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Letter To The Editor

Editorial

The Malaysian Journal of Medical Sciences in Its 18th Year: A Look at the Journal's Growth

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Abstract

As a small—although growing—journal based in Malaysia, the *Malaysian Journal of Medical Sciences (MJMS)* has faced several challenges in the past, such as promoting our journal as well as making sure our article bank does not go empty. However, we strive to improve ourselves by taking all means necessary to increase the quantity and, most importantly, quality of our publications, as well as to increase our journal's visibility and citability. This editorial will focus on *MJMS* statistics throughout 2011—where *MJMS* turned 18—as well as future plans for our journal.

Keywords: *manuscripts, publishing, reports, special events, statistics*

Introduction

The year 2011 marked the 18th anniversary of the *Malaysian Journal of Medical Sciences (MJMS)*. In human years, 18 is the start of the transitional phase from adolescence to adulthood, and over the years, *MJMS* has experienced tremendous growth to become one of the top 10 Malaysian journals in the medical field as well as in the top 20 of all Malaysian journals (1). To celebrate our anniversary, a fresh, purple-themed cover was introduced for the then newly published *MJMS:* Volume 18, Issue 1. A month later, in February 2011, we received an excellent gift from PubMed: *MJMS* had been accepted for indexing in the renowned biomedical database. This indexing allows greater visibility and citability of our publications, to the benefit of the scientific community in general as well as *MJMS* and our contributors in particular. This editorial will provide a look at our 2011 submission and publication statistics and our future plans for *MJMS*.

The "In" Box: Manuscript Submission and Review

New submissions

Since the introduction of the online manuscript submission via ScholarOne Manuscripts in June 2009, the number of submissions has been increasing year by year. The total number of submissions in 2011 were 195, 30.0% more than the figure reported in the previous 2009–2010 audit (2). On average, we received 16 manuscripts each month, with peaks in the middle and the end of the year (Figure 1). The majority of the submissions were original articles (60.0%), followed by case reports (27.2%) (Figure 2). Submissions were received from all continents, especially among the Asian countries (Table 1). As with the previous 2009–2010 audit (2), we received most contributions from Malaysia, followed by India and Iran.

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Pre-review screening

In the middle of 2010, *MJMS* introduced a stricter pre-review screening. Previously, a manuscript was checked for suitability and formatting; now, a compulsory plagiarism screening is enforced. This is to ensure that all manuscripts are original and have good readability before they are forwarded to our reviewers.

In the 2011 pre-review screening, a total of 104 manuscripts (53.3%) were unsubmitted and returned to the authors. This high unsubmission rate was mainly because of detection of minor "copy and paste" texts (which we assumed that authors had unintentionally left in the final version of their manuscript), authors' failure to follow the journal's format, as well as incomplete submission of the required files. We understand that some of the authors are submitting for their first time and/or are not familiar with our requirements, and it is one of *MJMS* visions to help authors from developing countries to publish their works; therefore, we had chosen to unsubmit—with additional guidelines given—rather that reject these papers prior to review. Authors are allowed to re-submit their works;

Figure 1: Submission of manuscripts to the Malaysian Journal of Medical Sciences from 1 January to 31 December 2011, according to month of submission.

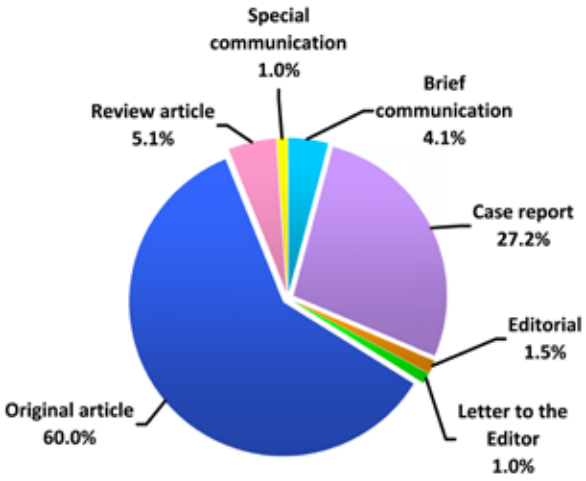

Figure 2: Submission of manuscripts to the Malaysian Journal of Medical Sciences from 1 January to 31 December 2011, according to manuscript type.

