me as a learner	2.81	2.38	2.29	2.00	2.51*
49. I feel confident to ask the questions I want	2.12	2.38	2.10	2.33	2.20
11. The atmosphere is relaxed during the ward teaching	2.44	1.08	1.52	1.50	1.84*

Student social self-perception (SSSP)					
4. I am too tired to enjoy this course	2.60	2.17	2.29	1.33	2.30*
14. I am rarely bored of this course	1.40	1.79	1.86	1.67	1.61
15. I have good peers in this kulliyyah	3.37	3.08	2.90	2.67	3.13*
19. My spiritual and social life are good	2.94	2.75	2.48	2.58	2.76
28. I seldom feel lonely and friendless	1.85	1.88	2.19	2.50	2.00
46. My accommodations are pleasant	2.50	2.58	2.76	2.50	2.57
3. There is a good support system for students who become stressed	2.19	1.71	1.52	1.58	1.88*
OVERALL	**132.06**	**112.20**	**110.05**	**105.83**	**120.12**

Note: * P < 0.05
Negative items are in italics

44, with 11 items included. This domain scores suggest that the respondents had a favourable impression of their teachers. For domain 3, there was not much difference in scores across years, and the mean overall scores fell to 19.42. Scores on domain 4 reveal positive perceptions of the atmosphere; the total mean score was 27.78. Lastly, domain 5 scores suggest that the respondents' social self-perceptions were in the category of average with the total mean of 16.23. This domain illustrates the students could tolerate their social environment, incorporate with their teaching and learning activities in the campus.

Differences of means in learning environment in the Bachelor of Nursing programme

Table 3 describes the mean differences in learning environment by year of study. The null hypothesis is rejected at the 5% significance level because a Bonferroni post hoc test shows a significant mean difference between mean Year One and mean Year Two scores [19.85 (9.33 – 30.38)], three [22.01 (11.00 – 33.03)] and four scores [26.22 (12.64 – 39.82)].

Discussion

The survey results suggest that the Kulliyyah of Nursing, IIUM has achieved a more positive than negative status, which is just a level below the highest category of achievable scores. Students of the innovative curricula tend to show more satisfaction with their educational environments, compared to students of the traditional curricula (13). Higher DREEM scores tend to indicate more student-centred curricula, while those offering conventional curricula commonly score less than 120 out of 200 (13). Even though the IIUM's total mean scores are above 200, many students perceive that IIUM does not have a student-centred approach; scores were low (mean = 1.93) for item 13 (The teaching is student-centred). This is possibly because there is no integration between subjects, which may cause them much difficulty in utilising available learning resources effectively. An integrated curriculum is one of the strategies that could be introduced to enhance student-centred education (1). In another study, it was found that among three medical schools in the Middle East (King Faisal University (KFU) in Saudi Arabia, which has a traditional curriculum; and Arab Gulf University (AGU) in Bahrain and United Arab Emirate University (UAE), which have innovative curricula) students at AGU and UAE perceived their learning environment as more satisfactory compared with students at KFU. This was reflected in the mean total DREEM scores of 127.00 for AGU, 125.00 for UAE and 111.00 for KFU respectively.

In the present study, the overall DREEM score is 120.12 out of a maximum 200, from four groups of nursing students at the Kulliyyah of Nursing, IIUM. The Year One group had the highest score, with a mean of 132.06. The Year Two, Three and Four group students' overall mean DREEM scores were in the range of 105.83 to 112.20. The findings are in line with those of Hla et al. (14), who noted a trend for reduced scores in the senior years. It was suggested that this trend could be due to the fact that students genuinely believed that the learning environment was deteriorating, and thus were psychologically tired of being a student and looking forward to leaving student life. The students' perceptions in Year One could have been high initially, and dissatisfaction may have crept in as the novelty of joining a nursing student body wore off.

Table 2: Total of each domain score across all years of the Bachelor of Nursing programme at IIUM

Domain	Year	(n)	Mean (SD)
Domain 1			
Students' Perception of Learning (SPoL) – 12 items	1	(48)	31.43 (3.994)
	2	(24)	26.79 (5.500)
	3	(21)	25.48 (4.966)
	4	(12)	25.17 (3.857)
Overall: **28.54 / 48.00**			
Domain 2			
Students' Perception of Teaching (SPoT) – 11 items	1	(48)	31.98 (3.629)
	2	(24)	24.38 (4.490)
	3	(21)	25.33 (5.072)
	4	(12)	25.12 (3.157)
Overall: **28.13 / 44.00**			
Domain 3			
Student Academic Self – Perceptions (SASP) – 8 items	1	(48)	20.83 (3.117)
	2	(24)	18.67 (4.498)
	3	(21)	18.14 (3.610)
	4	(12)	17.50 (2.393)
Overall: **19.42 / 32.00**			
Domain 4			
Students' Perception of Atmosphere (SPoA) – 12 items	1	(48)	30.94(4.304)
	2	(24)	26.42(5.241)
	3	(21)	24.76(5.029)
	4	(12)	23.17(2.552)
Overall: **27.78 / 48.00**			
Domain 5			
Students' Social Self -Perception (SSSP) – 7 items	1	(48)	16.85(3.390)
	2	(24)	15.96(4.154)
	3	(21)	16.00(3.178)
	4	(12)	14.83(2.125)
Overall: **16.23 / 28.00**			

Table 3: Mean differences in learning environment by year of study

Variable	(n)	Mean (SD)	F stat (df)	P-value
Year One	48	132.06 (14.18)		
Year Two	24	112.20 (19.40)	17.61(3, 103)	<0.001
Year Three	21	110.05 (16.89)		
Year Four	12	105.83 (9.27)		

Two local studies assessing students' learning environments using the DREEM questionnaire were from the International Medical University, which recorded a mean score of 129.30 (14), and the Dental Training Institute of Malaysia, which cited a mean DREEM score of 121.50 (15). A study of final year medical students in Trinidad reported an overall mean DREEM score of 109.9 (16). A large-scale study, involving medical students from both final and earlier undergraduate training years, showed a mean DREEM score of 118.00 in a Nigerian medical school and 129.00 in a Nepalese medical school. Interestingly, the Nigerian study had been analysed according to gender and academic year and was found to have statistically significant differences for gender and academic year (17). One of the largest samples (n = 968) reported an overall mean DREEM score of 128.80 for medical students in the UK (18).

There are also a few studies which have demonstrated higher overall mean DREEM mean scores. In Malaysia, a study by Intan (19) reported a high mean DREEM score of 134.42. Intan's study was carried out in one of the private nursing colleges in Kota Bahru. In a series of UK learning environment studies, Miles and Leinster (20) recorded the highest mean DREEM score—142.91. Their study measured medical students' perceptions of the learning environment by asking about their expected and actual perceptions. Interestingly, the expected mean DREEM mean score was much higher (152.46) when compared to the actual DREEM mean score. Roff et al. (17) reported (in another study in the UK which attempted to measure whether the learning environment perceived by students varied at different teaching hospital centres) a relatively high mean DREEM score of 139.00.

Differences of means in the learning environment

It is interesting to note that from the overall DREEM score in the study, we can summarise that there are significant differences between the DREEM scores across the four-year nursing programme at IIUM. Mean responses of the four groups were compared to determine which year-groups significantly differed from one another. The results of these comparisons indicated large differences between all the years (mean differences were in the range of 19.85 to 26.22). Obvious differences were clearly seen between Year One and Year Four. It is possible that Year One students' scores were influenced by their expectations and knowledge that they were coming to a new nursing school (20). First year students' scores might have been higher due to the fact that they had only been at the Kulliyyah of Nursing for six months when they were asked to complete the questionnaire and they had therefore not yet experienced many stressful aspects of the learning environment, such as relating theoretical knowledge to the clinical practise environment. Moreover, the apparent differences in how the different groups experienced the learning environment at the institution highlight differences in their degree of experience in both the institution and the curriculum. For instance, it is possible to identify some stress points among final year students due to their more challenging teaching and learning activities (17).

This feedback from our students will inform a revised curriculum aimed at enhancing the quality of the learning environment in this Bachelor of Nursing programme. Issues will be addressed by the Curriculum Review Committee in 2010. Notwithstanding, a short-term strategic plan has been implemented in order to deliver an optimally conducive learning environment for junior nursing students at all year levels.

The researchers would like to investigate students' insights relating to the items that were scored as unsatisfactory by conducting focus groups in the near future. The focal elements are those items with a mean score of less than two. This is because any items with a mean of less than two represent poor learning environments, and by conducting focus groups, we may learn what the main problems are and how they might be addressed

Recommendations

Nursing students in the Kulliyyah of Nursing value theory and clinical practise and the possibilities they offer in the process of becoming a nurse and a professional. First and foremost, it is important to recognise and accept the negative viewpoints of the students, with regard to features of their learning environment. The Kulliyyah should be able to provide a suitable, conducive and harmonious learning environment at the right time, so that theory and practice can complement each other.

Based on the study findings, we suggest specific plans of action in order to provide a quality learning environment for Bachelor of Nursing students. The recommendations are as follows:

1. Prepare detailed documentation for the Curriculum Committee on the findings of the DREEM inventory as baseline information for the next curriculum review.
2. Provide information on student perceptions of their learning environment to each Kulliyyah member. This will potentially influence each member in facilitating the planning and implementation of student-centred (rather than teacher-dominated) curriculum.
3. Plan and implement a strategic faculty development programme to focus on student-centred learning for academic staff members.
4. Provide strong student support facilities for counselling, sporting and cultural activities on the campus. The Kulliyyah should be aware that students need to not only focus on their studies but should also have the opportunity to experience extra-curricular activities and meaningful experiences on campus.
5. Improve scheduling so students are kept informed and prepared for their learning activities.
6. Create a harmonious learning environment during students' clinical postings and provide them with detailed, clinical learning objectives.
7. Stimulate and facilitate students' efforts at integrating theory components with practice and help them to approach learning as a lifelong process, rather than as mere factual learning.
8. Reward teachers for excellence in teaching and leadership so that they are motivated in their careers.

Conclusion

This small study has provided useful information on student perceptions of their learning environment by using the DREEM inventory. The study identified mean overall DREEM scores of 120.12/200 from four groups of IIUM Bachelor of Nursing students. Although the overall learning environment score of this Kulliyyah was observed to be just one step below 'excellent', there were eight items out of the 50 that showed mean scores of less than 2.00 that should be examined more closely, as they indicate problem areas. Subsequently, a focus group discussion should be performed as a follow-up to explore further the actual learning environment problems in the Kulliyyah of Nursing. These findings need to be interpreted with caution, as the size of the sample from each year was quite different, as previously discussed. The recommendations arising from this DREEM study at IIUM include the need for the creation of a supportive environment, in addition to designing and implementing interventions to remedy unsatisfactorily elements of the learning environment for more effective and successful teaching and learning.

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Author's contributions

Conception and design, data collection, analysis and interpretation, drafting of article, obtaining funding: NMS
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ORIGINAL ARTICLE

Prognostic Factors of Severe Traumatic Brain Injury Outcome in Children Aged 2-16 Years at A Major Neurosurgical Referral Centre

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Abstract

Background: **Traumatic Brain Injury (TBI) in children has been poorly studied, and the literature is limited. We evaluated 146 children with severe TBI (coma score less than 8) in an attempt to establish the prognostic factors of severe TBI in children.**

Methods: **The severity of TBI was assessed via modified Glasgow Coma Score for those more than 3 years old and via Children Coma Score for those under 3 years old. Clinical presentations, laboratory parameters and features of Computerised Tomography brain scans were analyzed. Outcomes were assessed at 6 months with the Pediatric Cerebral Performance Categories Scale; the outcomes were categorised as good or poor outcomes. Correlations with outcome were evaluated using univariate and multivariate logistic models.**

Results: **A low coma score upon admission was independently associated with poor outcome. The presence of diabetes insipidus within 3 days post-TBI (OR: 1.9), hyperglycaemia (OR: 1.2), prolonged PT ratio (OR: 2.3) and leukocytosis (OR: 1.1) were associated with poorer outcome.**

Conclusion: **Knowledge of these prognostic factors helps neurosurgeons and neurocritical care specialists to manage and improve outcome in severe TBI in children.**

Keywords: *severe traumatic brain injury (TBI), children, prognostic factors, Pediatric Cerebral Performance Categories Score, neurosciences*

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in the paediatric age group. In developed countries, paediatric trauma mortality still represents more than half of all childhood fatalities: 18 times more common than brain tumours (1). However, many aspects of paediatric neurotrauma still remain unclear as the literature focusing on the paediatric population per se is very limited. In fact, guidelines for management of paediatric TBI were mainly derived from adult guidelines (2).

The fact that paediatric TBI patients are more prone to develop brain swelling support the idea that maturing brain reacts to insult in a different way (3). Several prognostic factors, such as age group, gender, pupillary reactivity, Glasgow Coma Score (GCS) on admission, serum glucose level, total white blood cell (TWBC) counts, platelet counts, coagulation derangement, computerised tomography (CT) scan features and grading, have been validated in various studies to predict outcome in adult neurotrauma. However, the impacts of these factors are poorly understood in paediatric TBI. The predictive value of GCS was reported to be low in one local paediatric TBI study (4). Not infrequently, those with GCS scores of 3 to 5 upon admission may still recover with independent function (5).

The role of glucose level is somewhat controversial in the paediatric neurotrauma literature (6). Parish et al. reported that hyperglycaemia was not a poor prognostic factor in paediatric TBI, as is true in the adult population (7). However, Michaud et al. later demonstrated

that hyperglycaemia was associated with poor neurological outcome in a larger series (8). Cochran et al. observed that paediatric severe TBI patients with admission serum glucose levels > 300 mg/dL (16.65 mmol/L) were uniformly more prone to death (9).

Chiaretti et al. found that delayed activated partial prothrombin Time (aPTT), low platelet count, elevated fibrin-fibrinogen degradation products (FDP) and low fibrinogen were associated with poor outcome in their paediatric TBI series, which consisted of 60 patients. Kuo et al. however, demonstrated that only FDP > 1000 μg/mL upon admission to the hospital in children with GCS scores of 7–12 was associated with a poor outcome (10).

Most subjects in the series on prognostic factors were from developed countries with sophisticated systems of regional organization coupled with experienced trauma centres, which allowed for rapid evacuation, monitoring and treatment of these patients (11,12,13). Experienced staff and equipment such as ventilators and intracranial monitoring are still luxury items in Malaysia.

The aim of this study is to identify factors associated with the outcome of paediatric severe TBI that can be identified early, during the first few hours after admission. We hope to use these findings to predict the outcome of severe TBI to guide treatment strategies in Malaysia.

Materials and Methods

We performed a cross-sectional analysis investigating children aged between 2 to 16 years presenting with severe TBI treated in Kuala Lumpur Hospital (HKL) from January 2001 until December 2006. Patients were managed according to a standard departmental protocol that includes artificial ventilation and sedation with midazolam/morphine infusions. Patients were positioned in the supine position with the head elevated 30 degrees. The following parameters were kept within the desired ranges: temperature < 37.0 °C; partial pressure of carbon dioxide ($paCO_2$) 35–45 mmHg; intracranial pressure (ICP) < 20 mmHg; cerebral perfusion pressure (CPP) within 60–70 mmHg. We also performed surgical evacuation and decompression for lesions with mass effects and decompressive craniectomy for refractory intracranial hypertension. Data regarding initial coma score, pupillary reactivity, motor score, presence of hypotension (defined as less than the 5th percentile according to age-appropriate systolic blood pressure [AASBP]) and development of diabetes insipidus (DI) within 3 days were retrieved from hospital notes. Laboratory results for serum glucose, prothrombin time (PT) and aPTT ratio, international normalized ratio (INR), platelet counts and TWBC upon admission were recorded. CT scans were graded according to the Marshall classification, the presence of brain swelling, traumatic subarachnoid haemorrhage and intraventricular haemorrhage. Peak ICP and lowest CPP were recorded for those patients who had undergone ICP-CPP targeted therapy. Outcomes at 6 months were assessed with the Pediatric Cognitive and Performance Categories (PCPC) scale. Patients were categorised as having a "good outcome" or a "poor outcome". Data entry and analysis were done using the Statistical Package for Social Sciences (SPSS) version 12.0. We used logistic regression to develop a model of risk factors for poor outcome from paediatric severe TBI. Independent variables were entered into the logistic model in a stepwise fashion with a significance cut-off of $P < 0.25$. We interpreted a P-value of less than 0.05 as significant at a 95% confidence interval (CI). Hosmer-Lemeshow goodness-of-fit testing established the best model—forward likelihood. The research protocol was approved by the ethical committee of Universiti Sains Malaysia in 2006.

Results

One hundred and sixty-seven children with severe TBI were admitted to HKL neurosurgical intensive care unit (ICU) between January 1 2001 and December 31, 2006, after exclusion criteria applied. Only 146 patients out of 167 were included in the study as the rest were lost upon follow up. The median age of patients was 13 years with a mean of 11.7 years and standard deviation of 4.2 years. The majority of the patients (133, 91.1%) were older than 4 years; 13 patients (8.9%) were less than 4 years; 123 patients (84.3%) were male and 23 (15.7%) were female. The majority of the patients (107, 73.3%) were of Malay origin. Eighty-nine cases (61%) had good outcomes according to the PCPC scale at 6 months. There were 35 cases of deaths (24%). Most of the cases were referrals from other centres (83.6%); 24 cases (16.4%) were direct admissions. The most common mechanism of injury was road traffic accidents (RTA), which accounted for 118 cases (80.8%); followed by fall from height, 14 cases (9.6%); 8 cases of unknown mechanism (5.5%); 2 cases from contact sports (1.4%) and another 2 cases from assault (1.4%).

Univariate analysis of outcome showed statistically significant differences in AASBP (P

= 0.006), coma score on admission (P = 0.038), motor response (P = 0.007), pupillary reactivity in those with equal and not dilated pupils (P = 0.001), presence of DI (P < 0.001), serum glucose level (P = 0.001), TWBC counts (P = 0.043), aPTT ratio (P = 0.03), PT ratio (P < 0.001), INR (P = 0.009), peak ICP value (P = 0.028), minimum CPP value (P = 0.001), Marshall CT grading (P = 0.025), presence of brain swelling (P = 0.009) and presence of IVH (P = 0.042). ICP monitoring and ICP-CPP directed therapy were only available in 39% of severe TBI in children aged 2–16 years old during the study period. These measures were not included in the logistic model.

The multivariate logistic regression model with the forward LR (likelihood ratio) method concluded that coma score on admission (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.04–7.92), presence of DI (OR, 7.16; 95% CI, 1.74–29.50), PT ratio (OR, 23.17; 95% CI, 2.99–179.50), glucose level (OR, 1.19; 95% CI, 1.00–1.42) and TWBC counts (OR,1.08; 95% CI, 1.01–1.61) upon admission were predictors of outcome in paediatric severe TBI.

The odds of having poor outcome are 7.2 times higher in those who develop DI within the first 3 days following TBI (OR, 7.16; 95% CI, 1.74–29.50). The odds of having poor outcome if the admission coma score was 3 to 5 is almost 3 times (OR, 2.88; 95% CI,1.04–7.92) higher than those with admission coma score of 5 to 8. Every increase in PT ratio of 0.1 significantly increases the odds of a poor outcome by almost 2.3 times; the change can be as little as 2.99 and as high as 179.46 at the 95% confidence level. The odds of poor outcome is 1.2 times greater with every increase of 1 mmol/L in glucose level upon admission and the change can be as little as 1.01 and as high as 1.42 (95% CI). Every increase in TWBC by 1 x 10^3 mm^3 increases the odds of a poor outcome by 1.1-fold; the change can be as little as 2.99 and as high as 179.46 (95% CI).

Discussion

Sixty-one percent of severe TBI children achieved good outcome at 6 months in our series. This was slightly better than the outcome of adult severe TBI in Singapore, which was reported to be 51.2% (14). Immature brain has greater neuroplasticity as compared to adults, and this property will be lost due to myelination as patients grow (15,16). However, the percentage of good outcomes was reported to be as high as 90% in the literature (17). The higher rate is probably because other studies on TBI in paediatric patients included mild, moderate and severe cases of TBI.

Our analyses did not find any association between age groups and outcome. This finding did not support the classic paediatric neurotrauma paper by Levin et al. (12). A recent study in the Indian population also failed to demonstrate age less than 4 as a factor affecting outcome (18). Poor outcome in those less than 4 years old of Levin's series is probably due to the high occurrence of non-accidental injury (NAI) in that age group. NAI is often associated with poor outcome as reported in the literature (19). There were no cases of NAI during the period of study in children aged 2–16 years old after excluding those less than 2 years old. Furthermore, the four centres involved where Traumatic Coma Data Bank (TCDB) data were collected were actually treating a small percentage of all the paediatric TBI during the study period. Therefore the sample was not truly representative.

We found no significant difference between outcome and gender in our study on severe TBI. Although Kraus et al. have reported 1.75 times greater risk for poor outcome in adult females, they actually included both moderate and severe TBI patients (20). Our findings support the more recent study on gender differences in outcome in an Asian population that included both adult and paediatric groups (21).

The coma scale that we used (Modified Glasgow Coma Scale for those > 3 years old and Children's Coma Scale for those < 3 years old) was reliable in predicting outcome in severe TBI in children. This modified scale is more appropriate in children as the total score for each component was equivalent to that obtained with the GCS, which made comparison with adult literature possible. The reliability of GCS in children with TBI has been questioned from time to time as it has great inter-observer discrepancies (4,5) Motor score upon admission was associated with poor outcome in univariate analysis but not observed in the logistic model after various variables were fixed.

There is no doubt that early hypotension contributes to secondary brain injury and subsequent poor outcome (22). Only eight cases (5.5%) had systolic blood pressure (SBP) less than AASBP upon admission in our series. This is probably due to the fact that most of our patients were referred from other hospitals (84.6%); those who were haemodynamically unstable would have been managed in other hospitals as they were not fit for transportation. Our univariate analysis did show that hypotension (defined as less than the 5th percentile of AASBP by the Brain Trauma Foundation in 2000) was associated with poor outcome; however this was not demonstrated in

multivariate analysis.

We suggest that the definition of hypotension in children in the context of TBI should be reconsidered. Vavilala et al. retrospectively reviewed the effect of various AASBP percentiles on outcome in children less than 14 years old and found that those with AASBP < 75th percentile (instead of 5th percentile) were more likely to exhibit poor outcome, even when SBP was more than 90 mmHg. The values of SBP in the National Task Force table have been derived from normal children and were according to their height. The cut-off point for hypotension in children with severe TBI should be set higher, probably at the 50th or 75th percentile of the SBP table by the National Task Force, or should be based on tables with values derived from critically ill or head-injured children. The recently published IMPACT study also called for reconsideration of SBP in the adult guidelines (23). They found that the outcome improved as SBP increased up to 135 mmHg.

ICP monitoring was available in 39% of severe TBI in children aged 2–16 years old during the period of study in HKL. In fact, Morris et al. reported that 59% of total severe TBI (children and adults) received ICP-CPP directed therapy in the UK. There were significant variations in the management of intracranial hypertension (24). From univariate analysis, peak ICP and minimum CPP values were associated with poor outcome at 6 months. The mean ICP of the good outcome group was 26.4 mmHg (*P*-value = 0.028), which is higher than the classical threshold for treatment for intracranial hypertension (20–25 mmHg). Minimum CPP values appeared to be more significant than ICP with *P*-value of 0.001. Thus, in selected cases, a higher limit of ICP may be acceptable as long as an adequate CPP can be maintained, as has been suggested in the adult guidelines for managing severe TBI by the Brain Trauma Foundation (BTF). There might also be age differences in the specificity of ICP and CPP in association with outcome as pointed out by Chambers et al. (25). Studies on the predictive value of ICP and CPP in terms of outcome can only be done in centres where all the severe TBI patients (coma score <8) are subjected to ICP-CPP directed therapy.

Our study also demonstrated that children with severe TBI who developed DI within 3 days post-trauma have a mortality rate of 71%. Boughey et al. reported a higher mortality rate of 86% in their study on 2014 patients of TBI from all age groups (26). There were 4 patients who developed DI within 3 days post-TBI who eventually exhibited good outcomes. This group might represent those with pure skull base injury or injury to the posterior pituitary instead of flow problems due to elevation in intracranial pressure or restriction of flow to the hypothalamic-pituitary axis due to cerebral oedema (27).

Our study confirms the deleterious effect of glucose on injured paediatric brain. The IMPACT study also demonstrated similar linear associations with outcome in the adult TBI population (28). Studies have shown that hyperglycaemia exacerbates the impact of ischemia and hypoxia in the injured brain, worsening secondary brain damage. The mechanisms involved include hyperosmolarity, lactic acid production, alterations in neuronal pH and increased excitatory amino acids. Researchers have shown substantial reduction in mortality in critically ill patients (non-diabetic) treated with early intensive insulin therapy (29). Further study on the effect of aggressive glucose normalization in the management of children with severe TBI should be carried out.

The importance of coagulopathy in paediatric TBI is increasingly being recognised (11,18,30,31). In view of the high incidence of coagulopathy in paediatric severe TBI, routine laboratory screening of coagulopathy was considered cost effective and has become standard practice in some centres as a component of the initial work-up of paediatric age group TBI (31). Chiaretti et al. suggested that D-dimer, FDP and fibrinogen be included as an initial screening test in paediatric TBI (30). At our centre, baseline coagulation tests were done on those with children with severe TBI. This included PT ratio, INR, aPTT ratio and platelet count. D-dimer, FDP and fibrinogen levels were not routinely available in our centre. Among the coagulation markers in our study, only PT ratio was associated with poor outcome with a high degree of accuracy in the multivariate study. aPTT ratio was associated with poor outcome in univariate analysis but not in the logistic model. PT ratio instead of aPTT ratio is crucial in determining outcome. This is explained by the fact that the coagulation cascade is initiated by the release of thromboplastin from the damaged brain tissue, which primarily activates the extrinsic clotting cascade and not the intrinsic pathway (32). In fact, brain tissues have the highest level of thromboplastin as compared to any other tissue in the body (33).

The IMPACT study in adult TBI demonstrated prognostic effects of PT and platelet count, only among other coagulating factors (28). They also emphasised the importance of correcting coagulopathic syndromes and called for further vigorous study on outcome with treatment of these abnormal values. The pathophysiology of

hypercoagulation state in TBI is multifactorial and rather complex. Blood loss due to systemic or cranial injury may induce bleeding diasthesis by depleting platelet and clotting factors whereas the injured brain may itself induce a hypercoagulation state by releasing the pro-coagulant tissue factor thromboplastin. The fact that platelet counts were not associated with outcome in paediatric TBI is explained by the fact that platelet counts are usually higher in this age group.

Leukocytosis was found to be an independent predictor of outcome in children as reported in the adult literature. This is the first series evaluating the impact of TWBC counts in predicting outcome in children with severe TBI. The adult series also observed a significant correlation between coma score on admission and higher TWBC counts in severe TBI (34). However, the IMPACT study did not include TWBC counts in their analysis of prognostic value of laboratory parameters in adult TBI (28).The fact that TBI in children was associated with decreased cell-mediated immunity further complicates the issue (35). Neutrophil count would probably be a better predictor of outcome in TBI than TWBC counts.

Cerebral swelling (corresponding to Marshall Grade III) was present in 48.6% of the patients during the study period. This figure is similar to that in the paediatric literature, with a range of 26%–44% (36,37). Although the significance of cerebral swelling in paediatric TBI has been controversial, our study demonstrates cerebral swelling was associated with poor outcome in only 44% of patients (32 out of 72 patients). The fact that cerebral swelling was not associated with poor outcome in multivariate analyses supports the notion that the mechanism of cerebral swelling is probably different and less malignant than the mechanism in adults, which has consistently been associated with poor outcome in the literature (38).

Marshall classification did not significantly affect outcome in multivariate analyses. This could be due to the high occurrence of cerebral swelling corresponding to Marshall Grade III in paediatric TBI. The analysis of Marshall classification in our study is limited by the definition of mass and diffuse lesions, especially in those cases with a combination of both. Some surgeons would operate upon diffuse injuries with small components of mass lesions in the critical region. According to the Marshall classification, the grading of mass lesions is performed according to the serial CT scan performed within 12 hours after the surgery. This was not done routinely in all our post-operative patients, mainly because of limited resources. A recent study suggests that combinations of individual CT predictors rather than Marshall classification were more reliable for prognostic purpose in adult TBI (39).

The IMPACT study demonstrated that CT scan characteristics were important predictors of outcome in adult TBI; those characteristics include class III and IV diffuse injury, brain swelling and the presence of traumatic subarachnoid haemorrhage (tSAH) (40). The presence of tSAH and IVH were found not to predict the outcome of paediatric TBI.

Conclusion

Our series represents one of the largest series of severe TBI in children in our region and represents the urban Malaysian population. We have concluded from multivariate analyses that low coma score at admission, development of hyperglycaemia, leukocytosis and prolonged PT ratio serve as useful indicators in predicting outcome in children with severe TBI, aged 2–16 years old. The roles of AASBP, Marshall grading, presence of cerebral swelling and IVH were not established in the logistic regression model, although these have shown significance in univariate analysis (Table 1). Age and gender do not affect outcome in severe TBI in children. ICP and CPP could not be included in our analyses as only selected cases received ICP-CPP targeted therapy during the period of this study.

The use of coma scale in children must be according to developmental age and comparable with the adult GCS. The measurement of coma score should be standardised to avoid confusion in analysis of the neurotrauma literature. By using modified GCS for those older than 3 years old and CCS for those younger than 3 years old, we have demonstrated that coma score can predict outcome in children with TBI.

The definition of hypotension in children with TBI based on AASBP should be reconsidered. Values derived from those critically ill or TBI patients should be made available. Coagulation derangement (prolonged PT ratio) predicts outcome better than other laboratory parameters such as glucose and TWBC (odds ratio of 2.3 compared to 1.2 and 1.1), thus full coagulation profiles that include D-dimer, FDP and fibrinogen level should be available during initial work-up in severe TBI patients.

This study demonstrates preliminary evidence of a relationship between the various factors predicting outcome in children with severe TBI. A prospective trial confirming our findings is needed in the future before we can make definitive recommendations regarding patient management.

Table 1: Univariate analysis of prognostic factors of severe TBI in children aged 2 to 16 years old in HKL from 2001 to 2006

	Poor	Good	*P*-value
Demographic, no. (%)			
Age group			0.085[a]
2 to 4 years	5 (3.4)	8 (5.5)	
5 to 10 years	14 (9.6)	20 (13.7)	
11 to 16 years	38 (26.0)	61 (41.8)	
Gender			0.992[a]
Male	48(32.9)	75(51.4)	
Female	9 (6.2)	14(9.6)	
Clinical, mean (SD)			
SBP (mmHg)	114.0(20.0)	115.7(16.8)	0.568[b]
Clinical, no.(%)			
AASBP			0.006[a]
<AASBP	7(4.8)	1(0.7)	
>AASBP	50(34.2)	88(60.3)	
Coma score			0.038[a]
3–5	18(12.3)	15(10.3)	
6–8	39(26.7)	74(50.7)	
Motor response			0.007[a]
< 5	38(26.0)	39(26.7)	
5	19(13.0)	50(34.2)	
Pupil reactivity [c]			0.001[d]
Reactive	19(22.1)	62(72.1)	
Non-reactive	5(5.8)	0(0)	
Diabetes Insipidus			<0.001[a]
Absent	37(25.3)	85(58.2)	
Present	20(13.7)	4(2.7)	
Laboratory, mean (SD)			
Glucose (mmol/L)	9.22(3.163)	7.72(2.13)	0.001[b]
TWBC (x 10^3 mm^3)	17.93(6.38)	15.79(5.70)	0.043[b]
Platelet counts (x 10^3 mm^3)	97.4(13.8)	88.0(9.5)	0.627[b]
aPTT ratio	1.30(0.72)	1.05(0.18)	0.003[b]
PT ratio	1.39(0.28)	1.23(0.17)	<0.001[b]
INR	1.46(0.41)	1.29(0.23)	0.009[b]
Intracranial pressure monitoring, mean (SD)			
Peak ICP value (mmHg)	37.3(23.2)	26.4(9.4)	0.028[b]
Minimum CPP value (mmHg)	48.6(12.4)	58.5(9.0)	0.001[b]

Table 1: Univariate analysis of prognostic factors of severe TBI in children aged 2 to 16 years old in HKL from 2001 to 2006 (cont.)

	Poor	**Good**	***P*-value**
Radiological, no. (%)			
Marshall Classification			0.025[a]
Grade I & II	19(20.0)	40(42.1)	
Grade III & IV	20(21.1)	16(16.8)	
Brain swelling/cerebral oedema			0.009[a]
Absent	20(13.7)	51(34.9)	
Present	37(25.3)	38(26.0)	
IVH			
Absent	47(32.2)	83(56.8)	
Present	10(6.8)	6(4.1)	
tSAH			
Absent	51(34.9)	82(56.2)	
Present	6(4.1)	7(4.8)	

[a] Chi-square test
[b] Independent t-test
[c] Pupil reactivity in equal and not dilated pupil
[d] Fisher exact test

Table 2: Multivariate analysis of prognostic factors with binary logistic regression model of severe TBI in children aged 2 to 16 years old treated in HKL from 2001 to 2006

	B	**Adjusted OR (95%CI)**	***P*-value**
Diabetes insipidus			
Absent	-	1	
Present	1.969	7.161(1.738–29.497)	0.006
Coma score on admission			
3–5	1.056	2.875(1.044–7.915)	0.041
6–8	-	1	
PT ratio	3.143	23.172(2.992–179.459)	0.003
Glucose level	0.178	1.194(1.001–1.424)	0.048
TWBC	0.079	1.082(1.008–1.161)	0.029

Constant = -0.349
B: Beta coefficient
OR: odds ratio, CI: confidence interval
Forward LR stepwise multiple logistic regression model applied.
Final model was tested with Hosmer-Lemeshow goodness-of-fit test (*P*-value=0.455)
Overall percentage correct = 74%
PT= prothrombin time
TWBC= total white blood cell

Our results have the potential to impact future patient management protocols in severe TBI in children, as well as to aid in the design of neuroprotective trials. If prospective trials confirm our findings on hyperglycaemia and coagulopathy, then aggressive and early control of glucose level with insulin and normalization of PT ratio with fresh frozen plasma would become standard practice in children with severe TBI.

Author's contributions

Collection and assembly of data, provision of study materials or patients: CHK, MS All authors have contributed equally to the conception and design, critical revision of the article.

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ORIGINAL ARTICLE

Superselective Embolisation in Acute Lower Gastrointestinal Haemorrhage: A Single Institution Experience

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Abstract

Background: **Superselective embolisation has been recognised as integral in the management of lower gastrointestinal haemorrhage. It has also reduced the need for emergency surgery. The objective of this case series was to describe the lower gastrointestinal haemorrhage cases seen in our centre, its diagnosis and the role of superselective embolisation in patient management.**

Methods: **All patients who underwent superselective embolisation from January 2008 until April 2009 in our centre were analysed. Data were collected from the hospital electronic medical records.**

Results: **Four patients (three males) with a mean age of 81 years were analysed. Multidetector computerised tomography and digital subtraction angiography were positive in all patients. Superselective embolisation with platinum microcoils was performed in all patients (n = 4). Technical success was achieved in all patients (100%).**

Conclusion: **Superselective embolisation in the treatment of lower gastrointestinal haemorrhage is safe and effective with a very high technical success rate.**

Keywords: *gastrointestinal haemorrhage, therapeutic embolisation, spiral computerised tomography, medical sciences*

Introduction

Massive lower gastrointestinal haemorrhage (LGIH), which is defined as bleeding in the bowel beyond the ligament of Treitz, remains a challenge in its diagnosis and management. It is usually associated with a mortality rate of 5 to 12% and can approach 40% in severe haemorrhage (1).

Diagnosing the cause and site of the active haemorrhage remains a problem. Multiple modalities are available, such as colonoscopy, radionuclide imaging, multidetector computerised tomography (MDCT) mesenteric angiography and digital subtraction angiography (DSA), all of which have their own advantages and disadvantages (2). However, with the recent advancement in CT technology, MDCT mesenteric angiography has become the modality of choice in the detection and localisation of the sites of haemorrhage (3–5). Emergency surgical interventions in massive LGIH usually are associated with high mortality rates and high re-bleeding rates(1). Bookstein et al. first described intra-arterial embolisation using modified autogenous blood clots for LGIH (6). However, this method suffered criticisms because of its association with ischaemic complications (7).

Recent advancement in technology and the availability of smaller coaxial microcatheters up to 2 F in size and guidewires have made superselective angiography and embolisation of the causative distal bleeding artery technically feasible. This has enabled superselective embolisation (SSE) to be performed safely and with significant reduction in the risk of postembolisation ischaemia. The technical success of SSE is usually around 97 to 100% (8–10). The majority of these patients do not need further interventions after the embolisation (8–10). Long-term follow-up in patients who underwent SSE also yielded favourable results, with less than 20% requiring readmission for further LGIH (11, 12). The objectives of this case series were to describe the LGIH cases seen in our centre, its diagnosis and the role of SSE in patient management.

Materials and Methods

All patients who underwent SSE for LGIH from January 2008 to April 2009 in Universiti Kebangsaan Malaysia Medical Centre were identified retrospectively via the hospital electronic medical record (EMR). Review of the patients' EMR, which included demography, site of haemorrhage and preembolisation examinations, was also performed. All patients with suspected LGIH in our centre were referred to the on-call interventional radiologist (IR) or IR fellow. Since January 2008, all patients with suspected LGIH underwent MDCT mesenteric angiography as a preembolisation examination. The MDCT images were interpreted by the on-call IR, either in the hospital or through the internet from home. Only patients with positive MDCT (with contrast extravasation into the bowel lumen) underwent DSA of the mesenteric arteries with an intention for SSE (Figure 1, 2 and 3). With this information, the angiography team was mobilised. In patients with negative MDCT (no contrast extravasation into the bowel lumen), no DSA was performed. However, if the patient re-bled, a repeat MDCT was urgently performed.

Nuclear scintigraphy, using technetium 99m (99mTc) red blood cell-labelling, is available in our centre. However, this examination was noted to be time consuming and with poor anatomic localisation (13). Yoon et al. (3) had observed that MDCT gives a sensitivity, specificity, accuracy, positive predictive value and negative predictive value of 90.9%, 99%, 97.6%, 95% and 98%, respectively, for detecting acute gastrointestinal haemorrhage. They also showed that the location of contrast extravasation shown on MDCT corresponded exactly with the contrast extravasation on DSA. With this information, nuclear scintigraphy using 99mTc red blood cell-labelling was only reserved for chronic LGIH where other investigations had failed. MDCT was the first choice in acute LGIH.

MDCT was performed with a 64-slice MDCT (Siemens Sensation 64) in multiple phases. DSA was performed with a DSA machine (Single plane Toshiba KXO 200 & Biplane Philips Allura X-Per FD20/10). Coeliac, gastroduodenal, superior mesenteric and inferior mesenteric arteriograms were performed in all patients. A positive DSA was defined when there was active contrast extravasation seen (Figure 1, 2 and 3). In patients with a positive DSA, a coaxial microcatheter with a micro guidewire (FasTracker-325 microcatheter; Boston Scientific) was introduced just proximal to the bleeding site. A superselective arteriogram (SSA) was then performed to further demonstrate the active contrast extravasation (Figure. 1, 2 and 3). Embolisation was then performed with platinum microcoils (Hilal Embolisation Microcoils; Cook) of variable length after consultation with the surgical team. A repeat SSA was performed postembolisation. A technical success was defined when hemostasis was secured with no active contrast extravasation seen in the postembolisation arteriography (Figure 1, 2 and 3).

Results

From January 2008 until April 2009, there were 4 patients who presented with LGIH and had SSE performed. The mean age of the patients was 81 (73 to 88) years. There were three males and one female. MDCT of the mesenteric arteries was positive in all patients in which contrast extravasation was seen into the bowel lumen. On MDCT, the location of haemorrhage was seen in the ascending colon (n = 2), descending colon (n = 1) and splenic flexure (n = 1). On DSA, contrast extravasation was seen from the superior mesenteric (n = 2) and inferior mesenteric (n = 2) arteries. All embolisation procedures were performed with platinum microcoils (n = 4). There was complete cessation of haemorrhage in all 4 patients postembolisation, with a technical success rate of 100% (Table 1). The time interval between the MDCT and DSA was less than 3 hours, except for in one patient. One patient had a longer time interval of 7 hours between the MDCT and DSA due to some logistical problems.