Table 1: Submission of manuscripts to the Malaysian Journal of Medical Sciences from 1 January to 31 December 2011, according to geographical region

Region	Number
South–East Asia	
Malaysia	93
Indonesia	2
Thailand	1
South Asia	
India	43
Bangladesh	4
Pakistan	2
Middle East	
Iran	23
Palestine	4
Iraq	2
Saudi Arabia	2
Armenia	1
Jordan	1
Oman	1
East Asia	
Japan	1
Africa	
Nigeria	6
Cote d'Ivoire	1
Europe	
United Kingdom	2
Germany	1
North America	
United States	1
South America	
Brazil	1
Cuba	1
Oceania	
Australia	2
Total	**195**

however, only 63 manuscripts (60.6%) were re-submitted and sent for review.

In addition, the pre-review rejection rate had increased from 16% (2) to 26.1%. The majority of these rejections were due to plagiarism (14 manuscripts), whereas the other were rejected because their contents were unsuitable for publication in our journal (4 manuscripts).

Peer-review and decisions

The average number of days for a manuscript to receive its first peer-review decision was 33.9 days (SD 16.8). Most of these first decisions were either major revisions (46.1%) or rejections (46.1%). The overall rejection rate has increased from 51.7% (2) to 62.7%, and original article have the highest rejection rate (69.8%) (Table 2). Some of the reasons cited for rejections were lack of novelty and significance, inaccurate analysis, poor presentation of findings, and lack of in-depth discussion. Many reviewers had also commented on the quality of English of these manuscripts, a problem that has been lingering for quite some time.

The "Out" Box: Publication

From the 2011 submissions, 41 manuscripts (37.3%) were accepted for publication, making the total number of manuscripts in our article bank 51. The average number of months from acceptance to publication was 4.3 months (SD 2.0), a slight reduction from the 2009–2010 figure, 4.7 months (2). Starting in October 2011, all manuscripts accepted for publication are uploaded for preview on our website. Therefore, the long wait for a print or e-publication in an assigned issue is no longer a problem as the content is made available shortly after acceptance. The accepted manuscripts are usually assigned according to their topics, as we like to have a balance between clinical and research papers, and their accepted dates. We had increased the number of publications per year from 48 in 2010 to 56 in 2011. Timeliness had also improved: Volume 18 issues were finalised and published within the first month of their respective publication dates.

Overall Review and Future Plans

The number of manuscripts submitted and the equally high number of manuscripts rejected can be interpreted in many ways, for example, stricter review criteria and competitiveness. However, we worry if this might be a sign of a decrease in the quality of manuscripts submitted by authors. There is a substantial pressure among researchers to publish as many papers as possible and to publish them quickly. As a result, some authors submit carelessly written manuscripts of poorly designed studies; some even resort to plagiarising other articles to complete theirs. Our editorial team and our reviewers work hard to ensure that the quality of articles published in *MJMS* are of an international standard.

The next mountain that we are planning to conquer is getting into the Thomson Reuters' scientific database, which indexes "the world's most important and influential journals" (3) and has a very rigorous selection process. Many qualitative and quantitative factors such as publishing standards, citation data, and internationality are evaluated; therefore, the MJMS team will need to improve our journal in these aspects.

Table 2: Final decisions of manuscripts submitted to the Malaysian Journal of Medical Sciences [a], according to manuscript type

Type	Total	Accepted		Rejected	
		n	%	*n*	%
Original article	63	19	30.2	44	69.8
Case report	28	11	39.3	17	60.7
Review article	8	3	37.5	5	62.5
Brief communication	5	2	40.0	3	60.0
Editorial	3	3	100.0	0	0.0
Letter to the Editor	2	2	100.0	0	0.0
Special communication	1	1	100.0	0	0.0
Overall	**110**	**41**	**37.3**	**69** [b]	**62.7**

[a] The analysis included manuscripts with an original submission date and a final decision date from 1 January to 31 December 2011 only. [b] Out of 69 manuscripts, 47 were rejected in the first round of review, 4 were rejected in subsequent reviews, and 18 were rejected pre-review (14 due to plagiarism and 4 due to unsuitable submissions).