Discussion

Superselective embolisation in the management of acute LGIH has been increasingly accepted in most centres all over the world. This method was noted to be safe and effective in the acute management of LGIH. SSE also played a major role in patients with poor comorbid conditions. It allows for rapid haemostasis of the bleeding arteries, enabling the patient to be resuscitated and stabilised prior to a major surgery. The first known attempt of transcatheter embolisation was described by Bookstein et al. in 1974 using modified autogenous blood clots (6). However, early reports observed a high percentage of bowel necrosis postembolisation (7). This was due to the use of larger catheters (6F Cobra Catheter), which did not allow for a SSE to be performed.

However, with the current technology, especially with the availability of microcatheters, platinum microcoils and polyvinyl alcohol (PVA)

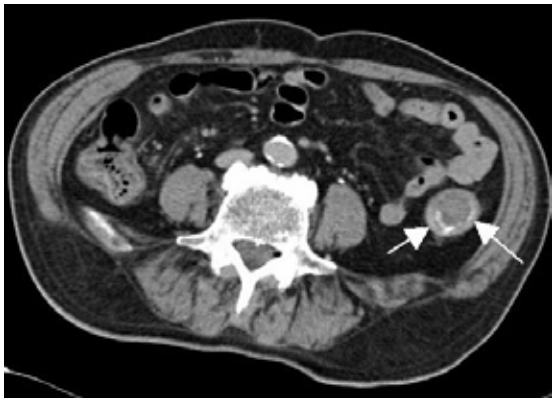


Figure 1A

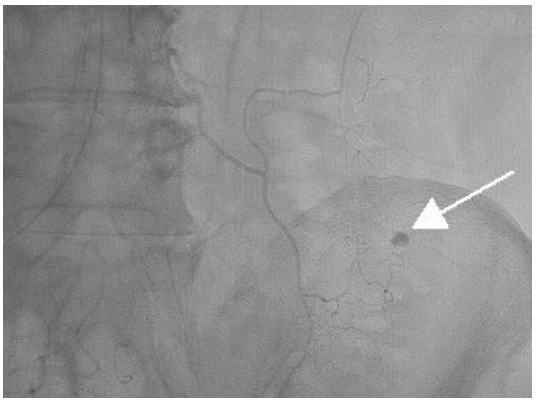


Figure 1B

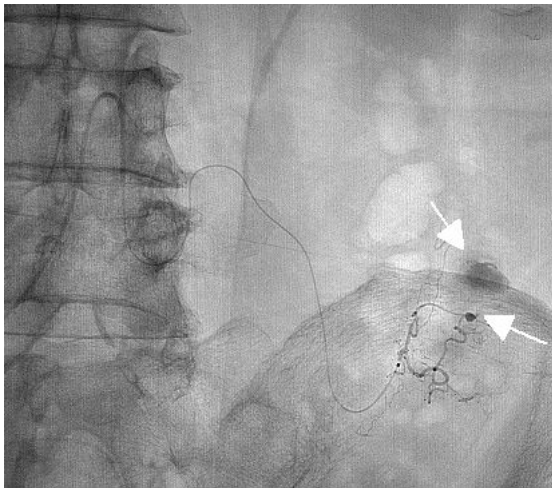


Figure 1C

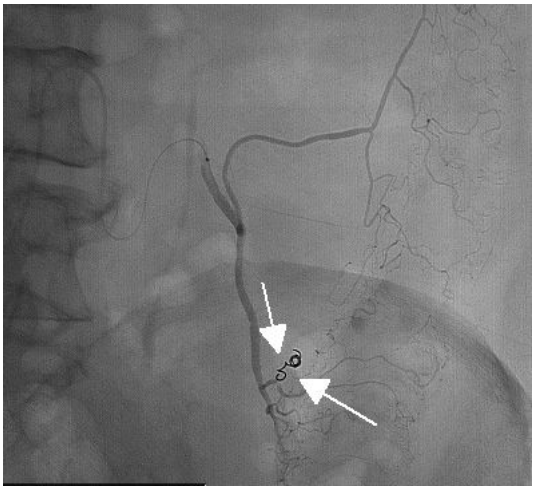


Figure 1D

An 88-year-old man with massive LGIH. Initial colonoscopy failed to determine the cause due to the presence of blood clots.

Figure 1A : Axial MDCT showing contrast extravasation in the descending colon (arrows)
Figure 1B : Inferior mesenteric arteriogram showing contrast extravasation from the descending branch of the left colic artery (arrow)
Figure 1C : Superselective arteriogram (SSA) of the descending branch of the left colic artery showing contrast extravasation at the same location (arrows)
Figure 1D : SSE was performed with 2 platinum microcoils (arrows) with no residual contrast extravasation seen postembolisation

particles, a SSE of the bleeding arteries can be performed at the level of the vasa recta or marginal artery of Drummond. Luchtefeld et al. reported a 82% technical success rate with only 6% of patients developing bowel necrosis (14). Funaki et al. also reported a 96% success rate with 7% of patients developing bowel necrosis (15). In the recent literature, the results have been better. Tan et al. reported a 97% technical success rate with only 3% of patients developing postembolisation ischaemia (9). Lipof et al. reported a 97% technical success rate with 7% of patients developing postembolisation ischaemia (8). Koh et al. reported a 100% technical success rate with 5% of patients developing postembolisation ischaemia (10). This is similar to our case series, in which we had achieved a 100% technical success rate.

On long-term follow-up, Ahmed et al. reported that only 4 out of 20 patients were readmitted to the hospital for further acute LGIH at 1, 2, 12 and 16 months (11). Maleux et al. reported that 8 out of 39 patients developed re-bleeding post-SSE, with 6 of them re-bleeding within the first 30 days (12). On long-term follow-up, the estimated survival

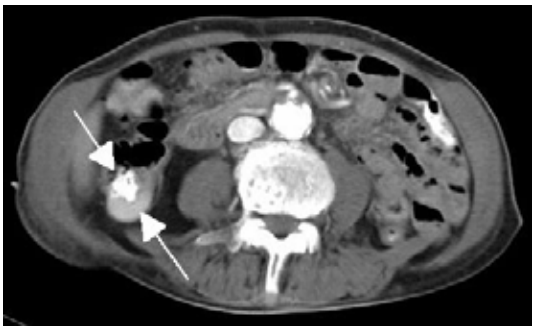


Figure 2A

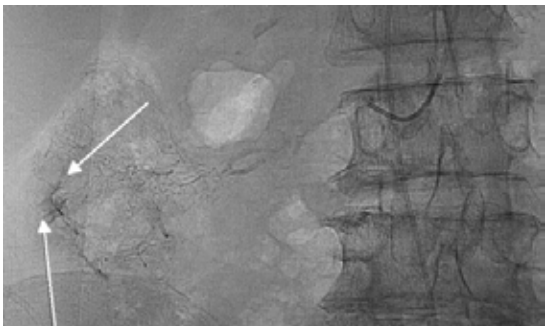
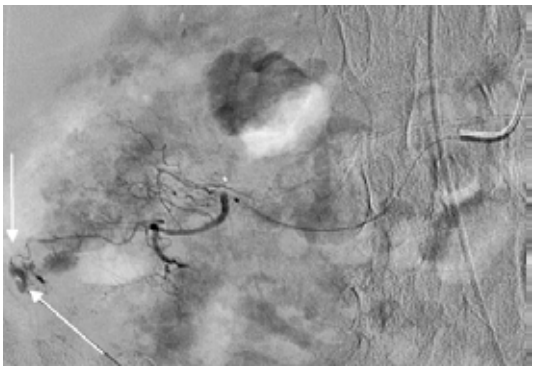


Figure 2B



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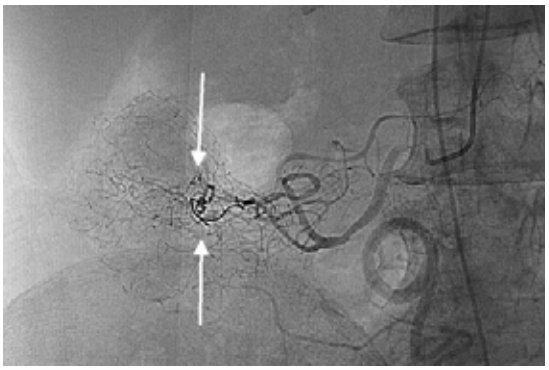

Figure 2D

An 81-year-old man with end-stage renal failure presented with massive LGIH.

Figure 2A : Axial MDCT showing contrast extravasation in the ascending colon (arrows)
Figure 2B : Superior mesenteric arteriogram showing contrast extravasation from the distal branches of the middle colic artery (arrows)
Figure 2C : SSA showing more obvious contrast extravasation from the distal branches of the middle colic artery (arrows)
Figure 2D : SSE was performed with 2 platinum microcoils (arrows) with no residual contrast extravasation seen postembolisation

rates of their patients were 70.6%, 56.5%, and 50.8% after 1, 3, and 5 years, respectively.

There are many types of embolic materials that can be used in SSE, such as platinum microcoils, PVA particles, glue and gelfoam (8–12). In the initial days, intraarterial vasopressin infusion was the method of choice in LGIH, which leads to arterial vasoconstriction and bowel contraction. This then leads to a lower blood flow into the affected bowel. However, these patients require intensive care unit (ICU) monitoring due to complications, such as myocardial ischaemia, peripheral ischaemia, hypertension, arrhythmias and hyponatremia (1). Today, intraarterial vasopressin infusion is no longer used, and the other embolic materials mentioned above are used (8–12). In our series, platinum microcoils were used in all patients.

From these case series and literature reviews, we would like to suggest an algorithm for the management of LGIH, as shown in Figure 4. This algorithm is applicable only in centres with MDCT and IR services. However, in centres without an IR service, MDCT of the mesenteric arteries in multiple phases should be performed to localise the site of the acute LGIH. With the MDCT findings, the patient can be referred to the nearest centre with IR service if the patient is fit and stable. If the patient is not fit and is unstable, the MDCT findings will help the surgeon to localise the site of haemorrhage and perform a segmental colectomy.

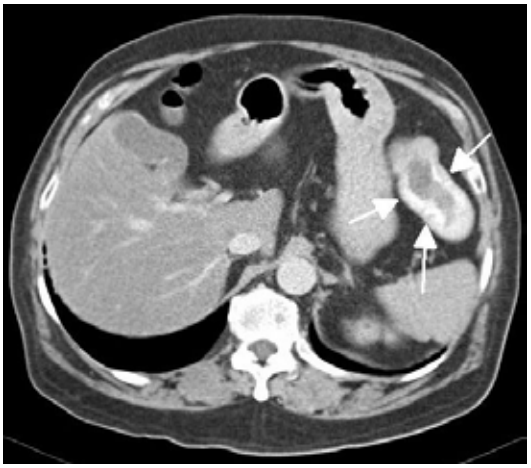

Figure 3A

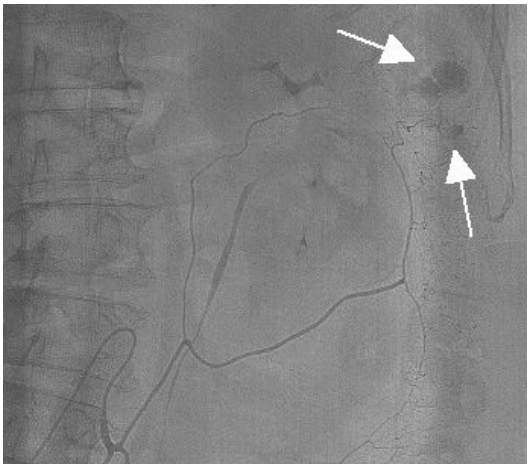

Figure 3B

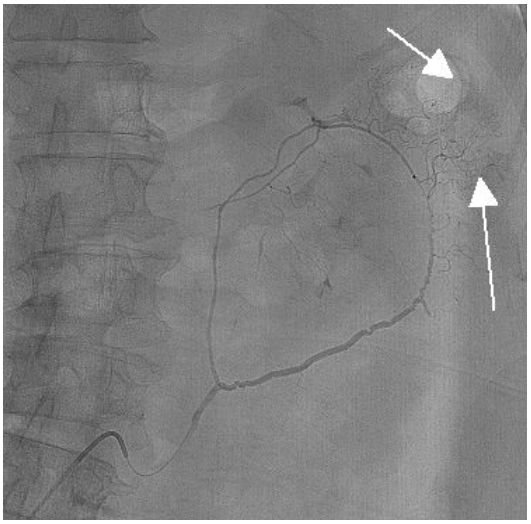

Figure 3C

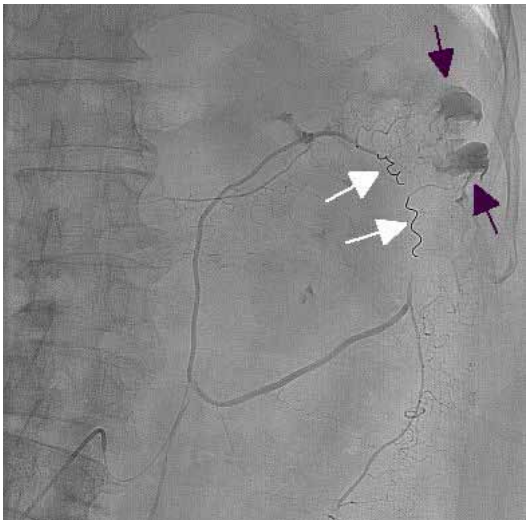

Figure 3D

A 73-year-old man with a 4-day history of fresh rectal bleeding. Colonoscopy showed diverticular disease with extensive blood clots.

Figure 3A : Axial MDCT showing contrast extravasation in the splenic flexure (arrows)
Figure 3B : Inferior mesenteric arteriogram showing suspicious contrast extravasation from the ascending branch of the left colic artery (arrows)
Figure 3C : SSA of the ascending branch of the left colic artery showing contrast extravasation (arrows)
Figure 3D : SSE was performed with 2 platinum microcoils (white arrows). Note the pooling of contrast in the region of the splenic flexure from the extravasation of the previous arteriograms (black arrows)

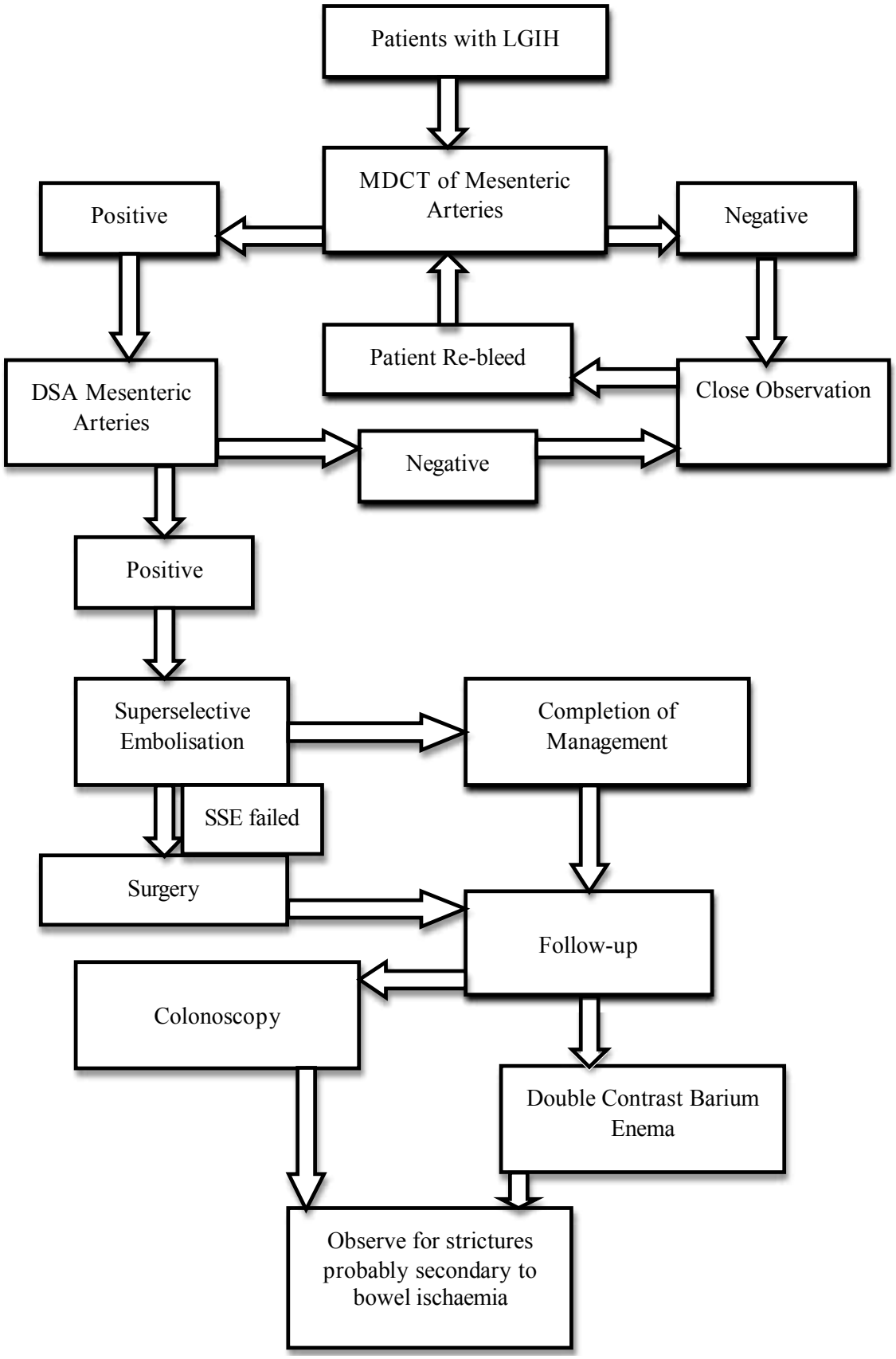

Figure 4: Algorithm in the management of LGIH

Table 1: Details of patients and site of haemorrhage

No.	Age / Sex	Location of contrast extravasation in:		Time Interval between CT and DSA	Bleeding artery	Treatment	Results
		MDCT	DSA				
1	88/M	Descending Colon	IMA	2 hours	Left Colic Artery	2 microcoils	Hemostasis secured
2	81/M	Caecum & Ascending Colon	SMA	7 hours	Middle Colic Artery	2 microcoils	Hemostasis secured
3	73/M	Splenic Flexure	IMA	2 hours	Left Colic Artery	2 microcoils	Hemostasis secured
4	83/F	Ascending Colon	SMA	3 hours	Right Colic Artery	2 microcoils	Hemostasis secured

Abbreviations: M=male, F=female, SMA=superior mesenteric artery, IMA=inferior mesenteric artery

Conclusion

SSE has a major role in the management of acute LGIH. In centres with IR services, it should be considered as the first choice of treatment. This is due to a very high technical success rate, reaching almost 100%, coupled with a very low incidence of postembolisation ischaemia.

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Author's contributions

Conception and design, final approval of article: ZM, ASM
Data collection: ARMR, RZ, ASM
Data analysis and interpretation: ARMR, RZ, ASM
Darfting of the article and critical revision: ARMR, ASM
Provision of study materials or patients: ARMR, RZ, ZM, ASM

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Malaysian Journal of Medical Sciences, Vol. 16, No. 4, Pg 42-49, October - December 2009

SPECIAL COMMUNICATION

Dreams In Jungian Psychology: The use of Dreams as an Instrument For Research, Diagnosis and Treatment of Social Phobia

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Abstract

Background: **The significance of dreams has been explained in psychoanalysis, depth psychology and gestalt therapy. There are many guidelines in analytic psychology for dream interpretation and integration in clinical practice. The present study, based on the Jungian analytic model, incorporated dreams as an instrument for assessment of aetiology, the psychotherapy process and the outcome of treatment for social phobia within a clinical case study.**

Method: **This case study describes the use of dream analysis in treating a female youth with social phobia.**

Results: **The present findings supported the three stage paradigm efficiency in the Jungian model for dream working within a clinical setting, i.e. written details, reassembly with amplification and assimilation. It was indicated that childhood and infantile traumatic events, psychosexual development malfunctions, and inefficient coping skills for solving current life events were expressed in the patient's dreams.**

***Conclusion*: Dreams can reflect a patient's aetiology, needs, illness prognosis and psychotherapy outcome. Dreams are an instrument for the diagnosis, research and treatment of mental disturbances in a clinical setting.**

Keywords: *dream, jungian approach, social phobia, psychotherapy, medical sciences*

Introduction

Dreams have been traced in mankind civilisation, and Aeppli (1955) noted the dreams are a quite personal aspect of human experiences (1). Freud's pioneering work on the interpretation of dreams extended our knowledge of dreams as a part of clinical practice in psychology (2). Historically, the significance of dreams for clinical interpretation has been considered by psychoanalysis, analytical psychology and gestalt therapy approaches. There are many guidelines in analytic psychology that help therapists to integrate a basic approach to dream interpretation into clinical practice. There are various viewpoints on dream emergence, importance and interpretation in the disciplines of literature, religion, medicine, sociology and psychology (3). As Jung cited, one would do well to treat every dream as though it was a completely unknown project, look at it from all sides, take it in one's hand, carry it around, and let one's imagination play around with it (4).

Theoretical and Research Bases

The present article is primarily based on Jung's seminal work, which has been clarified and extended through years of clinical investigation by Hall (5), Whitmont (6) and Whitmont and Perera (7) on the exploration of dreams in the aetiology of mental disorders and psychotherapy prognosis. Guided by a therapist, clients must come to grips with powerful, unconscious archetypical complexes that are in constant and submerged flux. The archetypes of the shadow and the anima-animus are two domains of the principal oppositional and tumultuous unconscious forces that must be reconciled. The therapeutic modality that is most commonly used to bring these and other archetypes to conscious awareness is dream work. Analytical psychotherapy attempts to create a communicative link between the conscious and unconscious and make the unconscious understandable through dialogue, association and interpretation of what may appear to the individual

to be quite illogical and completely undecipherable (8). Based on analytical psychology, the goal of a treatment program is to incorporate and clarify the role of dreams as an instrument for the assessment of aetiology, psychotherapy process and treatment outcome in social phobia.

Dreams have two major implications in clinical practice, exploration of the aetiology of mental illness and the resulting therapy trend and outcome. From an aetiological point of view, dreams focus on the important unprocessed mental and emotional issues of the day or during the life span; thus, dream work can quickly bring the most important issues that a person is dealing with on a subconscious level to consciousness. On the other hand, dream work without therapy is not necessarily effective in reducing the emotional and mental disorders that may surface. Dreams process current situations that trigger these mental disturbances and then attempt to reverse the underlying fears and misconceptions through a process called "compensation" (9). Jung observed that dreams are driven by a natural tendency to bring resolution and closure to unfinished emotional and mental problems of the day (10,11,6). When we sleep and dream, episodic memory is disconnected; therefore, we cannot recall the specific event, but the emotional context of that event, if unresolved, comes to the surface to be processed. Those emotions arouse early threat reactions as well as underlying fears and misconceptions that have become part of our internal model of reality in our belief systems. External events that do not fit that internal model become new threats to the model (9). The dream not only illuminates the current issue or threat, but tries to accommodate it by finding a "fit" between the current experience and our internal model. When the internal model is corrupted by old fears and misconceptions, dreams illuminate those barriers and "compensate" by projecting adjustments in order to achieve a "fit" (2,6,9,10,11,12,13). Consistent with natural and necessary expressions of life force, dreams provide access into unconscious areas of life. They convey specific and appropriately timed messages that can assist the dreamer with problem-solving, artistic inspiration, psychological development and spiritual deepening, and they are important for healing (7). Through dreams, a patient's inner aetiology of mental disorder and his or her reaction to psychotherapy may be expressed as symbols, metaphors, analogies and stories that are rooted in personal and collective levels of unconsciousness.

From the therapeutic point of view, the metaphors and analogies are somewhat obvious, but this is not the case with all dreams. Every dream reveals information about the dreamer's psychological and physical dynamics and spiritual process. Dreams also touch upon relationship issues projected from past, problematic in present or newly emerging situations. Hereby, dreams facilitate the working through of old patterns that impede relationships. Dreams may be about the therapist, others, life's work and need gratification, the unconsciousness, or the Self. Whitmont and Perera (7) discussed the roles of dreams for the reality of the therapist, transference reactions, inner therapist, countertransference dynamics, the process of therapy, and the therapist's dreams about the patient comprehensively. To better understand the patient's dreams for psychotherapy, one should take note of the dream language. The "language" of the dreaming mind is unique; it is how the dreaming brain communicates, and the information being processed is predominantly represented by association, symbol, metaphor and visual imagery (6,9,10,11,12,13). Dreams communicate using image combinations, just as we communicate with word combinations in waking life. Dreams are similar to garlic, which may smell unpleasant but is quite effective for our health. Dreams may be unfavourable in appearance but understanding their latent messages facilitates the healing of individuals' mental health issues and personality enhancement. The mystery of dreams for human mental health accomplishment is more obvious when combined with Jung's notion about human nature. Jungians view humans in a positive sense and believe that they are inherently predisposed to make their individual mark in the world. This individuation process is not accomplished by merely obtaining fame and glory through material achievement or notoriety (14). In fact, dream exploration is a means for individuation and actualisation attainment. Dreams act as the purest form from which to draw on the vast storehouse of the unconscious, and often emerge as the most fruitful source of therapeutic material. Dream work is a fundamental core of analytical therapy (15,16). Despite the importance of dreams for mental illness diagnosis, there is little evidence for their application in the prediction of psychotherapy outcome, and few useful guidelines for the clinical interpretation of a patient's dreams.

Case Presentation

I would like to present a brief description from my work as the therapist for Lida (a pseudonym). Her treatment was free-of-charge since it was carried out in a community-based Psychological Outpatient Clinic in Ferdowsi University of Meshed,

Iran, that offers services to the city inhabitants and outpatients. Treatments are provided to potential patients as brief therapies that are suitable for consultations emerging from their life events or critical situations. Patients assessed initially by a psychoanalyst and a clinical psychologist (who is a supervisor rather than a therapist) for the adequacy of the type of treatment offered for their particular condition and are then provided psychotherapy or referred to a different treatment facility.

Presenting Complaints

The problems that Lida presented were social phobia and public fears. No concerns about mood, other anxiety disorders, or other symptomatology were expressed by Lida or her family and friends. She reported increasing anxiety and worry that included physiological, cognitive, and behavioural symptoms during the course of each semester as classes approached. When I first began to work with Lida, a 22-year-old university student, she was quite anxious and was diagnosed with social phobia based on the DSM-IV. She avoids public talking and her academic performance during the past two semesters particularly declined. Her social phobia is sometimes accompanied by transit panic and depressive symptoms but there was no evidence for a comorbidity disorder. Her problem began in adolescence and increased with entrance to university. She was reared in a family with a history of maladjustment behaviours and did not experience trustful and calm relationships with her parents. She is more avoidant of men than women. Her father was quite rebellious, over demanding and advising alike a clergy, which generally frustrated her. Lida believed femininity to be inferior and was more interested in masculine roles. She did not have satisfactory relationships with women, including her mother. She underestimated the significance of her feminine needs and showed little interest in and a hostile approach to femininity, except seductive behaviours for capturing men. She participated in 30 therapeutic sessions using the Jungian approach.

Assessment

Lida's fitness for psychotherapy was evaluated the basis of the DSM-IV diagnosis criteria in the patient sample (17). The presence of sub-clinical personality disorder features or traits was also recorded and ruled out. Commensurate with university-based samples, the community outpatients in our clinic primarily experienced psychological disorders with a mild to moderate range of severity. This mild to moderate range of impairment was evidenced within the DSM-IV diagnostic categories, clinician rating scales, and self-report measures. Similarly, each patient provided written informed consent to be included in the research program.

Case Conceptualisation

There are more words written on the subject of dreams and their function from a wide variety of different perspectives than on any other subject within depth psychology. This is true for both psychoanalysis and analytical psychology. We know that dreams reflect personal ego strength and know a good deal about how to define dreams, dreams' mechanisms and their myths and symbols in analytic psychology and psychoanalysis; however, there is lack of evidence on their role in psychological aetiology and their contribution to the prediction of psychotherapy outcome and patient prognosis. As Jung noted, a dream never expresses itself in a logically abstract way but always in the language of parable or simile, which is a characteristic feature of primitive language (18). We agree with Whitmont and Perera (7), who noted that images, symbols, allegories, and rebuses are the main languages of dreams in clinical practice. Since dreams operate in an altered state of consciousness, they are a primary process that is beyond of man rational categories for space and time and they integrate potent materials from past, present and future. This information may even come from archetypal levels with which the dreamer is quite unfamiliar. Our perception of dreams may be visual, auditory, proprioceptive or kinesthetic. Such images are also apparent in ancient and sacred pictographic writings. Allegorical aspects of a dream describe objective, or outer, and subjective, or inner, situations that are to be brought to the dreamer's psychological attention. Allegorical refers to rationally understandable facts and psychological dynamics that have been ignored or have been out of reach of the consciousness.

Symbols shows what can be seen only through a glass darkly. In Jung's definition, a symbol is the best description or formula of a relatively unknown fact that is none the less organised or postulated as existing (19). Symbols point to existential or ever superpersonal significance as a basic concern of psychic life. They also express the need for meaning in life that is beyond sensation and instincts. All products of the unconscious that come to awareness have similar functions as symbolic messages. Archetypes are the birthing agents of symbols and these symbols are commonly

found in dreams. Dreams are the avenue of egress for the unconscious to gain awareness, and are the axis on which psychotherapy revolves. Jung's symbols are different from Freud's symbols. For Jung, symbols are intuitive ideas that have not yet formed, as opposed to Freud's view that symbols are symptomatic signs released into conscious awareness (18). Finally, a rebus is a representation of a phrase by pictures. These pictures might more or less clearly suggest syllables words or ideas. Hence, the most important aspect of dream work in analytical psychology is its interpretation, which, according to the Jungian conceptualisation, involves three steps in clinical practice (3).

In the first step, the dreamer writes the details of the dreams as quickly as possible after awakening (15). This provides a clear understanding of the exact details of the dreams before the memory of the specifics becomes convoluted, commingled or distorted. In writing the dream content in specific detail, the client attempts to describe and clarify the context of the dreams. Context specification is important because it keeps the therapist from injecting premature associations and attempting to interpret the dreams too early. In this first step, the therapist questions the client incisively to ensure that both client and therapist understand the exact content; sequence of dream events; dreamer's feelings about dream images; whether the dream is a repetition of a previous dream or is one in a series of dreams; and the power, strength, or valence of the dream. A series of dreams allows greater confidence in the interpretations than does one isolated dream. A series of dreams provides a clearer perspective of basic or developing themes (15). The more powerful the dream, the more important the message the dream is attempting to reveal to the dreamer's conscious ego and psychic system.

In the second step, the dream is reassembled with amplifications in mind. The gathering of associations and amplifications in progressive order on one or more of three levels, which include personal, cultural, and archetypal segments, helps to identify the core maxims of the dream images (3). Amplification of a dream is analogous to "peeling" the three layers of a complex: personal associations; images of a more cultural or transpersonal nature; and the archetypal level of amplification (20). In many dreams, the order of events holds much of the secret of the dream. Questions are open-ended and do not focus on the specific questions found in step one. Rather, amplifying questions help the client to discover the larger picture and set the stage for expanded understanding of the dream. Therapist questions during the reassembly/amplification step could include: "What do you think the dream wants to tell you?", "How do you see the dream now?", and "How do you feel about the dream?" To further amplify the dream, the therapist may use a fairy tale or anecdote that parallels or explains something related to it. Amplification does not involve interpretation but rather adds information to the client's story or reframes it. The purpose of this step is to help the client recognise similarities between his or her personal experience and its archetypal configuration (21).

Finally, in the third step (or the assimilation phase), the therapist and the client make conscious sense of the dream (3). An important aspect of the third step is for the client to come to the point where he or she can answer the therapist's questions regarding dreams conscious attitude against the dream compensation and dreams symbolic attitude in the client's unconscious world (15). In a new paradigm, James and Gilliland (22) specified these steps in written details, reassembly with amplification and assimilation respectively. We suggest that dream interpretation and analysis may be particularly useful in treating social phobia, in which the phobic origins are unconscious and imaginary, such as infantile trauma or archetypal themes. In this context, the present case study describes the use of dreams analysis to treat a female youth with social phobia. The case also highlights the utility of dream as an instrument for diagnosis, aetiology and intervention in clinical psychotherapy.

Analytical therapy typically involves four stages of treatment: confession and catharsis, elucidation, education, and transformation. While each stage seems final and may be sufficient for a return to mental health, none is complete in itself. Even transformation is not an endpoint (18). The treatment provided focuses on the patient's chief complaint and its underlying core conflict. Psychotherapy is guided by explicit goals that the patient and therapist discuss and agree to work upon. In the present study, we used dream interpretation as the foundation of our exploration of Jungian therapy. We assessed patient improvement from pre- to post- treatment with the Comparative psychotherapy process scale (CPPS). The CPPS is a measure of psychotherapy process that is designed to assess therapist activity, process variables, and psychotherapy techniques used during the therapeutic hour (23). The scale consists of 20 items rated on a 7-point Likert Scale ranging from 0 ("not at all characteristic"), 2 ("somewhat characteristic"), 4 ("characteristic"), through 6 ("extremely characteristic"). The CPPS may be completed by the patient, the therapist,

and/or an external rater. One unique feature of the items on the CPPS is that they were derived from empirical studies that compared and contrasted Psychodynamic-Interpersonal and Cognitive-Behavioural oriented approaches to treatment. This scale consists of two subscales: a Psychodynamic-Interpersonal subscale (PI; 10 items) and a Cognitive-Behavioural subscale (CB; 10 items). The PI subscale measures therapist and patient activity found in empirical research to be emphasised significantly more in a Psychodynamic-Interpersonal oriented treatment than in a CB treatment. Items include

- focus on affect and the expression of patients' emotions
- exploration of patients' attempts to avoid topics or engage in activities that hinder the progress of therapy
- the identification of patterns in patients' actions, thoughts, feelings, experiences, and relationships
- emphasis on past experiences
- focus on patients' interpersonal experiences
- emphasis on the therapeutic relationship
- exploration of patients' wishes, dreams, or fantasies (23)

Likewise, the CB subscale consists of items that are significantly more characteristic of Cognitive-Behavioural oriented therapy. Items include

- emphasis on cognitive or logical/illogical thought patterns and belief systems
- emphasis on teaching skills to patients
- assigning homework to patients
- providing information regarding treatment, disorder, or symptoms
- direction of session activity
- emphasis on future functioning

Coefficient Alpha for the PI and CB subscales (N=101 rated sessions) are both reported as 0.93 (23). Therapy outcomes for the present case were evaluated from two perspectives: patient self-report of social functioning (work, family, and leisure) and therapist ratings on CPPS. In the present study, patient improvement and functioning was assessed during pre- and post- treatment intervals via CPPS by herself, her family, her classmate and the therapist.

Course of Treatment and Assessment of Progress

We primarily evaluated Lida's series of dreams for exploration of her social phobia aetiology and prognosis of psychotherapy outcome. Her first dream in the initial phase of psychotherapy was as follows:

> *"My friend and I are sitting in a window that was like the one in our school at university, but my friend seems calm and confident and I fear falling down."*

We know that the earth is a symbol for femininity in depth psychology while the issue of femininity is embarrassing for Lida due to earlier disadvantaged experiences. Therefore, fear of falling into the earth in the above dream directly adheres to her core aetiology and basic problem for identity attainment. She has a latent and unconscious paradox toward the feminine-masculinity spectrum that primarily originated in her personal unconscious experiences from infancy to adolescence. It is apparent that she is dissatisfied with her feminine self in comparison to other females. This assumption was supported by the associations and dream clarification of her dream. Psychoanalytically, her dream adhered to identification abnormality in early childhood and psychosexual development. Her associations mostly confirmed the feminine nature of the earth symbol rather than a fear of failure in university tasks. This dream highlighted the nodal aetiology and future orientation of her psychotherapy, and dream helped her to follow her confession and catharsis. The dream served as a "guideline for the direction of therapy" and "a prediction of the outcome" in the Jungian sense that most dreams have a forward-looking momentum, a prospective dimension. Therefore, her analytical therapy focused on childhood traumas that explain her phobia, especially sexual abuse at the hands of her brother. These associations helped her to overcome childhood maltreatments and to develop a new attitude toward her masculine and feminine archetypes. Now, we note her dream message after several sessions. Her second dream, in the middle phase of psychotherapy, was as follows:

> *"I am returning from cemetery and going to my uncle's house, and I have a big dark covering on over of my head. There is no one on the street. I sense someone following me, turn back, and see a male following me. I don't acknowledge him, but I walk more and more quickly and he does as well. I enter a place in row and it is raining, and the big dark cover on over my head is completely wet. I feel the male who is following me wants to hang me. I run and he chases me, but something stops me. I push open a door to run away, but he gets me and begins to strangle me. I think he is the angel of death."*

This is a type of combined imagery that portrays her attempt to run from her inner world of silence, aloneness and social avoidance to a prosocial world. The cemetery and dark cover on her head may address innate hopelessness and rigid mental imaginations that severely distressed her. She attempts to change these feelings and also fears from this alteration. Her associations to the uncle showed that he is likeable, rational, religious, flexible, and responsible man who compensates for her father's irresponsibility. The uncle association increases her hope, peace and faith. Furthermore, it shows her tendency for change, which was inhibited by masculine ideas and negative experiences with men in the form of abuse. The present imagery indicates her inner struggle to overcome psychotherapy obstacles that originated in the personal unconscious level. As aforesaid, the clinical interview confirmed a history of abuse by close relatives such as her brother and that escaping from he was not possible. Dream clarification and perception of its emotional amplification with free recall of the above traumatic experiences during sessions primarily helped her in terms of emotional catharsis and stabilisation, and then she moved toward the transpersonal or collective unconscious level. For example, the uncle and rain may highlight the transpersonal levels of masculine and redemption archetypes. The dream served as a "guideline for the direction of therapy" and "a prediction of the outcome" in the Jungian sense. Here, psychotherapy focused on her detailed childhood self-disclosure and attempt to develop more efficient self-protective social skills. The present dream serves as a good means for elucidation and educational goals in treatment. Her third dream, in final phase of psychotherapy, was as follows:

> *"I am in an unfamiliar house. An animal like a cat wants to get our chickens, and I am running to get away from it while it attacks me. When it approaches me, I break its back, and the people beside me call for me to try again, until I finally capture it."*

In depth psychology, unfamiliar home is an allegory for foreign departments of the intrapsychic world. Her dream shows new insights for the exploration of unconsciousness boundaries in her personality, especially for anima. She attempted to kill a cat, which may indicate her tendency to control her undesirable manners such as anger, hostility and ill-will in the animus and persona sectors. It guides psychotherapy toward necessity of patient balance in introversion-extraversion spectrum because she was only noticed to people beside her rather than her innate world. Dream was addressed to her shadow, anima and animus for a logical balance in her four psychological functioning and their usefulness for her transformation during the psychotherapy. During dream clarification and interpretation, we discussed all of these archetypes in the therapeutic sessions. This dream operated as a prospective dimension for her psychotherapy. For instance, she was very seductive and had many mysterious sexual impressions and evil-like behaviours toward males in interpersonal relationships that resulting in a context for her abuse. Similarly, she was inattentive to her thoughts, sensations, feeling and intuitions. Otherwise, she primarily followed the masculine stereotypes. This prospective insight helped Lida to monitor seductive behaviours, which threaten her security in social contexts, diminish her animus orientations, and balance her main psychological functioning. Her fourth dream, in the final phase of psychotherapy, was as follows:

> *"I am in an exam session and a female is that the instructor of the course. She sits in front of me and notices that I am somewhat afraid. As I begin to answer, I see a coin with the word DOCTOR on its surface, but on its other side is written "myself". When I encounter a problem, I immediately look at it to find out "what to do".*

This dream involves a symbol that is directive and healing for the patient. Furthermore, it expresses her congruency with feminine nature, sense of internal empowerment and search for meaning with feelings of internal comfort and self-faith. The dream also suggested that the psychotherapy could be terminated. It indicates her transformation, improvement and cure outcome in the reality world that is correspondent to her improvements within external environment. Based on her associations, recordings and homeworks of the four psychic functions, dream clarification and interpretation confirmed the above assumptions. The present dream functioned as "inner healing symbol" exploration in the Jungian sense. It demonstrates a forward-looking momentum for the patient and guides her toward self fulfilment of everyday problem solving tasks as well as the end of treatment.