Figure 3: Malaysian Journal of Medical Sciences Quick Response Code.

To enhance the quality and quantity of publications, especially among developing countries, a "challenge" was submitted on the Scientists Without Borders website at the end of 2010. We are pleased to have received good responses from scientists of various fields who volunteered to review and edit for *MJMS*. We would like to express our sincere gratitude to our reviewers and editors for their contributions.

MJMS has also taken part in educating the research community, especially those in Universiti Sains Malaysia, on the various aspects of a good publication—from writing and technical tips, to what the reviewers and editors look for in a manuscript. We believe that, as the publishing world goes digital, researchers should also equip themselves with knowledge of digital technology (or at least have assistants who do so).

Our journal has been online since 1995, and we have been progressing digitally ever since. The print version of Volume 19 will be displaying our Quick Response Code (Figure 3); our readers will be able to access our website from their mobile devices and download articles for references. We also plan to assign digital object identifiers to all articles; this will help increase accessibility and citability of our publications by having permanent links and cited-by linking. Furthermore, our publisher, the Universiti Sains Malaysia Press, is tapping into the possibility of our journals (including *MJMS*) going mobile through iPad and Android devices, although it may take some time to develop the application. We look forward to seeing our journal fully available anytime, anywhere, and on any platform in the future.

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References

1. SCImago. SJR—SCImago Journal & Country Rank [Internet]. Scimago Lab; 2007 [cited 2012 Mar 18]. Available from: http://www.scimagojr.com.

2. Dewiputri WI, Mohamad I. MJMS at the dawn of its electronic era. *Malays J Med Sci*. 2010;**18(1)**:1–5.

3. Thomson Reuters. The Thomson Reuters journal selection process [Internet]. Thomson Reuters; 2012 [cited 2012 Mar 18]. Available from: http://thomsonreuters.com/products_services/science/free/essays/journal_selection_process/

Review Article

Cytoadherence and Severe Malaria

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Abstract

Malaria is a disease that causes enormous human morbidity and mortality. One feature of mature *Plasmodium falciparum*-infected erythrocytes leading to the development of severe malaria is thought to be cytoadherence and blockage of the microvasculature. Therefore, an understanding of mechanisms that mediate parasite adhesion leading to malaria pathology is needed to yield new treatments for malaria. However, to date, cytoadherence-associated pathology is still under debate. Is cytoadherence needed to develop severe malaria? This review will discuss the available information on associations of cytoadherence with the development of severe malaria.

Keywords: *cerebral malaria, cytoadherence, endothelium, malaria*

Introduction

Malaria is a serious burden, particularly to low and middle-income countries, and a major contributor to morbidity and mortality. The aetiological agents of malaria to humans are recognised as 6 distinct protozoan species of *Plasmodium*: *Plasmodium falciparum* (1), *Plasmodium vivax* (2), *Plasmodium malariae* (3), 2 species of *Plasmodium ovale* (*P. ovale curtisi* and *P. ovale wallikeri*) (4), and *Plasmodium knowlesi* (5), which was recently recognised as the 6th human *Plasmodium* after cross infection from long-tailed Macaca monkey to humans was reported in Malaysia (6–9). *P. falciparum* has often been seen as the most clinically significant infection due to an association with mortality and the intensity of infection in some regions of sub-Saharan Africa, but *P. vivax* has a wider geographical distribution, and its categorisation as benign has been challenged (10). What is clear is that an episode of *P. falciparum* malaria in a non- or semi-immune host can lead to severe malaria (SM) if untreated, with a high risk of death. However, recently a study from Papua New Guinea and Malaysian Borneo extended the pattern of severe disease by showing a strong association of *P. vivax* (11) and *P. knowlesi* (8) infection, respectively, to SM and death. Studies of the pathology of SM were started in the late of 19th century by 2 Italian pathologists Marchiafava and Bignami (12), where they found, post-mortem, the presence of higher parasite load in a comatose malignant blood fever patient compared with in those with benign fever. They saw high parasite levels and parasite pigment predominantly retained in the tissue microvessels compared with in the peripheral circulation, as well as the existence of necrosis and alterations in the endothelium of the cerebral vessels. This discovery and subsequent observations have led to a suggestion that the preferential accumulation of parasitised red blood cell (pRBC) in tissues might be linked to the disease and its severity. The manifestations of SM are highly variable and are determined by factors from both the human host and the parasite. The most common clinical features of SM are high fever, respiratory distress, vascular obstructions, metabolic disturbances (e.g., acidosis), multi-organ dysfunction (e.g., renal failure), severe anaemia, and cerebral malaria (CM); these features differ among areas of varying transmission intensity and between adults and children. This creates problems in comparing studies as the clinical definitions can vary and the impact of cytoadherence on these variable clinical outcomes is difficult to define. Some aspects of SM occur because the parasite has developed mechanisms to escape the host immune system, which we will discuss later,