Conclusions and recommendations to clinicians

According to the case assessment during pre- and post-treatment intervals via CPPS by herself, her family, her classmate and therapist, she improved significantly. Analytically, the present essay indicated that rebellion originated in animus and childhood maltreatments, and manifested itself in dreams as male figures in female with social phobia. Childhood and infantile traumatic events, psychosexual development malfunctions, and inefficient coping skills for solving current life events may express themselves as features in a patient's dreams (24,25,26). Dreams as a core regulator of the life force can help patients achieve a balance of anima, animus, persona and shadow archetypes of personality, which is beneficial for a therapist's psychotherapy prognosis (3,27). As Jung (15,18) noted, dream work is a fundamental core of analytical psychotherapy. Dreams can reflect patients' psychological and physiological needs and prognosis or outcome of psychotherapy. Khodarahimi (3) pointed out that the patient's dreams have direct implications for the aetiology of the illness and psychotherapy outcome and prognosis. Dreams' clinical workings tend to divulge to actual reality of the therapist. It exemplifies the transference reactions, the inner therapist, the countertransference dynamics, the process of therapy, and the therapist's dreams about the patient. Dream is an instrument for diagnosis, research and treatment of mental disturbances in a clinical setting. In conclusion, the present findings support Jung's notions of dream significance and its application in four stages of treatment (15,16). However, the present findings are limited as they are from a case study on social phobia. Further research should examine dream roles in aetiology, prognosis and treatment of other psychological disorders at both individual and collective levels in inpatients and outpatients within diverse cultural contexts.

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BRIEF COMMUNICATION

Challenges in the Management of Nasopharyngeal Carcinoma: A Review

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Abstract

Nasopharyngeal carcinoma (NPC) is a non-lymphomatous, squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx, an area that shows varying degrees of differentiation. Although relatively rare worldwide, NPC has substantial incidence and mortality in populations in Southeast Asia and in people with Southern Chinese ancestry. In Malaysia, NPC is a leading cancer type. In the clinic, NPC presents on a very wide spectrum. Therefore, a high degree of suspicion on the part of the clinician and an increased awareness by the patient is essential for the recognition of an early lesion. Early detection of the cancer is important as it affects the patient's prognosis and the mode of treatment. Managing patients with NPC is very challenging as patients usually present late when the cancer is already in an advanced stage. Here, we review the challenges in the management of NPC.

***Keywords*:** *nasopharyngeal carcinoma, management, challenges, medical sciences*

Introduction

Nasopharyngeal carcinoma (NPC) manifests itself in multiple forms and may present to different medical specialists. Many patients with NPC present with an advanced stage of the disease, resulting in a poor prognosis. Reasons why patients present with such a late stage of NPC include the following: a delay in seeking medical advice; the confusing nature of the presenting symptoms, which are misleading to the clinician; the difficult nature of a clinical examination of the nasopharynx, even for experienced clinicians; and the spread of a silent submucosal lesion with a normal appearance during examination of the nasopharynx.

The average time between the appearance of NPC symptoms and the first consultation is about six months (1). The patient's symptoms often include epistaxis, nasal obstruction, decreased hearing, tinnitus, neck masses, headache, diplopia, facial numbness, hypoaesthesia, trismus, ptosis or hoarseness. NPC is often diagnosed due to Trotter's triad, a combination of conductive deafness, elevation and immobility of the ipsilateral soft palate, together with pain on the side of the head, which represents symptoms of local invasion (1). A study conducted in Hospital University Sains Malaysia (2), found that the most common presentations of NPC in patients are neck masses (commonly unilateral), followed by headache and epistaxis. Other symptoms may include unilateral nasal obstruction, tinnitus, diplopia, otalgia, bilateral deafness, blindness and dysphagia. Besides the above symptoms, cranial nerves are also commonly affected. The most common cranial nerve affected is the sixth, followed by maxillary division of the fifth and twelve nerve palsies.

Diagnosis and screening

With such a wide spectrum of clinical presentations, it is important to have a high index of suspicion for early diagnoses of NPC. Early identification of NPC is important for patient treatment and prognosis. To establish the correct diagnosis, thorough patient history and physical examination are important. The clinical examination must include a complete examination of the head and neck, including all levels of the neck and cranial nerve function. A nasoendoscopy

is mandatory during diagnosis of NPC. The nasoendoscope and postnasal mirror may reveal an exophytic tumour. Unfortunately, many tumours remain submucosal and difficult to diagnose.

Laboratory investigations, including full blood count and erythrocyte sedimentation rate (ESR), are essential because repeated epistaxis may cause anaemia and a raised ESR increases the possibility of an underlying lymphoma. In addition, hearing assessment using audiometry may indicate a compromised eustachian tube function due to tumour compression that leads to hearing impairment. Visual test, visual acuity and visual field are also important during diagnosis of NPC, especially for patients presenting with visual symptoms or eye signs.

Radiological examination remains one of the most important approaches for NPC diagnosis, evaluation and staging. The density of NPC tissue is often similar to that of soft tissue. Therefore, detection of a tumour depends on the displacement or erosion of the normal anatomy and the uptake of the iodinated intravenous product by the tumour. Most often, computerised tomography (CT) is the investigation method of choice. CT seems to be better at detecting cortical bone erosion, whereas magnetic resonance imaging (MRI) appears superior at clearly delineating the tumour edge, determining the vascular nature of the lesion and identifying intracranial extension. With the modern spiral CT scan, it is possible to examine the skull base down to the abdomen to visualise the presence of any metastasis (1). As this technology is still not widely available in Malaysia, the other imaging modalities, such as chest X-ray and abdomen ultrasound are sufficient. The tumour can then be staged based on the International Union Against Cancer/American Joint Committee on Cancer (UICC-AJCC) system (1997) (3). Histopathological examination of the biopsy material obtained from the nasopharynx will confirm the diagnosis of NPC. Based on histopathological examination, NPC can be divided into three categories, World Health Organization (WHO) type 1, type 2 and type 3 (WHO classification) (4). All of the above examinations are the standard diagnostic practice locally and internationally.

Several studies have been conducted to determine a screening method for NPC (5–10). In Southern China, where NPC is endemic, Epstein-Barr virus (EBV) serology has been used for population screening for NPC. Identification of EBV genomic latent membrane protein-1 (LMP-1) by a nasopharyngeal swab is able to diagnose NPC with an 87.3% sensitivity and a 98.4% specificity (11). Use of an nasopharyngeal brush biopsy has also demonstrated the presence of EBV DNA with a sensitivity of 90% and a specificity of 99% (7). The high cost involved in this diagnosis method means that it is still not justifiable to do in every patient suspected of having NPC. In our centre, we use a nasopharyngeal brush biopsy in situations that are difficult to interpret by other diagnostic modalities.

Treatment

The majority of NPC patients are treated radically with the goal of curing the patients in the early stages of the disease. Patients with distant metastases at the time of presentation and those medically unfit for treatment receive palliative treatment and symptomatic care. Radiotherapy is the primary treatment modality for NPC at all disease stages (12). The primary tumour and the neck are treated even in patients without palpable nodal disease. However, the treatment area must be extended to include the base of skull if there is evidence of cranial nerve involvement. Standard radiotherapy doses are more than 7000 cGy. The lower aspect of the neck and supraclavicular region receive 5000 cGy through the use of an anterior field. The brain stem and spinal cord are blocked, so that they do not receive more than 4500 cGy and the optic chiasm does not receive more than 5000 cGy.

Intensity-modulated radiotherapy has achieved excellent locoregional control of NPC (13). A study that prospectively assessed salivary functions confirmed the gradual recovery of parotid function within two years after the completion of intensity-modulated radiotherapy. Satisfactory dosimetric results were also achieved with this treatment approach for recurrent NPC, and the degree of short-term control was encouraging. Other attempts to enhance the biological effects of radiotherapy have been reported. These attempts include accelerated fractionation, accelerated hyperfractionation, and a combination of one or more of these treatment approaches with chemotherapy. However, hyperfractionation radiotherapy for NPC should be used with care. A study of accelerated hyperfractionation by 2D radiotherapy planning reported an increase in radiation damage to the central nervous system without an improvement in tumour control.

Surgical therapy has a secondary role and is generally considered for patients with residual cervical lymphadenopathy after radiation therapy, or for patients that develop cervical metastases after radiation therapy. Due to its location, the nasopharynx has traditionally been considered unresectable. Wei et al. (14) popularised the

maxillary swing procedure for nasopharyngectomy in the treatment of recurrent NPC post-radiotherapy. This technique is now the current practice locally and worldwide. In this procedure, the maxillary antrum with the hard palate attached to the anterior cheek flap is turned laterally as an osteocutaneous flap. After removal of the recurrent tumour by nasopharyngectomy, the maxilla is repositioned to its original location and anchored by plates and screws.

Alternatively, nasopharyngectomy can be performed via the infratemporal approach (15). For this surgical technique, an extended radical mastoidectomy is initially carried out followed by the transection of the external auditory canal. The facial nerve is displaced inferiorly, and the temporalis muscle is retracted. Bone in the skull base is removed, starting at the glenoid fossa and continuing to the infratemporal fossa, to expose the eustachian tube and the tissue of the parapharyngeal space. The internal carotid artery is exposed from the middle ear to the foramen lacerum, and the middle meningeal artery and the mandibular branch of the fifth cranial nerve are separated. Tumours in the nasopharynx can be removed en bloc, with the surrounding tissue extending to the contralateral nasopharyngeal wall. The mobilised temporalis muscle is used to fill the surgical defect, after which the middle ear cavity and temporal area are filled with abdominal fat.

For patients with advanced locoregional disease (stages III and IV), a combination of chemotherapy and radiation is given. Prasad showed a combination of radiotherapy and CT prolonged the survival rate of patients at a late stage of NPC (16). Chemotherapy can be given neoadjuvantly, concurrently, adjuvantly, or in a combination of these approaches. A study examining the three basic approaches to chemotherapy (neoadjuvant, concurrent, and adjuvant) showed that concurrent chemoradiotherapy is the most efficacious. The chemotherapy agents (anti-neoplastic agents) commonly used to treat NPC patients include cisplatin and 5-fluorouracil.

Residual or recurrent disease in the nasopharynx used to be managed with a second course of external radiotherapy (17). The treatment dosage is normally greater than the initial radiation dose. Although a salvage rate of 32% has been achieved, the cumulative incidence of late sequelae after re-irradiation is 24% with a treatment mortality of 1.8%. To avoid the high incidence of complications resulting from re-irradiation, stereotactic radiotherapy and brachytherapy have been used for patients with small localised tumours in the nasopharynx where surgery is not warranted, or is undesirable. Stereotactic radiotherapy, when used for the management of a residual or recurrent tumour, is associated with a two year local tumour control rate of 72%. Intracavitary or interstitial bracytherapy may allow a high radiation dose to be delivered to the tumour within the nasopharynx while sparing the normal tissue that would be irradiated beyond tolerance limits by the external beam treatment. Brachytherapy is of little value when the disease extends much beyond the nasopharynx (18) .

Circulating free EBV DNA has been reported in patients with NPC (13,19). The quantity of free plasma EBV DNA as measured by real-time quantitative polymerase chain reaction is related to the stage of the disease. The number of copies of EBV DNA before and after treatment is significantly related to the rates of overall and disease-free survival (20). A study has reported that the level of post-treatment EBV DNA compared with pre-treatment EBV DNA is a good predictor of progression-free survival (21).

Of note, survivors of NPC have an impaired, health-related quality of life (22). Patients who survive the disease have several late complications, many of which result from the effects of radiation on the dose-limiting organs adjacent to the nasopharynx and neck nodes. The most debilitating sequelae are neurological complications. These complications can include serious disorders, such as temporal lobe necrosis, cranial nerve palsies and dysphagia. Also, less obvious effects include memory loss, cognitive dysfunction and neuropsychological dysfunction. Despite the effectiveness of radiation and chemotherapy on the management of NPC, local or regional failure presenting as a persistent or recurrent tumour still occur. With modern advances in techniques and combined modalities of therapy, these morbidities could be minimised and preferably prevented altogether.

Prognosis

As with most tumours, the extent of NPC, as embodied in the TNM staging system, is the most important prognostic factor. A report in 1990 (23) showed that besides the T and N stages, other prognostic factors include the size and degree of fixation of neck nodes, the patient's sex and age, the presence of cranial nerve palsy and ear symptoms at the time of presentation. The size of the lymph node and the extent of the ear symptoms likely suggest the lack of recognition of nodal size and paranasopharyngeal extension

in the T and N staging system used at that time. In 1992, a study (24) reported that the tumour's histological type and the radiotherapy dose and coverage were significant independent prognostic factors. Paranasopharyngeal extension was an independent prognostic factor correlated with adverse local tumour control and increased distant spread (25). A large variation in tumour volume is present in T stages of different staging systems, and primary tumour volume represents an independent prognostic factor of local control. The validity of tumour volume has been confirmed in patients with T3 and T4 tumours. There is an increased risk of approximately 1% in local failure for every cubic centimetre increase in the primary tumour volume (26,27).

Conclusions

NPC presents clinically on a wide spectrum. Therefore, a high index of suspicion on the part of the clinician and an increased awareness by the patient are essential for recognition of an early lesion. Advances in treatment techniques and combined modalities of therapy are necessary to improve the patient's outcome and prognosis.

Author's contributions

All authors contributed equally to the design, data analysis and interpretation, drafting of the article, critical revision and final approval of the article.

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BRIEF COMMUNICATION

Retrospective Review of Outcomes of a Multimodal Chronic Pain Service in a Major Teaching Hospital: A Preliminary Experience in Universiti Sains Malaysia

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Abstract

Background: **Chronic pain is a common medical issue. Beside chronic devastating pain, patients also suffer dysfunction more generally, including in the physical, emotional, social, recreational, vocational, financial, and legal spheres. Integrated multidisciplinary and multimodal chronic pain management programmes offer clear evidence for relief of suffering and return to functional lifestyles.**

Materials and Methods: **This retrospective review was performed in order to evaluate one-year outcomes among all newly referred patients of the multimodal chronic pain service at Hospital Universiti Sains Malaysia (HUSM). All patients received multimodal pain therapy, including pharmacological, physical, and psychological therapy, exercise, and pain intervention. The variables evaluated were based on a patient's global pain assessments, which were made using the Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI), modified by patient self-report, and were taken within days to months of commencing our multimodal pain regime.**

Results: **A total of 169 patients were enrolled in this study. Out of this number, 102 (60.4%) were seen at the pain clinic, and 67 (39.6%) were referred while they were inpatients. About one-third of the patients had chronic pain due to cancer. Our data showed that 128 (75.7%) of our chronic pain patients were successfully managed when ≥50% of pain relief (as measured by their VAS score) was achieved at any point during the course of the study period. In addition, 104 patients (61.5%) showed improvement in their modified ODI by 50% or more.**

Conclusion: **A multimodal chronic pain service plays a significant role in managing chronic pain patients in a major hospital, as it is capable of delivering comprehensive and attainable care to manage refractory and intractable chronic pain.**

Keywords: *chronic pain service, visual analogue scale, modified Oswestry Disability Index, multimodal pain therapy, multidisciplinary pain management, medical sciences*

Introduction

Chronic pain is defined as pain that persists beyond three to six months after tissue injury. Nonmalignant chronic pain is a condition in which pain continues despite completed healing of damaged tissue and for which no biologic cause has been demonstrated (1,2). Musculoskeletal pain is most common and includes arthritis, low back pain, myofascial pain syndrome, neuropathic pain, and chronic headache (3). The most common malignant chronic pain (cancer pain) is from tumours that metastasize to the bone (4).

The prevalence of chronic pain has been reported to be high in many studies. A World Health Organization (WHO) cross-continental survey, conducted in 26 000 primary care patients in 15 centres in Asia, Africa, Europe, and the Americas, indicated that one in five adults suffers from chronic pain (range, 6–33%) (5). This agrees with epidemiological studies that have estimated similar ranges of chronic pain prevalence in the general adult population to be about one in six (range 2–40%) (6). Another prevalence study

found that severe or significant chronic pain occurs in 6–14% of the general population of Scotland (7).

Chronic pain is a multidimensional problem that can detrimentally affect physical and psychological aspects of an afflicted individual's life, daily activities, and work (5,7) and may greatly impact healthcare expenditures (8). These in turn, lead to enormous social costs in the form of lost productivity and unrelenting, needless suffering. Internationally, pain is recognized as an impediment to health and dignity, and hence, alleviating pain and maintaining dignity even through the terminal phases of an illness is recognized as a necessity (9,10). Despite its widespread occurrence and measures to improve pain management, the current evidence indicates that pain continues to be under-treated and under-diagnosed for a variety of reasons, even in major service hospitals (1,11). With regards to this issue, the International Association Study Of Pain (IASP) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) now encourages hospitals to develop comprehensive programmes for assessment, treatment, and documentation of pain, as well as the institution of quality improvement efforts related to pain management (10).

The primary goal in chronic pain treatment is to improve the patient's level of function and capacity for return to work (RTW), while decreasing as much as possible the frequency and intensity of pain while simultaneously reducing medication consumption (12,13). The multimodal or comprehensive pain management approach in a biopsychosocial model has been accepted as a standard chronic pain management strategy. It is an integrated multidisciplinary treatment for groups with a closely coordinated therapeutic approach (1). Numerous meta-analyses and critical reviews of integrated multidisciplinary chronic pain management programmes offer clear evidence that this treatment approach can offer relief of suffering and return to a functional lifestyle (12,14). The multimodal regimen is superior to unimodal pain treatments (including surgery, pharmacologic intervention, spinal stimulators and intrathecal opioid pumps) in terms of pain reduction, improved physical functioning, and returning patients to the workforce (15). Nevertheless, implementation of the concept of multimodal and multidisciplinary chronic pain management is still beginning in various Asian countries (16). This study evaluates our preliminary experience and overall achievements one year after commencing this service in our institution.

Materials and methods

This retrospective review evaluates the outcomes of our one-year-old chronic pain service, from May 2007 to May 2008 in Hospital Universiti Sains Malaysia (HUSM). All new referrals for chronic pain management of cancer pain and non-cancer pain that came from either the pain clinic or inpatient wards were enrolled into this study. Patient data were obtained from the pain management unit registry. The cohort was divided by source (pain clinic or ward referral) of the patients entering multimodal (combined) chronic pain therapy. All chronic pain patients were subjected to standard multimodal pain therapy as appropriate, which consisted of physical, exercise, occupational, pharmacological, and psychological therapy, as well as interventional pain management.

Physical therapy mainly consisted of heat therapy (hot packs, ultrasound or short wave), transcutaneous electrical nerve stimulation (TENS), massage, and myofascial release, whereas therapeutic exercise involved active and passive stretching, as well as strengthening exercises in suitable cases. Oral medications consisted of paracetamol, nonsteroidal anti inflammatory drugs (NSAIDs), muscle relaxants, antineuropathic agents, antiresorptive agents, steroids, and opioids (OxyContin or slow-release morphine) when appropriate. The parenteral analgesic agent of choice was either intravenous parecoxib (Dynastat) or morphine sulphate, which was only given to inpatients. A fentanyl patch was advocated when a switch to a slow-release opioid was considered. Counselling and cognitive behaviour therapy was performed informally by one pain physician during each consultation, due to a shortage of staff. Patients with significant psychological disorders such as psychosomatic and somatisation disorders were referred to a psychiatrist for expert treatment. Pain intervention was defined as an injection performed under fluoroscopic guidance and was indicated when patients failed to respond to conservative treatment (physical therapy, exercise and oral medication). The number of patients were then compared and analyzed by variables such as demographic characteristics and patient responses to intervention, including measuring pain intensity by the Visual Analogue Scale (VAS) and functional disability by the modified Oswestry Disability Index (ODI), version 2.0 (17).

As an objective measurement of pain, a linear 100 mm VAS was routinely used in all patients at the first visit and upon improvements in pain if they occurred within the year. Similarly, assessment of the modified ODI was routinely

carried out using a questionnaire that consisted of ten questions. Patients were required to choose the best answer for each section to describe their pain and limitation. The maximum points possible for each question was five, and the maximum score for ten questions was fifty. The total modified ODI score from each patient was expressed as a percent. The modified ODI scoring and relevant level of disability is summarized in Table 1.

For outcomes measurement, improvement in pain (measured by the VAS) and functional/ physical activity (assessed by the modified ODI) were measured within the year-long study period after commencing our multimodal pain regimes, regardless of the total number of follow-up examinations and pain interventions done. Re-evaluation of the VAS and modified ODI were done during follow-up appointments for pain clinic patients, whereas ward referral patients were evaluated on a daily basis at the pain clinic upon discharge from the ward. To measure the overall effectiveness of the multimodal pain management strategy, the VAS and modified ODI were categorized into two groups: the first group; patients who exhibited a reduction by ≥50% in both variables, the second group; patient who showed a reduction of less than 50%. Reassessment of the modified ODI was performed regardless of the patients' VAS score throughout the study period. Fifty percent was taken as a standard figure when quick and brief assessments for improvement in pain and disability status were made. This figure has been widely used as a simple assessment tool in many pain studies and practices. The number and percentage of variables in pain management outcomes were then compared between the two groups of chronic pain patients.

Table 1: The modified Oswestry Disability Index (ODI)

Modified ODI score (%)	Level of disability
0–20	Minimal disability
21–40	Moderate disability
41–60	Severe disability
61–80	Cripple, pain impinges on all aspects of patient's life
81–100	Patients are bed-bound or exaggerating their symptoms

Results

A total of 169 new chronic pain patients were managed by the HUSM chronic pain service between May 2007 and May 2008. Of this figure, 57 (33.7%) were male, and 112 (66.3%) were female (Table 2). Of these new cases, 102 (60.4%) were seen in the pain clinic, and 67 (39.6%) belonged to the ward referral group. The proportion of orthopaedic patients was the highest, with 106 (62.7%) patients, followed by 18 (10.7%) neurosurgical patients (Table 3). The subgroups divided by aetiology showed that non cancer-related chronic pain and chronic back pain patients were the highest in proportion, accounting for 102 (60.3%) and 101 (59.7%) patients, respectively (Table 3). Patients with cancer-related pain dominated the ward referral group, accounting for 55 (84.6%) of these patients, whereas chronic back pain were more

Table 2: Sociodemographic characteristics of 169 new patients treated by the HUSM chronic pain service (from pain clinic and ward referral) from May 2007 to May 2008.

Patient distribution (*n*=169)	Numbers *n*(%)
Age	
Years (means ±SD)	44.7 ±15.5
Gender	
Male	57 (33.7)
Female	112 (66.3)
BMI	
Under weight	30 (17.8)
Normal	42 (24.9)
Overweight	75 (44.4)
Obese	22 (13.0)
Ethnicity	
Malay	144 (85.2)
Chinese	20 (11.8)
Indian	5 (3.0)
Marital status	
Married	109 (64.5)
Not married	60 (35.5)
Occupational status	
Employed	121 (71.6)
Unemployed	73 (28.4)

Data are presented as n (%) or mean ± standard deviation

common in the pain clinic group, accounting for 80 (79.8%) of patients.

Our data also showed that modified ODI and VAS scores were higher in the ward referral group as compared to the pain clinic group (48±5.0 vs. 24±4.2 [ODI] and 8.2±1.3 vs. 6.5±1.4 [VAS], respectively). Patients who belonged to the ward referral group were more likely to be severely disabled, whereas patients from the pain clinic were moderately disabled. Our data showed that 128 (75.7%) of our chronic pain patients were successfully managed by achieving a reduction in the VAS ≥50% at any point during the study period (Table 4). Between groups, a reduction of the VAS ≥50% was more often observed in the ward referral group compared to the pain clinic group (91% vs. 65.7%). Evidence for functional/physical restoration was also apparent, as 104 (61.5%) patients showed improvement in their modified ODI by ≥50%; this effect was predominantly noted in the pain clinic group (67.6%) (Table 4). The total number of pain intervention procedures performed under fluoroscopy was 111 cases, which were done on a total of 76 new chronic pain patients (45%) (Table 5).

Discussion

Chronic pain is a common experience and is costly for both the individual and the health service. International prevalence rates of chronic pain (IASP criteria specifies duration of at least three months) range from 11.5–55.2%, with a weighted mean prevalence of 35.5% across the nation (18). Chronic pain, especially if left untreated, is associated with general physical, psychological, and social distress. Employment, daily activities, and measured dimensions of

Table 3: Demographic characteristics of new chronic pain patients from the pain clinic and from inpatient ward referral who were managed by the HUSM chronic pain service from May 2007 to May 2008.

Patient distribution	Pain clinic *n*=102	Ward referral *n*=67	Total *n*=169
Relevant disciplines			
Orthopaedic surgery	81	25	106
Neuroscience	10	8	18
Surgery	5	9	14
Medicine	3	4	7
Oncology	5	8	13
Family medicine clinic	4	0	4
ENT	0	4	4
Obstetrics and gynaecology	2	0	2
Cancer/non cancer in origin			
Cancer-related pain	12 (11.5)	55 (84.6)	67 (39.6)
Non cancer-related pain	90 (88.5)	12 (15.3)	102 (60.3)
Spine in origin			
Back pain	80 (79.8)	18 (27.7)	101 (59.7)
Non back pain	22 (20.2)	49 (72.3)	68 (40.3)
Pain duration			
Years, average ± SD	4.3 ± 2.4	2.5 ±1.8	
VAS* at first visit			
(0-10 cm scale, average ± SD)	6.5 ± 1.4	8.2 ± 1.3	
Modified Oswestry Disability Index at first visit			
(% ± SD)	24 ± 4.2	48 ± 5.0	

Data are presented as n (%) or mean ± standard deviation
* VAS= Visual analogue scale

Table 4: Pain score based on Visual Analog Scale (VAS) and general improvement in functional/physical activity score based on modified Oswestry Disability Index (ODI) among new chronic pain patients following multimodal pain therapy, divided into ward referral and pain clinic groups

Patient responses	Patient group		Total *n*(%)
	Pain clinic *n*(%)	Ward referral *n*(%)	
Reduced VAS by ≥50%			
Yes	67 (65.7)	61 (91)	128 (75.7)
No	35 (34.3)	6 (9.0)	41 (24.3)
Improvement in modified ODI by ≥50%			
Yes	69 (67.6)	35 (52.2)	104 (61.5)
No	33 (32.4)	32 (47.8)	65 (38.5)

general health are increasingly and negatively affected by the presence of chronic pain (7). These patients have typically lost their independence and are reliant upon medications and the aid of others, contributing to the development of behavioural patterns of general passivity. Thus, due to these inter-related biopsychosocial distresses, chronic pain patients are finally subjected to disability (19).

In addition to the negative psychological and physiological effects, undermanaged pain imposes a heavy economic burden. In the United States, lost productive time (measured in terms of absenteeism as well as reduced productivity while at work) due to common pain conditions such as arthritis, back pain, headache, and other musculoskeletal pain cost $61 billion a year (in 2002 US$) (20). In addition to lost productive time, chronic pain increases healthcare utilization due to more frequent primary care visits and hospital admissions (a 2-fold increase) as well as emergency department visits (a 5-fold increase), compared with no chronic pain (8).

The primary goal in the treatment of chronic pain is to improve the patient's level of function and capacity to RTW by decreasing as much as possible the frequency and intensity of pain while simultaneously reducing medication consumption and additional use of health care resources (12,13). Unfortunately, chronic pain has a low rate of recovery. The average annual recovery rate from chronic pain was reported to be 5.4% after a four-year follow-up period in a study that examined the course of chronic pain in a community study population (13). Nevertheless, other data from a 30-year experience suggested that treatment of patients with chronic pain is best achieved via a multimodal and multidisciplinary team approach (12). Numerous meta-analyses and critical reviews of integrated multidisciplinary chronic pain management programmes offer clear evidence of opportunities to relieve suffering and allow patients' return to functional lifestyles (12,14). In a review of 13 multidisciplinary chronic pain management centres, multimodal therapy was found to be superior to unimodal pain treatments (including surgery, pharmacologic intervention, spinal stimulators and intrathecal opioid pumps) in terms of pain reduction, improved physical functioning, and ability to return patients to the workforce (15). Furthermore, multidisciplinary treatment of chronic pain has been associated with reduced utilization of medical services compared to chronic pain patients treated with other approaches, even in countries with national health insurance (15). In terms of longevity of the benefits of integrated multidisciplinary programs, a follow-up study of patients seen 13 years after treatment supported maintenance of gains from therapy (12,14). Cognitive-behavioural therapy (CBT) is a well-known, important subset that is incorporated into multidisciplinary pain management programmes. This structured programme requires active participation from patients and is based on intensive mental, emotional, and physical rehabilitation in order to improve coping skills and health-related quality of life (12).

We would like to emphasize that our subject population of 169 patients is an underestimation of the actual number of new chronic pain patients seen in our hospital over the course of a year. For example, referral rates of chronic pain patients from the family medicine clinic were still low (2.3%), despite its potential for eventually becoming the main source of chronic pain patients. In addition, many neuropathic pain patients were successfully managed by the neurological team and

Table 5: List of pain intervention procedures done under fluoroscopic guidance on a total of 76 chronic pain patients from May 2007 to May 2008

Pain procedure	Frequency (*n*)	Percent (%)
Epidural steroid	28	25.2
Epiduroplasty	12	10.8
Sacroiliac joint injection	11	9.9
Piriformis injection	10	9.0
Facet joint injection		
Lumbar	11	9.9
Cervical	3	2.7
Paravertebral block	3	2.7
Radiofrequency ablation		
Sacroiliac joint	5	4.5
Lumbar facet	3	2.7
Neuroma	1	
Large-joint injection (triamcinolone or hyaluronic acid)	8	7.2
Discogram	2	1.8
Subscapularis muscle injection	3	2.7
Prolotherapy	2	1.8
Brachial plexus block	2	1.8
Others	7	6.3
Total	**111**	**100**

were only referred to pain clinic if the physician was unable to manage refractory or intractable pain cases. From our observations, we believe that some clinicians were still unaware of the new chronic pain service. HUSM is a tertiary-care hospital that serves a population of five million in northeast Malaysia. Obviously our figures are underestimated, if comparisons are made with previous epidemiological studies in US that have estimated the chronic pain prevalence in the general adult population at about one in six (range 2–40%) (6), whereas severe or significant chronic pain occurs in 6–14% of the general population (7). Nevertheless, data describing the prevalence of chronic pain in Asian countries are limited. The prevalence of chronic pain in the Hong Kong population has been reported to be 10.8%, which is comparable to rates in western countries (16). However, we report that our 169 new chronic pain patients should be taken as clinically significant, as they had refractory and/or intractable chronic pain that required expert management from pain specialists. Presumably, prior to the establishment of chronic pain service, the number of chronic pain patients remained high, with these cases likely being under-treated, which led to persistent pain and disability.

Chronic pain is undertreated

Current evidence indicates that chronic pain continues to be undertreated. A recent nationwide survey of the general population showed that 75% of subjects who had experienced moderate to very severe pain within the previous two weeks had sought medical attention, but 44% of those who did so had not had significant pain relief (21). Likewise, in a European survey of more than 46,000 respondents, 40% of adults with chronic pain were found to be inadequately managed (22). A similar issue was observed in our study, in which the mean VAS in the pain clinic and ward referral groups at the first visit was quite high, at 6.5±1.4 and 8.2±1.3, respectively. The VAS was exceptionally high in the ward referral group, as most patients (84.6%) had pain from advanced cancer. This finding is consistent with previous studies that

have shown that 90% of patients with advanced cancer experience severe pain. In addition, as many as 50% of patients may be undertreated for cancer pain (23,24). A paucity of knowledge and skill pertaining to pain management among clinicians was identified as the main reason contributing to inadequate pain management, especially for cases of intractable and refractory pain (11,25,26). This fact is consistent with our observation that most patients had already been treated with analgesics (single or multiple-drug regimens) by the time of referral by their primary physician, and yet their pain was still uncontrolled. Conversely, a study performed by Vallerand et al. (11) showed that caregivers with greater knowledge of pain management had significantly fewer barriers to treatment, supporting the importance of increasing caregiver's understanding of cancer pain management (11).

Other factors in the undertreatment of pain may arise from inadequacies and restrictions in healthcare systems, attitudes, beliefs, and fear on the part of physicians, patients, families, and society, all of which may contribute to the widespread undertreatment of pain in our society (11,23,25). With respect to attitudes and beliefs, Fishbain et al. (17) has mentioned two possible reasons why treatment at a pain facility was not considered. First, the attending orthopaedic physician did not know or did not believe that treatment in a multidisciplinary pain facility would be of value. Second, the patient's insurance may not have covered such treatment. Such a situation would have forced the attending orthopaedic physician to proceed with an alternative treatment (27).

Our sociodemographic data revealed that rates of increased age, gender (female), weight and obesity remained high with high incidences of chronic pain (Table 2). Studies have reported that overweight or obesity early in life is a risk factor for pain and that both pain and overweight or obesity negatively affect quality of life (28). The prevalence of chronic pain has been reported to be higher among women than men (20% versus 16%) and was increased with age; these results were consistent with our findings (29). Our data also showed that 71.6% of chronic pain patients were employed civilians. We agree that this data should be correlated with the specific nature of the job in order to be more meaningful. A more recent survey in Spain found that the most important work-related pain problems derived from maintaining the same posture and carrying out repetitive tasks (30).

Our data showed that orthopaedic patients comprised the largest proportion (62.7%) among the subgroups. The pain clinic was noticeably and predominantly attended by chronic back pain patients (79.8%), whereas the ward referral group was mostly composed of cancer-related chronic pain patients (84.6%) (Table 3). This finding agrees with the fact that low back pain is a worldwide major health and socioeconomic problem. Over 26 million adults experience frequent back pain, and two-third of Americans will have back pain during their lifetime (30). Meanwhile, other studies have reported that approximately 80% of Americans experience low back pain during their lifetime (3,30).

Improvement of VAS and modified ODI: the explanation

The VAS is recommended by the Agency for Health Care Policy and Research (AHCPR) as a pain assessment tool and is widely used in pain research (31), whereas the ODI is currently considered the "gold standard" for researchers to measure permanent functional disability, especially among chronic back pain patients (17). Improvement by 50% or more on the VAS and ODI is taken as an indicator of significant improvement, and this simple assessment tool is commonly used in clinical practice and researches. Most pain researchers have reported using the "pain reduced by ≥50%" metric to denote significant pain relief following intervention (32). Our study showed that 75.7% of our patients had ≥50% reductions in VAS score, which might be considered to be an overestimated value. Chronic pain is reported to have a low rate of recovery without intervention. For example, the average annual recovery rate from chronic pain was 5.4% after a follow-up period of 4 years in a study that examined the course of chronic pain in the community (13). Turk et al. (12) found that pain reduction across studies following multidisciplinary pain therapy was 37%, which was comparable to other pain treatment modalities; however the rate of return to functional work ranged from 48–65%, a significant improvement beyond pain reduction itself (15).

The high success rate in our multimodal pain treatment (75.7%) was strongly increased by a reduction in the VAS by ≥50% among the ward referral group (91.0%) which was dominated by cancer-related pain patients. We believe that our cancer-related pain patients responded much better to our pain treatment regime than non-cancer-related pain patients did for several reasons. Patients underwent proper assessment of pain in terms of severity, type, and cause of pain, resulting

in correct goals and direction of treatment regimes. We also noticed that most patients did well with slow-release opioid analgesics (OxyContin, slow-release morphine, fentanyl patches) and anti-neuropathic agents (gabapentin, amitriptyline, carbamazepine, clonazepam). Our finding is consistent with a longitudinal follow-up study done by Meuser T et al. (33), who reported that efficacy of pain treatment was good in 70%, satisfactory in 16%, and inadequate in 14% of patients, after the WHO guidelines for cancer pain relief were followed (33). Conversely, non-cancer-pain patients (chronic benign pain patients) tolerated both groups of medications poorly, as most of them suffered from adverse effects of the medications. We also noticed that some of our cancer patients benefited from regional nerve blocks while undergoing titration of opioid or antineuropathic agents to therapeutic levels. This technique was often employed for an intractable and mixed type of cancer pain. Another factor that also may play a role in our high success rate was the existence of a well-established oncology and radiotherapy department at HUSM, in which most of our cancer patients underwent complimentary radiotherapy or chemotherapy as part of our multimodal chronic pain therapy. None of our cancer patients required intrathecal catheterization for neuraxial opioid therapy.

Nevertheless, ≥50% reduction in VAS is a rather rough assessment of quantity of pain relief and is less specific. Previous pain studies often incorporated functional or physical activity scores along with the pain score in order to evaluate outcomes in a more meaningful way (15). Thus, we concluded that restoration of patients' functional or physical activity was an important complement to our overall assessment of patient responses. In our study, the degree of patient disability was measured by the modified ODI, which reported moderate (24±4.2) and severe (48±5.0) disability in the pain clinic and ward referral groups, respectively. This finding correlates with VAS scores, which yielded higher scores in ward referral group. Our data showed that overall improvement in the modified ODI by ≥50% was recorded in 61.5% of the patients and was more often observed in the pain clinic group (67.6%) (Table 4). Although improvement in pain score was greater in the ward referral group, improvement in their modified ODI was subtle (52.2%). We conclude that this was due to the characteristics of patients in the ward referral group because most of them had significant comorbidities and debility due to their status as advanced cancer patients. Nevertheless, it is known that level of activity does not necessarily correlate with pain intensity (34).

The psychosocial assessment of chronic pain

Even though functional measurements of pain such as the ODI have gained popularity, self-reports of some functional measurements may still be unreliable. Ideally, a single-dimension metric is not the best pain assessment tool, as chronic pain can have a significant psychosocial impact. Compared to people without chronic pain, those with chronic pain have a 4-fold increased risk for depression or anxiety (7). Estimates of the prevalence of depression among patients with chronic pain range from 31% to 100%, while pain complaints in depressed individuals range from 34% to 66% (35,36). In our work, counselling and cognitive behaviour therapy were done informally by a single pain physician during consultation, due to a shortage of staff. Patients who presented with significant psychological disorders such as psychosomatic and somatisation disorders were referred to a psychiatrist for expert treatment. Other more realistic psychosocial inventories such as the Beck Depression Inventory (BDI) or Pain Catastrophizing Scale (PCS) would be a better option for the variables measured in this kind of study. Alternatively, other multiple-dimensional methods for reporting pain, such as the McGill Pain Questionnaire (MGPQ) or Short Form Health Survey (SF-36), will be valuable if incorporated into the assessment of chronic pain patients in future studies (37). The SF-36 is a comprehensive pain measurement tool that is frequently used for measuring Health Related Quality Of Life (HRQL) and for following changes in HRQL after clinical treatments. It consists of eight scales that measure physical functioning, physical role (limitations in daily activities), bodily pain, general health, vitality, social functioning, emotional role (limitations in daily activities), and mental health.

Interventional pain management

Pain intervention procedures under fluoroscopic guidance were indicated when patients failed to respond to conservative treatment (refractory) and had persistently high VAS (VAS 7–10). This step is in accordance with the WHO fourth analgesic ladder recommendation, which states that interventional pain procedures are called for when the third analgesic ladder of pain management strategy has failed (12,14). The total number of pain interventions performed under fluoroscopy was 111 cases in 76 patients, who comprised 45% of our new chronic pain patients (Table 5). This high pain intervention rate can be attributed to several reasons. Some patients underwent multiple pain procedures at one time, as they presented with multiple pain diagnoses.