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so one of the features of CM (an important subset of severe cases) is that it is more common in semi-immune children in sub-Saharan Africa (13).

It is still unclear how infection with *P. vivax* and *P. knowlesi* lead to SM, and it is possible that research on understanding *P. falciparum*–derived SM may help us to understand and predict how *P. vivax* and *P. knowlesi* act. Once thought to be unique to *P. falciparum*, the ability of the mature pRBC to undergo a range of adhesive interactions (cytoadhesion), such as the binding of pRBC with endothelial cells (sequestration) and the interaction of pRBC with non-infected RBC (rosetting) and with other pRBC (auto-agglutination), is now thought to be shared with other species. One of the big questions in *P. falciparum* research is, "Is parasite adhesive behaviour linked to SM?" This question can now be extended to *P. vivax* and *P. knowlesi* with the discovery of adhesion to endothelial receptors by RBC infected with these species (8,14,15), although the timing and extent of cytoadherence in these 2 species differs from that of *P. falciparum*, with the latter exhibiting earlier (from 15 hours post-invasion) and more pronounced sequestration, whereas only the schizont stages of *P. vivax* and *P. knowlesi* show this phenotype.

One molecule identified on the surface of *P. falciparum* pRBC, known as *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1) encoded by *var* genes, has been correlated with *P. falciparum* cytoadherence (16–18). It has been thought that the antigenic switching between different PfEMP-1s constitutes an important virulence factor by facilitating the parasite's escape from the host's immune response, thus establishing chronic infection (19,20). Considering the potential harmful effect of *P. falciparum* cytoadherence to the host, early treatment or even prophylaxis would be highly desirable in preventing cytoadhesion and progression of disease. Unfortunately, falciparum malaria has become increasingly refractory to chloroquine (21,22), the cheapest and most widely available antimalarial, and this emergence of drug resistance in Southeast Asia and Africa was closely associated with the increased incidence of SM (23) . The World Health Organization advises all countries experiencing antimalarial drug resistance (including monotherapies such as chloroquine, amodiaquine, or sulfadoxine-pyrimethamine) to use combination therapies, preferably those containing artemisinin derivatives (artemisinin-based combination therapies, ACTs).

Recent clinical trials in Asia and Africa using ACTs showed improved recovery of SM patients (24,25), but mortality reported shortly after hospital admission (within 48 hours) was still high despite the administration of highly effective anti-parasitic drugs. This finding is consistent with our recent data showing that after exposure to drugs, killed pRBC were still able to cytoadhere (26), which has led us to suggest that this persistent mortality may be due to the effects of adherent pRBC in the microvasculature. Is there any way of reducing this mortality? Perhaps adjunct therapies that can block and reverse the pathogenic effect of pRBC adhesion will lighten the disease burden. However, before embarking on this course, what evidence is there that cytoadherence is involved in SM?

pRBC Cytoadhesion

Why and how does parasite cytoadherence–related morbidity take place? Several hypotheses associated with the binding of pRBC in the microvasculature have been proposed and reviewed elsewhere, such as i) changes of the RBC and pRBC rigidity (27–29), ii) pro-inflammatory induction of the adhesion-receptor expression (30,31), iii) binding of pRBC to specific adhesion receptors on endothelial cells (32), iv) endothelial activation (33–35), and v) malaria toxins (36), with various levels of evidence to support them. However, there are also more recent discoveries such as the relevance of platelets and microparticles as well as the role for the coagulation cascade in mediating pRBC binding to endothelial cells (37,38).

A major question is how *P. falciparum* has adapted to bind in the microvasculature to such an extent that mature pRBC are rarely seen in the peripheral circulation, unlike other human-invading malaria parasite species. An important difference in *P. falciparum* is the modification to the surface of the host erythrocytes to become rigid and inflexible by exporting specific proteins to the RBC membrane during the intra-erythrocytic stages. This reduction of flexibility of RBC makes their circulation through the microvasculature difficult and favours pRBC adhesion to endothelial cells (39).

In 1985, MacPherson et al. (40) reported higher levels of pRBC in the cerebral vessels of adults dying from CM compared with in non-CM cases, demonstrating the preferential accumulation of pRBC in the brain being linked to CM; this is consistent with the findings of Marchiafava and Bignami (12). The MacPherson

study identified the contact point for pRBC in vivo as a knob-like structure, which had previously been demonstrated in in vitro studies. Knobs are distortions on the surface of *P. falciparum* pRBC caused by deposition of knob-associated His-rich protein (KAHRP) at the cytoplasmic side of the pRBC membrane (41); these knobs contain several other proteins including PfEMP-1 as well as ring-infected and mature parasite–infected erythrocyte surface antigens (42). It is generally accepted that PfEMP-1 is largely responsible for pRBC adhesion in *P. falciparum*, and various associations between *var* gene expression and complicated or uncomplicated disease have been reported. However, are knobs essential to establish an interaction in the microvasculature? Some other *Plasmodium* species such as *P. brasilianum*, *P. vivax*, and *P. malariae* also have knob-like structures but do not always exhibit cytoadherence properties, suggesting that these membrane modifications are not identical to those seen with *P. falciparum* (14,43). Biggs et al. (44) demonstrated that knobless *P. falciparum* could bind to host receptors, although later work (45) showed that a KAHRP knockout line could not bind under more physiological flow conditions.

What Factors Mediate Adhesion of the pRBC in Host Microvasculature?

Several receptors on endothelial cells have been shown to support interactions with pRBC, including thrombospondin; CD36; immunoglobulin superfamily cell adhesion molecules, e.g., intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule, (VCAM), platelet endothelial cell adhesion molecule, and neural cell adhesion molecule; selectins, e.g., P-selectin and E-selectin; integrin αvβ3; globular C1q receptor; and glycoaminoglycans, e.g., chondroitin sulphate A (CSA) and heparin sulphate (35). With such a diverse collection of host receptors, how might one investigate associations between disease and specific adhesion phenotypes? It has been reported that ICAM-1 and CD36 are the most commonly used adhesion receptors by patient isolates, except in placental malaria (46), and correlations with severe and uncomplicated disease have been suggested (47), which has often been a starting point for clinical studies. It has been proposed that synergism (or at least co-operation) between these two receptors makes the binding of pRBC stronger (48,49). Therefore, it is not unusual that clinical studies examining the association between receptor usage and disease have concentrated on these two proteins, as indicated in Table 1 (31,45,46,50–58).

In addition to ICAM-1 and CD36, CSA is also one of the most common and successfully studied adhesion receptors. CSA provides the clearest example of an interaction of pRBC with an adhesion receptor in causing disease; however, this example of adhesion-related pathology does not come from endothelial cytoadherence but rather adhesion of pRBC to CSA in the placenta of pregnant women through a set of semi-conserved PfEMP-1 proteins (59–61). The restricted variation in this important facet of malaria pathology provides one of the most hopeful cases for the development of a disease-specific vaccine for malaria (62). In the case of placental malaria, the association of a specific *var* gene (*var2csa*) with adhesion and disease has been possible, but this has been much harder to define in other syndromes of SM, such as CM.