In addition, most pain procedures required repetition, either as recommended by protocol or as pain recurred. The list of intervention procedures is given in Table 5. Epidural steroid injection was the most common pain intervention procedure performed (25.2%), followed by lumbar and cervical facet joint injection (12.6%), epiduroplasty (10.8%), sacroiliac joint injection (9.9%), and piriformis injection (9.0%). However, no analysis was done to define the efficacy of the pain interventions employed, as this requires a randomized, double-blinded controlled trial. The improvement in our patients' pain and disability actually reflected the overall multimodal treatment regimens used in the biopsychosocial approach, rather than unimodal therapy. We conclude that vast skill and knowledge in pain management, the presence of up-to-date techniques, and drugs relevant to pain management that are delivered through multimodal pain therapy approaches are the main keys for success in chronic pain management.

Study Limitations

Because this survey was based on respondents' self-report, the quality and accuracy of the data cannot be determined, particularly for the extremely subjective disability score. In future studies, the modified ODI should also be administered during the pre- and post-treatment course so that outcomes can be compared. As another option, more objective tools for measuring disability may be utilized, such as the Short Form Health Survey (SF-36). In addition, our survey documented only two specific symptoms (pain intensity and physical disability), which are known to be associated in chronic pain. Clearly, many other conditions which have not been explored, such as psychological status, may interfere with the total picture of chronic pain.

The documentation of dependent variables (VAS and ODI) was completed serially. Patients who developed recurrent pain over the course of the study period were not re-entered into the study sample. On the other hand, patients who initiated treatment later in the study period probably did not have enough time to respond to the comprehensive biopsychosocial model of pain treatment; this clearly will affect the study outcome.

Implications for health care authorities

Despite the demonstrated effectiveness of multidisciplinary approaches for the treatment of chronic pain, only a small group of patients took advantage of the multidisciplinary pain clinics. Extra effort must be applied to promote awareness of this relatively new service among caregivers and chronic pain sufferers. In addition, although specialty pain clinics may be perceived as expensive ventures, their treatment outcomes can result in lower levels of patient disability. They are thus likely to impact on health care utilization and the economics of health care such that high front-end investments may result in long-term health care savings for the system as a whole.

Conclusion

A chronic pain service plays a significant role in managing chronic pain patients in a major hospital, as it is capable of delivering comprehensive care and management of refractory and intractable chronic pain. More patients will benefit from this novel service if referrals for pain management can be made early and often.

Author's contributions

Conception and design, drafting of article, critical revision of article: NAJ
Data analysis and interpretation; statistical expertise: ZS
Provision of patients; administrative support: MSA
Administrative, technical and logistic support: MO

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CASE REPORT

Alum Irrigation for the Treatment of Intractable Haematuria

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Abstract

Managing intractable haematuria is a daunting task. One cause of this condition is radiation-induced haemorrhagic cystitis. Several treatments for the condition have been proposed and one non-invasive option is alum irrigation. Here, we report on a 65-year-old woman with intractable haematuria secondary to radiation cystitis who was successfully treated with alum irrigation. Alum irrigation is safe, well tolerated and relatively cheap. A review of the literature and a comprehensive discussion on alum irrigation as treatment for haematuria is discussed here to create an awareness regarding this treatment option.

***Keywords*:** *intractable haematuria, radiation cystitis, alum irrigation, medical sciences*

Introduction

Intractable haematuria from the bladder can be life threatening and its management is challenging. Haemorrhagic cystitis is a condition that can cause intractable haematuria and has several causes, including pelvic radiation and systemic treatment with oxazophosphorine alkylating agents like cyclophosphamide. The incidence of radiation cystitis in general is between 3–15% (1). For the management of haemorrhagic cystitis, several different treatment modalities remain in use with varying degrees of success; one such treatment is alum irrigation. Here, we present a case of radiation-induced haemorrhagic cystitis that was successfully treated with alum irrigation. This case report will increase awareness among Malaysian medical practitioners regarding alum irrigation as a safe and effective option for the treatment of intractable haematuria.

Case Report

A 65-year-old Chinese woman was diagnosed with ovarian carcinoma 20 years ago and underwent a total abdominal hysterectomy and bilateral oophorectomy (TAHBSO) followed by external beam radiotherapy (1.5 Gy/fractions, 5 days/week for 4 weeks). Her postoperative and post-radiation course was uneventful until she presented with a 2 day history of frank haematuria, 20 years after TAHBSO. Laboratory investigations revealed normal renal function and coagulation profile. Ultrasound of the abdomen showed no evidence of calculi or focal renal lesions.

Cystoscopy was performed and demonstrated Radiation Therapy Oncology Group (RTOG) Grade 4 bladder telangiectasia, likely from radiation cystitis. No tumour or calculi were seen. Areas of bleeding were diathermized and bladder washout performed, however the haematuria persisted. This was repeated a number of times, nevertheless the haematuria continued. The patient was started on 1% alum irrigation at 250 mL/hr (6 L over 24 hours). She tolerated the treatment well, and after 24 hours the haematuria had stopped completely. Serum aluminium levels were normal and there were no signs or symptoms of aluminium toxicity. Before initiation of the alum irrigation, her serum aluminium level was 1.71 μmol/L and International Normalised Ratio (INR) was 1.02. After alum irrigation, her serum aluminium level was 3.07 μmol/L and INR was 1.34. She was discharged home the following day, after a period of clear urine was observed. At 3 months of follow-up, she had experienced no recurrence of haematuria.

Discussion

Complications of pelvic radiation include both acute and chronic bladder injuries. One sequela of chronic radiation-induced bladder insults is haemorrhagic cystitis. The incidence of haemorrhagic cystitis for cervical carcinoma treated with both intracavitary and external beam radiotherapy is reported at 6.5%. The median interval to developing haematuria following the completion of therapy was 35.5 months (2). Chronic radiation therapy can cause damage to the bladder submucosa, leading to necrosis of the vascular endothelium, vessel wall thickening and obliterative endarteritis. All of these changes result in hypoxia, hypovascularity and ischaemia, which can ultimately induce neovascularisation of vessels that are fragile and prone to bleeding.

There are many different treatments for haemorrhagic cystitis. Among these treatments are clot evacuation, continuous bladder irrigation, oral aminocaproic acid, oestrogens, endoscopic laser coagulation, intramural orgotein (free radical scavenger), alum irrigation, formalin, placental extract or prostaglandin administration, embolisation of iliac arteries, Helmstein's hydrostatic distension, hyperbaric oxygen, sodium pentosan polysulphate, silver nitrate, vasopressin, phenol, urinary diversion and cystectomy.

Alum irrigation for the treatment of haemorrhagic cystitis was first introduced by Floyd Csir to Ostroff and Chenault in 1982. Success rates are high with most reports placing rates at 75–100% (3–5). Alum is composed of either aluminium ammonium sulphate or aluminium potassium sulphate. As an astringent, aluminium acts by precipitating protein over bleeding surfaces. Its action is limited to the cell surface and interstitial spaces due to its low cell permeability. Hardening of the capillary endothelium occurs leading to decreased capillary permeability, contraction of intercellular space and vasoconstriction. As a result, local oedema, inflammation and exudation are also reduced.

There are two protocols for 1% alum irrigation. The first is to dissolve 400 g of potash of alum (McCarthy's) in 4 L of hot, sterile water. 300 mL of this stock solution is added to 3 L of 0.9% saline through a sterilizing filter and the bladder irrigated with up to 30 L of this solution in 24 hours. The second method is to dissolve 50 g of alum in 5 L of sterile water and irrigate the bladder at 250–300mL/h (5). Schootstra et al. used 0.5% alum by dissolving 300 g of alum (aluminium potassium sulphate) and 480 g of sodium chloride in 60 L of water, with the advantages of decreased aluminium toxicity and minimisation of colloid-like precipitation that can block the catheter (6).

The advantage of alum irrigation compared to other treatment methods for haemorrhagic cystitis is that it is generally safe, effective, well tolerated and cost effective. There is no need for regional or general anaesthesia unlike when using formalin, phenol, silver nitrate or hydrostatic bladder distension. It is a simple procedure that does not require open surgery or elaborate radiological procedures. In addition, local tissue histology is not distorted. The side effects of 1 % alum irrigation include suprapubic pain and bladder spasms. These side effects may be due to the fact that a 1% alum solution has a concentration of 1.05 g/L and a pH of 4.5. Normally, serum aluminium is excreted rapidly by the kidneys, with a potential excretion reserve of up to 30 times normal values. Renal insufficiency, accumulative absorption or massive absorption due to large absorptive surfaces, like a large bladder tumour, may cause aluminium toxicity. Aluminium toxicity causes neurofibrillary degeneration in the central nervous system which can lead to encephalopathy, malaise, speech disorders, dementia, convulsions and vomiting. It can also cause severe allergic reaction in susceptible individuals.

In summary, alum irrigation is a simple, safe, effective and well-tolerated, non-invasive option for the treatment of haemorrhagic cystitis. However, vigilance is still needed to avoid aluminium toxicity.

Author's contributions

Conception and design, drafting of the article, provision of study materials or patients, collection and assembly of data: CCKH
Critical revision and final approval of the article: CCKH, ZZ
Administrative, technical or logistic support: ZZ

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Malaysian Journal of Medical Sciences, Vol. 16, No. 4, Pg 69-72, October - December 2009

CASE REPORT

Calcification of the Alar Ligament Mimics Fracture of the Craniovertebral Junction (CVJ): An Incidental Finding from Computerised Tomography of the Cervical Spine Following Trauma

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Abstract

When performing a radiological assessment for a trauma case with associated head injury, a fragment of dense tissue detected near the craniovertebral junction would rapidly be assessed as a fractured bone fragment. However, if further imaging and evaluation of the cervical spine with computerised tomography (CT) did not demonstrate an obvious fracture, then the possibility of ligament calcification would be considered. We present a case involving a previously healthy 44-year-old man who was admitted following a severe head injury from a road traffic accident. CT scans of the head showed multiple intracranial haemorrhages, while scans of the cervical spine revealed a small, well-defined, ovoid calcification in the right alar ligament. This was initially thought to be a fracture fragment. Although such calcification is uncommon, accident and emergency physicians and radiologists may find this useful as a differential diagnosis in patients presenting with neck pain or traumatic head injury.

Keywords: *cervical spine, calcification, computerised tomography, injury, medical sciences*

Introduction

Calcification in the region of the upper cervical spine is rare, although a few cases have been reported involving calcification of the alar or transverse ligament of the atlas. The calcification usually develops as a result of traumatic injury or inflammatory disease and is especially prominent in the elderly (1–3). In patients with a history of trauma, alar ligament calcification can mimic a fracture of the craniovertebral junction (CVJ). As an uncommon normal variant, it is important for accident and emergency physicians; and radiologists, to be able to distinguish such calcification from a fracture. We present a head injury case where the calcification was only incidentally detected and was initially thought to be a fracture fragment.

Case Report

A 44-year-old man who was involved in a road traffic accident (RTA) was admitted for deterioration in his level of consciousness. An urgent cranial computerised tomography (CT) scan showed a large right temporoparietal extradural haemorrhage (EDH), a left temporal hemorrhagic contusion and multiple skull vault fractures. Due to the severity of the head injuries, a CT scan of the cervical spine was also performed. A small, well-defined region of calcified tissue was detected between the odontoid tip and the right occipital condyle (Figure 1). The pre-vertebral soft tissue at the upper cervical spine was not thickened (measuring about 4.6 mm at the C2 level on the mid sagittal multiplanar reformat [MPR]). There was no indication of occipito-atlanto dissociation (the basion-dental interval measured 4.3 mm, which is within the accepted normal range) (Figure 2). The rest of the cervical spine seemed undisrupted.

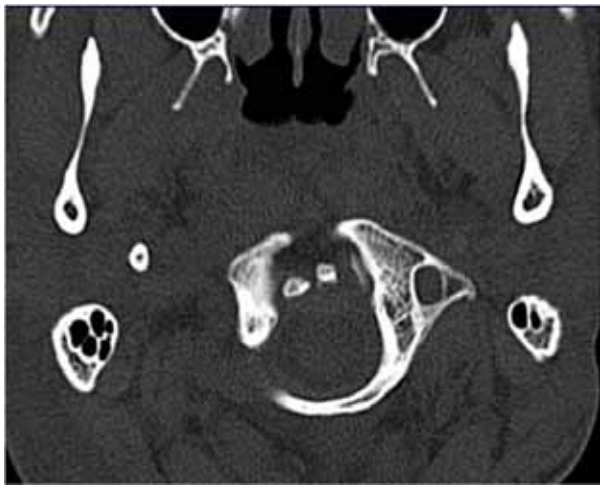

Figure 1: Axial CT scan of the cervical spine showing a small, well-defined, high-density region located between the odontoid tip and the right occipital condyle

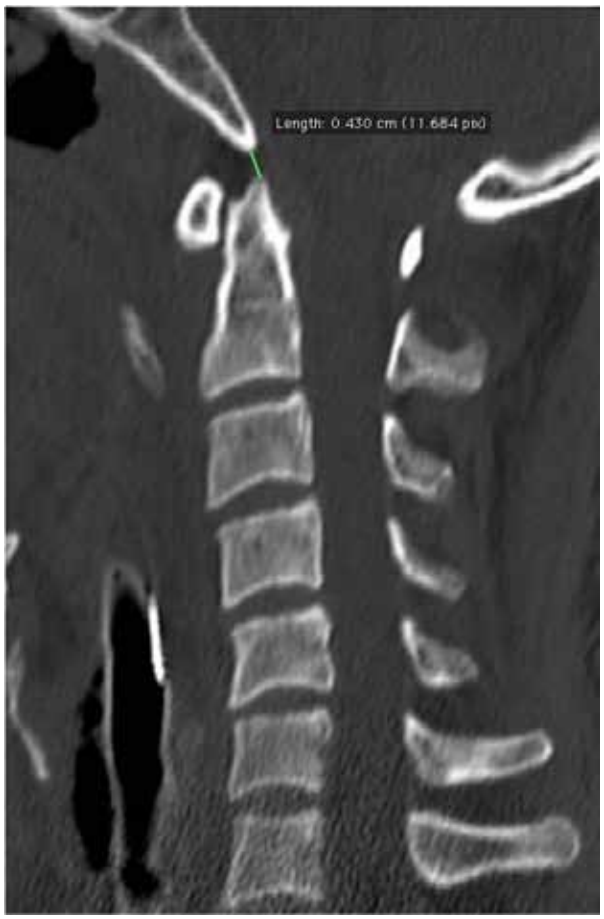

Figure 2: CT scan of the cervical spine (mid sagittal MPR) showing the basion-dens interval, which measures about 4.3 mm

In view of the RTA and severity of the head injuries, a fracture at the CVJ was initially suspected. However the origin of the fractured fragment could not be determined. On comparison with sagittal and coronal MPR images (Figure 3a & 3b), a well corticated structure (measuring about 6.5 x 3.8 x 4.0 mm) was identified between the right occipital condyle and odontoid tip. This indicated that the anomaly was a calcified structure rather than a fragment of bone. The adjacent occipital condyle, odontoid process and neural arch of the atlas showed smooth and well defined outlines. The soft tissue window (Figure 4a and 4b) showed the calcification was within the right alar ligament. Unfortunately, due to the severity of the head injuries, and despite evacuation of the intracranial haemorrhages, the patient succumbed ten days later.

Discussion

The alar ligaments originate bilaterally from the odontoid process and run cephalad and laterally to reach the medial aspect of the occipital condyle. They are strong, rounded structures that play an important role in stabilising the head during rotary motion of the CVJ. These ligaments can be easily studied using high-resolution magnetic resonance imaging (MRI) that includes a proton attenuation-weighted sequence. The orientation of the alar ligaments is highly variable and asymmetry is common in asymptomatic individuals (3,4).

Calcification in the alar ligament is very rare. It usually develops with increasing prevalence after the age of 40 and tends to occur following minor trauma or as a consequence of inflammatory disease (1–3). In our case, the calcification was observed in the right alar ligament, which is similar to the findings of Sim and Park (1). They detected a nodular calcification in the periodontoid area on the initial axial CT scan performed on their patient following a severe head injury. They had also considered the possibility of a fracture involving the odontoid process (type I fracture), the occipital condyle (type III fracture) or the neural arch of the atlas at the CVJ. MPR, MRI and a 3D-CT scan of the cervical spine were performed for further evaluation of the anatomy of the calcified structure. Serial, open-mouth views and dynamic radiographs of the cervical spine demonstrated a stable cervical spine and a persistent, constant cross-section calcification. On the basis of this series of examinations, they concluded that the nodular calcification occurred in the right alar ligament and was unrelated to trauma or inflammation and, therefore, was an incidental finding (1).

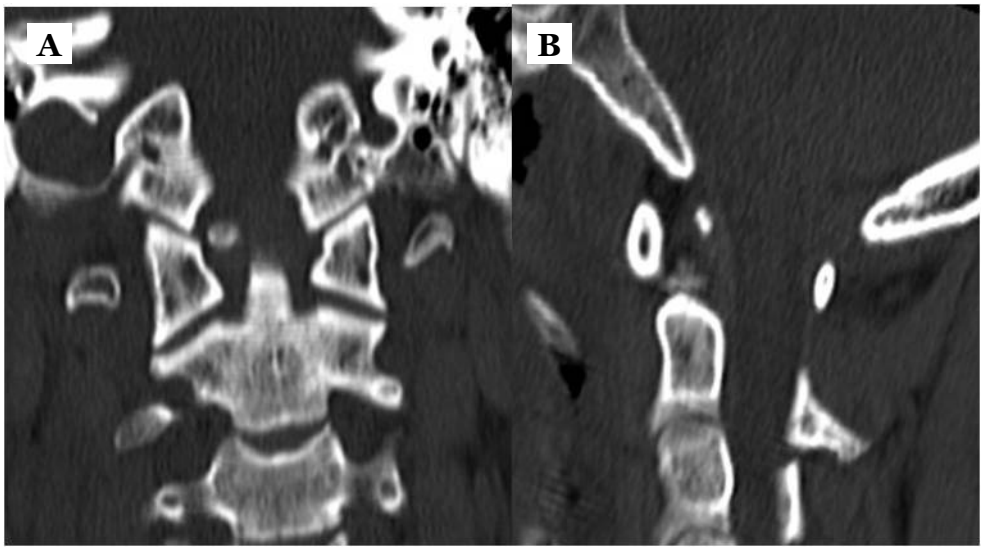

Figure 3: MPR images (bone window) from coronal (A) and sagittal (B) CT scans depict a well-defined, calcified structure located between the right occipital condyle and tip of the odontoid process. A slight atlanto-occipital subluxation can be seen. The rest of bony structures at the craniovertebral junction are normal.

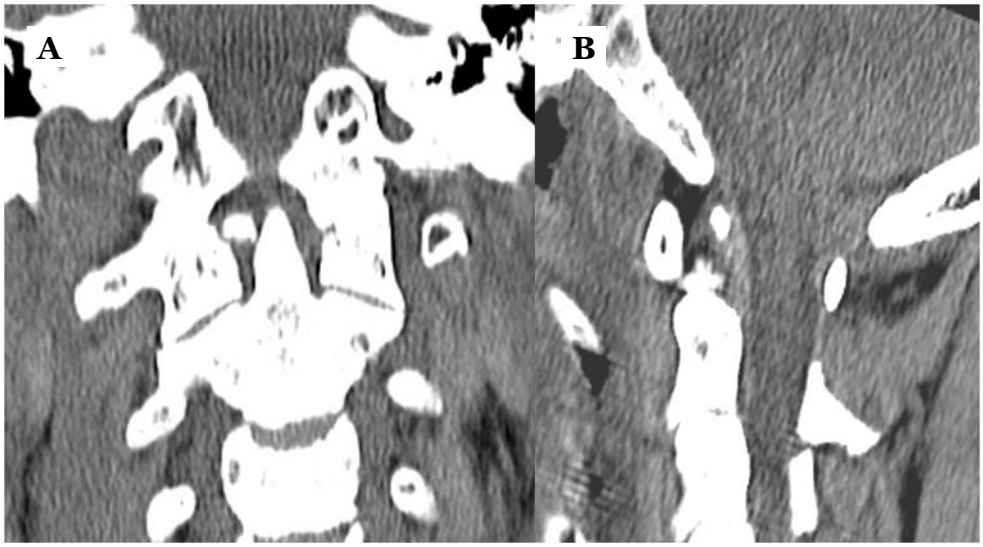

Figure 4: MPR images (soft tissue window) from coronal (A) and sagittal (B) CT scans show calcification along the right alar ligament. There is no evidence of surrounding soft tissue injury.