Another factor that has been postulated to have an association with host-mediated cytoadherence is the role of host pro-inflammatory cytokines. These cytokines have long been implicated in the pathogenesis of SM (63), where changes in cytokine plasma levels have paralleled the rise of temperature during fever paroxysms in SM (64), and an increase of pro-inflammatory cytokines, especially tumour necrosis factor (TNF), in CM in children especially from Africa and its correlation with mortality (65–68) have been observed. Nevertheless, how are these pro-inflammatory cytokines regulated and how might they mediate parasite adhesion and SM, or is this just a general effect? Other studies (33,69) have challenged the correlation of cytokines, especially TNF, towards malaria disease severity and claimed it is quite poor at predicting SM. It is thought that pro-inflammatory cytokines are central to the pathophysiology of systemic disease caused by infectious and non-infectious agents, and cytokines such as TNF and interleukin (IL)-10 have been proposed to have a protective role to clear the infections and to avoid inappropriate host responses that might lead to cell destruction and be harmful to the host. In the case of malaria and SM, high levels of pro-inflammatory cytokines TNF, IL-1, IL-6, IL-12, and interferon (IFN)-γ have been observed in patients with malaria, and low levels of IL-10 and tumour growth factor (TGF)-β have been correlated with fatal outcome (70). It is thought that these cytokines are produced by activated macrophages, dendritic cells, and, potentially, endothelial cells during the host response to pRBC and schizont rupture (36,71).

Table 1: Clinical studies on cytoadherence-related pathology in malaria

Study	Pathological feature	Adhesion molecule tested	Observation technique	Correlation with severity of disease
Marsh et al., 1988 (50) Subjects: 51 children Site: Gambia	• Cerebral malaria • Uncomplicated malaria	• CD36	• Static cell binding assay on C32 melanoma cells	Suggested that pH 6.9 mediates optimal binding of pRBC to CD36, but no correlation between parasite adhesion and disease.
Ockenhouse et al., 1991 (51) Subjects: 27 adults Site: Thailand	• Cerebral malaria • Acute renal dysfunction • Acute hepatic dysfunction	• CD36 • ICAM-1	• Static cell binding assay on C32 melanoma and CHO cells expressing CD36 or ICAM-1 • Protein binding assay	All patient isolates bound to CD36 purified protein and cells, but no association with disease.
Ho et al., 1991 (52) Subjects: 59 adults Site: Thailand	• Cerebral malaria • Severe malaria (without cerebral malaria or anaemia) • Uncomplicated malaria	• CD36	• Static cell binding assay on C32 melanoma cells incubated with TNF, IL-1, and IFN-γ	Severe malaria patient isolates showed higher binding to C32 melanoma cells compared with those of uncomplicated and cerebral malaria isolates. Cytokines did not enhance pRBC cytoadherence on C32 cells.
Chaiyaroj et al., 1996 (53) Subjects: 56 adults Site: Thailand	• Severe malaria with organ dysfunction	• CSA • CD36 • ICAM-1 • E-selectin • VCAM-1	• Static cell assays on C32 melanoma and CHO cells expressing E-selectin or VCAM-1 • Protein binding assay	All isolates bound to C32 melanoma cells. A small number of isolates adhered to ICAM-1, CSA, and TSP purified protein but not to E-selectin and VCAM-1 on CHO transfected cells. No correlation between severity and level of adhesion.
Udomsangpetch et al., 1996 (54) Subjects: 60 adults Site: Thailand	• Severe malaria with acute organ dysfunction • Cerebral malaria	• CD36 • ICAM-1 • E-selectin • VCAM-1	• Static cell binding assays on mouse L cells expressing CD36, E-selectin, ICAM-1, or VCAM-1	Patient isolates bound to CD36 10-fold higher than to ICAM-1, and no binding to VCAM-1 was observed. Therefore, CD36 binding could be associated with disease severity by allowing adhesion of a larger proportion of the parasite population.

Study	Pathological feature	Adhesion molecule tested	Observation technique	Correlation with severity of disease
Newbold et al., 1997 (55) Subjects: 150 children Site: Kenya	• Cerebral malaria • Severe anaemia • Non-severe malaria	• CD36 • ICAM-1 • VCAM-1 • E-selectin	• Static protein binding assay	CD36 was quantitatively the major receptor for all isolates, but some isolates bound strongly to ICAM-1, less to VCAM-1, and none to E-selectin. Binding to ICAM-1 was associated with disease, but not cerebral malaria.
Rogerson et al., 1999 (56) Subjects: 158 children Site: Malawi	• Severe malaria • Cerebral malaria • Severe anaemia	• CD36 • ICAM-1 • CSA • TM	• Static protein binding assay	Varied cytoadherence profiles from patient isolates; all isolates bound to CD36, and severe anaemia isolates had low binding to ICAM-1. No correlation with severe disease.
Heddini et al., 2001 (57) Subjects: 111 children Site: Kenya	• Severe malaria without cerebral malaria or severe anaemia • Cerebral malaria • Severe anaemia • Uncomplicated malaria • Control	• PECAM • CD36 • TSP • ICAM-1	• Static cell binding assays on mouse L cells expressing PECAM-1 and CHO cells expressing CD36 or ICAM-1 • Protein binding assays using FACS technique	Rosetting associated with blood group A and heparin-type receptors (e.g., heparin sulphate) were prone to severe malaria. Binding to multiple receptors promoted pRBC sequestration in the severe malaria group.
Cojean et al., 2008 (47) Subjects: 22 adults Site: France	• Uncomplicated malaria • Cerebral malaria • Severe malaria (without cerebral malaria)	• ICAM-1 • CD36	• Static cell binding assays on CHO cells expressing CD36 or ICAM-1	Binding of isolates from severe malaria showed no significant difference compared with uncomplicated malaria pRBC.
Chilongola et al., 2009 (46) Subjects: 155 children Site: Tanzania	• Uncomplicated malaria	• CD36	• Static protein binding assay	CD36 deficiency was protective in malarial anaemia.

Study	Pathological feature	Adhesion molecule tested	Observation technique	Correlation with severity of disease
Ochola et al., 2011 (32) Subjects: 101 children Site: Kenya	• Cerebral malaria • Severe anaemia • Uncomplicated malaria	• CD36 • ICAM-1	• Static and flow protein binding assays	High pRBC binding to CD36 was associated with uncomplicated malaria. High ICAM-1 binding under flow correlated with cerebral malaria.
Mayor et al., 2011 (58) Subjects: 46 children Site: Mozambique	• Severe malaria (with cerebral malaria, severe anaemia, respiratory distress, prostration) • Uncomplicated malaria	• CD36 • ICAM-1 • gC1qR	• Static protein binding assays	Higher levels of adhesion to gC1qR in isolates from children with multiple seizures.

Abbreviations: CHO = Chinese hamster ovary, CSA = chondroitin sulphate A, FACS = fluorescence activated cell sorting, gC1qR = globular C1q receptor, ICAM = intercellular adhesion molecule, IFN = interferon, IL = interleukin, PECAM = platelet endothelial cell adhesion molecule, pRBC = parasitised red blood cells, TM = thrombomodulin, TNF = tumour necrosis factor, TSP = trombospondin, VCAM = vascular cell adhesion molecule.

Several studies (72,73) showed that pRBC stimulate antigen-presenting cells macrophages and dendritic cells probably through direct or indirect interaction of PfEMP-1 via CD36, and it is known that CD36 is expressed on the surfaces of macrophages and dendritic cells. The biological role of these interactions is not clear. For example, there is conflicting data about the effect of pRBC adhesion on dendritic cells: some studies showed that decreased activation was associated with cytoadherence (74), while others showed that this adhesion process was not required for the modulation of dendritic cell activity (75). These findings in the literature are variable due to the use of different host species and parasite strains, at pre-erythrocyte or blood stages of infection (76). How might cytokines support pRBC binding to microvascular endothelium? One thought is that it is through endothelial activation. For example, TNF is known to act by increasing the expression of host adhesion molecules. TNF binding to TNF receptor type 2 induces recruitment of signal transduction that activates effector molecules and transcription factors, leading to a strong increase in the expression of ICAM-1, VCAM, and E-selectin. The involvement of TNF in the upregulation of adhesion molecules has been clearly reported in different in vitro and in vivo studies (49,77,78). However, does TNF induction alone do enough to exacerbate SM? If pathology of malaria was the result of a high level of TNF, patients with SM could be treated using TNF specific antibody. However, a trial using a monoclonal antibody against TNF did not show any protection and, in fact, worsened neurological sequelae in patients (68).