Kobayashi et al. (2) also reported calcification of the alar and transverse ligaments of the odontoid process in two patients presenting neck pain. Both patients had pharyngodynia and prior nuchal pain without previous history of trauma, and their symptoms had improved gradually with an anti-inflammatory drug therapy and neck immobilisation. CT scans revealed a nodular calcification in one patient and a poorly delineated calcified lesion surrounding the odontoid process in the other patient. Serial CT scans demonstrated that the calcifications shrank and disappeared with time. The authors assumed that the patients' symptoms could be related to an inflammatory reaction induced by deposition of calcium since secondary arthritis was not observed, and the symptoms subsided as the lesions decreased in size (2).

In our case, a cervical CT scan, performed to assess head injury, revealed a small, well-defined, ovoid of high-density tissue in the right periodontoid area along the course of the alar ligament. Initially, we also considered the possibility of it being a bone fragment, but comparison with the MPR

images was helpful in ruling this out. The calcified fragment was well corticated and the surrounding bones of the CVJ were well defined. There was no convincing evidence to show that the tiny fragment originated from any of the bones of the CVJ. No cervical fracture was identified. Furthermore, there was no evidence of soft tissue injury or indications of inflammation or arthritic changes accompanying the calcification. In view of this, we concluded that there was a calcification in the right alar ligament that was unrelated to the current trauma (making it an incidental finding). Unfortunately, the patient's conditions worsened and we were not able to perform other imaging such as MRI.

From our extensive literature review, there are few case reports of focal or nodular calcification of the alar ligament; only those reported by Sim and Park (1) and Kobayashi et al. (2) were found. A condition called crowned dens syndrome, describing neck pain due to calcifications surrounding the odontoid process, has previously been reported in conjunction with calcium hydroxyapatite (HA) and calcium pyrophosphate dehydrate (CPPD) crystal deposition diseases. In CT scans, the calcifications in these instances are seen to surround the top and sides of the odontoid process in a crown or halo-like distribution and commonly affect the transverse ligament (5,6). In our case, the calcification was focal and nodular and lay along the anatomical location of the alar ligament.

In conclusion, calcification of the alar ligament should be considered as a differential diagnosis in a traumatic craniovertebral injury, and this is especially true when the origin of a fracture is not clearly identified. Proper diagnosis is important because the treatment, which is beyond the scope of this paper, differs from fracture treatment and prevents unnecessary, prolonged, external immobilisation of the neck. Having said this, fracture of odontoid process (type I) and the occipital condyle (type III) should be carefully assessed and excluded if a bony fragment is detected, particularly in of the case of trauma.

Author's contributions

Conception and design, analysis and interpretation of data: SKCM, AAA
Data collection, drafting of the article, provision of study materials and patients: SKCM
Critical revision, and final approval of the article: AAA

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CASE REPORT

Acute Tonsillitis With Concurrent Kikuchi's Disease as a Cause of Persistent Lymphadenopathy

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Abstract

We present a young adult female with symptoms of acute tonsillitis and tender cervical lymphadenopathy. Despite a full course of oral antibiotics, she had persistent left lower cervical lymphadenopathy measuring 2.0 x 1.5 cm at 2 weeks post-treatment. Rigid and flexible scope examinations did not reveal any abnormalities in the nasopharynx, oropharynx or hypopharynx. Tuberculosis tests were negative and blood index results were normal. Fine needle aspiration cytology revealed a non-specific granulomatous inflammatory process. Excisional lymph node biopsy was performed, and the patient was diagnosed as having Kikuchi's Disease (KD). We would like to highlight the diagnostic challenges in detecting this condition and the importance of differentiating KD from tuberculosis and malignant lymphoma, the latter of which requires aggressive treatment.

Keywords: *histiocytic necrotizing lymphadenitis, Kikuchi disease, Kikuchi-Fujimoto disease, medical sciences*

Introduction

Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis) is a benign, self-limited disease of unknown cause that often manifests with persistently enlarged cervical lymph nodes that are unresponsive to antibiotic therapy (1). The disease was first identified by Kikuchi in 1972; this condition is primarily seen in young adult women, frequently of Asian origin, and is becoming increasingly recognized worldwide (2). The incidence of Kikuchi's disease (KD) ranges from 3% to 9% of all biopsy cases of neck lymph nodes (3). Approximately 30% of KD patients are mistakenly thought to have malignant lymphoma. Therefore, it is important for clinicians and pathologists to be aware of this benign, self-limiting entity and to differentiate it from non-Hodgkin's lymphoma, systemic lupus erythematosus (SLE), and carcinoma.

Case Report

A 22-year-old female presented with a five-day history of sore throat and fever with bilateral cervical lymph lymphadenopathy. Examination revealed a high fever of 38.5 °C, mildly enlarged inflamed tonsils and bilateral tender cervical lymphadenopathy. She was treated with a course of antibiotics for a week. She recovered well except for a persistent mobile left lower cervical lymph node measuring 2.0 x 1.5 cm, which did not regress even at 2 weeks post-treatment. There were neither other lymphadenopathies nor hepatosplenomegaly.

Investigations for tuberculosis (TB) were negative. White cell counts were normal. Fine needle aspiration cytology (FNAC) of the lymph node was suggestive of an acute granulomatous inflammatory process. Rigid nasal endoscopy and flexible nasopharyngolaryngoscopy did not reveal any abnormality in the nasopharynx or

hypopharynx. An excisional lymph node biopsy was performed and histopathological examination reported KD (Figure 1 and Figure 2). Further blood investigations for connective tissue screening (antinuclear antibody, rheumatoid factor) were negative. Levels of complements C3 and C4 were also normal. The patient recovered well after excisional biopsy of the lymph node. It has been 8 months since the surgery and there has been no recurrence.

Discussion

Diagnosis of KD is easily missed and readily underdiagnosed. It is more common than previously thought (4). Menasce et al. (5) performed a study in UK that reported that KD is still a poorly recognized entity and is frequently confused with malignant lymphoma. They re-examined 27 lymph node biopsies from 25 patients who were diagnosed with KD. Only three cases showed that the initial pathological diagnosis was Kikuchi disease; the most common suggested diagnosis was non-Hodgkin's lymphoma (5). Diagnosis of KD is rarely made as a provisional diagnosis until all other possible causes of cervical lymphadenopathy have been ruled out, especially in South East Asia region, where tuberculosis is endemic. In most cases, persistence of lymphadenopathy after completion of antibiotics will raise suspicion of this disease, which can only be confirmed by histopathological examination.

In this case report, KD is an incidental finding. Even though both acute tonsillitis and KD can present with cervical lymphadenitis, the presence of sore throat with inflamed tonsils favour the diagnosis of acute tonsillitis during the initial presentation. Acute tonsillitis would usually respond to a course of antibiotics, which is not the case for KD. Therefore, in this case, we postulate that KD occurred concurrently with tonsillitis.

Histologically, KD must be differentiated from non-Hodgkin's lymphoma, SLE and carcinoma. It is very important to differentiate between these diseases because the treatment regimen and prognosis are specific to each condition. Based on the histology of Kikuchi disease, it can be further divided into four subtypes: lymphohistiocytic type, phagocytic type, necrotic type and foamy cell type. Kikuchi et al. (2004) reported that lymphohistiocytic and phagocytic are the more common types, which constitute more than 80% of cases; the other two types are occasionally encountered. The symptom of high-grade fever greater than 39°C is commonly seen in cases of the necrotic type (6).

The typical pathology of KD permits differentiation from lymphoma, SLE, and infective lymphadenopathies (7). The classic morphology of KD includes patchy lymph node involvement centred in paracortical areas, extensive fibrinoid necrosis, absence of granulomatous reaction, and foamy histiocytes at the margins of the necrotic areas. Plasma cells are rarely noted and abundant predominantly extracellular apoptosis debris is present (8). Typical features of infiltration by blasts and histiocytes with extensive necrosis or karyorrhexis are shared with other conditions, such as malignant lymphoma, tuberculosis, and SLE (9).

The features that distinguish lymphoma from KD include the presence of cytologically bland histiocytes, absence of a prominent "starry-sky" appearance, presence of predominantly extracellular "nuclear dust," absence of neutrophils, eosinophils, and plasma cells in areas of necrosis and a predominance of T immunoblasts. Reed-Stenberg cells are also not a feature of KD. Pertaining to immunohistochemical studies, CD68 highlights crescentic histiocytes and plasmacytoid monocytes, unlike non-Hodgkin lymphoma, in which it shows sheets of B or T cells. In KD, immunoblasts are negative for CD15 and positive for LCA (CD45) (8).

Histologic features of SLE lymphadenopathy may not be distinguishable on a morphologic or immunophenotypic basis alone. Presence of numerous plasma cells, DNA deposition on vessel walls and extensive areas of acellular coagulative necrosis devoid of karyorrhectic material would favour the diagnosis of SLE (8). Even though KD is rarely associated with SLE, but its diagnosis can precede, postdate or coincide with SLE because lymphadenopathy is a common presentation in both conditions and histologically may be indistinguishable between them (10).

Although the aetiology of KD is unknown at present, it has long been speculated to be of autoimmune or infectious origin (2). Possible links between KD and systemic lupus erythematosus and a nonspecific hyperimmune reaction to a variety of infections, chemical, physical, and neoplastic agents has also been proposed for its pathogenesis. As in this case, the young female patient had presented with typical symptoms of an upper respiratory tract infection that resolved with oral antibiotics; however, the left lower cervical lymph node remained persistent. Further investigations, which included FNAC of the node, TB work-up and flexible scope examination of the nasopharynx and hypopharynx did not lead to any conclusion. Excision biopsy of the node had to be carried out to

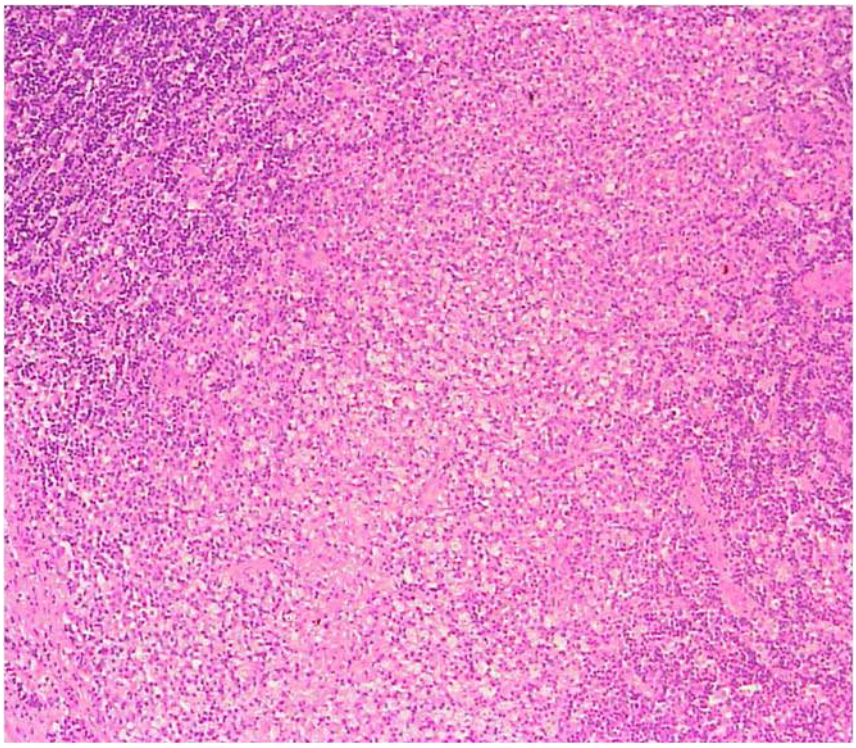

Figure 1: Area of focal necrosis admixed with karyorrhectic debris (Hematoxylin & Eosin, 40x magnification)

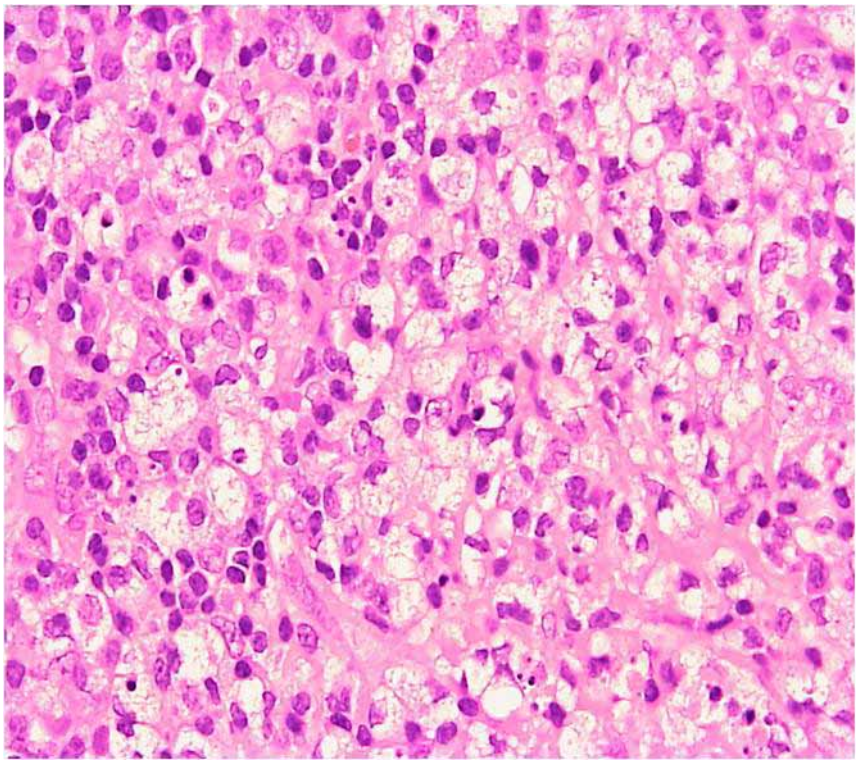

Figure 2: Higher magnification of karyorrhectic area composed of apoptotic bodies, foamy histiocytes and phagocytic histiocytes (Hematoxylin & Eosin, 300x magnification)

establish a KD diagnosis for this patient.

KD is a self-limiting disease; the lymphadenopathy slowly resolves after a few months. Prognosis is excellent, but about 3% of patients show recurrence of the disease within several years; one study reports this number to be 2% to 5% of cases (3). Some authors advocate the use of corticosteroids and reported faster healing responses in terms of lymphadenopathy disappearance. Meanwhile, other conditions that share similar clinical presentations, such as malignant lymphoma, SLE and tuberculosis, have specific, aggressive and prolonged treatments.

Conclusion

KD, although rare, has become a more recognized condition since it has been reported not only in Asia, but around the world as well. This diagnosis should be seriously considered, especially in patients presenting with fever and persistent cervical lymphadenopathy. Including this disease as a differential diagnosis when histopathological examination is requested will improve early detection. By identifying KD early, expensive and extensive investigations that may lead to unnecessary treatments can be avoided.

Author's contributions

Conception and design: MA
Provision of study materials or patients: GN
Collection and assembly of data, drafting of the article: HS
Data analysis and interpretation: NHS
Critical revision of the article: MA, PPSHA
Final approval of the article: PPSHA

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LETTER TO THE EDITOR

Non-detection of Acute Angiography-induced Cerebral Vasospasm by Transcranial Doppler Sonography amongst Patients with Subarachnoid Haemorrhage in Kelantan

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Keywords: *neurosciences, neuroradiology, angiography, vasospasm*

Dear Editor,

We conducted a study to determine the proportion of patients with spontaneous subarachnoid haemorrhage (SAH) who developed cerebral vasospasm (CVS) following cerebral intra-arterial digital subtraction angiography (IADSA) and to identify the angiography related risk factors that cause acute CVS following cerebral IADSA by using transcranial Doppler (TCD). A prospective study was conducted over an 18-month period from May 2007 until October 2008 at the Hospital Universiti Sains Malaysia (HUSM). A total of 8 patients above 12 years of age (5 males and 3 females, mean age ± SD: 54.1 ± 13.1) who presented with spontaneous SAH and fulfilled the inclusion criteria were enrolled into this study. Intra-arterial cerebral catheter angiography, even though it is the gold standard modality for assessment of the cause of SAH, is an invasive test with potentially significant neurological complications, with 0.07% to 0.3% risk of permanent stroke and an overall 1.8% risk of systemic complication (1). In patients with intracranial haemorrhage, particularly SAH, it is very difficult to determine whether the development of the neurological complications is part of the natural course of the disease or if it is caused by the diagnostic angiographic examination, which was performed before or during the time when CVS commonly occurs. This raises the question whether cerebral angiography itself could be one of the multiple factors causing the development of CVS among patients with SAH.

This study was undertaken to evaluate whether cerebral IADSA itself is the triggering mechanism for developing CVS in patients with SAH. The TCD was done according to the technique of Aaslid (2). The patients underwent IADSA examinations and the mean blood flow velocity (mBFV) values of the bilateral middle cerebral arteries (MCA) were obtained from the non-invasive TCD examination—which were performed within 6 hours before (the first TCD exam) and after (the second TCD exam) cerebral IADSA. Iso-osmolar non-ionic water-soluble iodinated contrast medium was used during the cerebral IADSA. A mBFV measurement of more than 120 cm/s during the second TCD examination was taken as indicator of angiography-induced CVS development. None of the subjects in this study developed angiography-induced CVS based on the TCD criteria, giving the rate of 0% for CVS. When the patients were compared according to changes in mBFV before and after IADSA, there was no statistical difference in mBFV ($P = 0.95$ and $P = 0.07$ for left and right MCA respectively). This study suggests that with the use of iso-osmolar non-ionic contrast medium, combined with improved catheterization techniques and the application of digital technology, cerebral IADSA can be performed with a zero rate of angiography-induced vasospasm in patients with SAH in HUSM. Thus the patients were not put at risk from the diagnostic procedures. Cerebral IADSA will continue to be an important diagnostic imaging modality in managing patients with SAH in the years to come.

To the authors' best knowledge, there is only one study with a similar methodology by Arslantas et al. (3) that has been published in the English-language literature. In that study, which was conducted in Turkey, the authors compared the changes in cerebral blood flow velocity before and after cerebral angiography by using TCD in patients with SAH undergoing IADSA. They used low-osmolar non-ionic contrast medium (CM). In that

study, 30 patients underwent TCD examination immediately before and after an angiography using continuous TCD monitoring in the angiography suite. They included only SAH patients with good clinical Hunt and Hess grades (grade I, Glasgow Coma Scale (GCS) 14 – 15 and grade II, GCS 12 – 13). However, they could not find a statistically significant difference between pre- and post-angiography mBFV of the MCA. Also, they found no significant difference in the clinical course before and after cerebral angiography as seen by changes in GCS (4).

In our study, we used iso-osmolar non-ionic CM and performed TCD of bilateral MCA in the neurology intensive care ward within 6 hours before and after cerebral IADSA to detect any possible angiography-induced CVS. All the clinical World Federation of Neurological Surgeon Scale (WFNSS) grades were included in this study. None of the patients in this study developed CVS after IADSA within the interval between IADSA and the second TCD examination. Similarly, we also could not find significant difference between mBFV before and after IADSA in this study.

Despite its wide acceptance, TCD ultrasonography can be affected by many variables, including a hyperdynamic state on the part of the patient. It is operator-dependent and the cerebral circulation is very complex (2,5). It may be more useful to follow trends than absolute numerical results. Generally, increases of 25 to 50 cm/s/day are considered ominous (5,6). Therefore, in future study of this kind, studying the difference in the TCD readings before and after IADSA would provide more accurate identification of acute angiography-induced CVS by TCD in patients with spontaneous SAH. The small sample size was another limitation of this study, which was due to strict patient selection criteria. A larger sample size is required for future study in order to gain a stronger degree of statistical significance. Based on the prevalence of post-angiography neurological complication of 0.3% reported by Cloft et al. (1), the sample size should include at least 30 subjects.

Author's contributions

Conception and design, darfting of the article: RJ, MSA
Data collection: NANJ
Data analysis and interpretation: RJ
All authors read and approved the final manuscript.

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