The pattern of pathology in malaria is variable, and the profound cytokine-mediated changes and tissue oedema seen in other infections are not characteristic of this disease, although some signs of these pathologies are available. Thus, it seems that malaria pathology can be linked to a pro-inflammatory response, but this is not enough to explain the disease. This is consistent with recent studies that have shown that in children, TNF level was a poor discriminator of severity of disease, whereas proteins associated with endothelial activation (e.g., angiopoietin-1, angiopoietin-2, von Willebrand factor [vWF], soluble ICAM-1) were relatively good markers (69).

Endothelial activation, in response to inflammatory mediators, collectively increases the expression of adhesion molecules, including E-selectin, ICAM-1, and VCAM-1, on the cell surface through the activation of nuclear factor κB signalling transduction. Increases of P-selectin on endothelial cells following activation have also been reported (79). P-selectin is different from other adhesion molecules as it is stored in endothelial cell specific storage vesicles called Weibel–Palade bodies, together with other molecules such as vWF. How Weibel–Palade

bodies are activated in malaria infection is still unknown; the parasite has a protein that can cause basophils to release histamine, which is known as *P. falciparum* translationally controlled tumour protein (80), but some reports have also suggested that activated platelets and fibrin might mediate the release of P-selectin and vWF (81). vWF recently has been found to be a good prognostic marker for SM in children, and it has been thought that vWF might mediates pRBC binding on endothelial cell via ultra-large vWF multimers by producing a bridge via platelets (81–85).

Scientists have speculated that the febrile temperature seen as a part of malaria infection might enhance cytoadherence. We know that a fever is due, in part, to the increase in TNF seen during infection, but does temperature elevation help pRBC to bind to endothelial cells? Udomsangpetch et al. (86) showed that PfEMP-1 expression was accelerated by febrile temperature and increased cytoadherence. However, this is contrary to other findings where febrile temperature affected intra-erythrocyte growth, and upregulation of PfEMP-1 was not seen (87). Recently, Pattanapanyasat et al. (88) showed that febrile temperature induced and enriched expression of phosphatidylserine on the pRBC membrane surface. Several studies (89–92) have reported that phosphatidylserine promoted pRBC binding to CD36 and thrombospondin. Febrile temperature can also lead to endothelial cell disruption (93). In a clinical trial (94), the use of antipyretic intravenous ibuprofen was able to control fever but delayed parasite clearance. This finding suggests that ibuprofen and fever reduction does not act to reduce cytoadherence as might be expected from previous work, and there is some evidence that fever temperatures might act in the opposite way to reduce endothelial cell binding (Craig, unpublished observations). There is also evidence showing that febrile temperatures may increase pRBC rigidity (95), and this finding might cause at least some of the reduced RBC deformity, leading to the vascular flow obstruction seen in SM; however, there is a need for further studies to confirm this. In the absence of a consistent association with inflammation and malaria pathology as well as the observation of preferential pRBC accumulation in microvessels in SM, researchers have turned to cytoadherence, and many clinical studies (31,45,46,50–58) have attempted to correlate adhesion with disease (Table 1), particularly with CM where cerebral pRBC sequestration is an invariant feature of the disease.

How Might Cytoadherence Cause SM?

As mentioned earlier, complex interactions, including the host inflammatory response and endothelial activation, may contribute to SM, but how does cytoadherence itself modulate the severity of the disease?

When *P. falciparum* infects an RBC, the parasite expresses proteins that are transported to the RBC membrane, causing changes in rigidity and shape of the infected RBC. This may lead to difficulties in RBC flow through the microvasculature, and studies in Thailand (39) and Bangladesh (96) have shown that increased rigidity and reduced flow through blood vessels were associated with severe disease. Other studies on the retinal vasculature (97–99) have shown that micro-haemorrhages and vessel changes, thought to reflect blockage, were highly predictive of CM.

The hypothesis is that adhesion of pRBC in the deep vasculature leads to organ dysfunction. What evidence do we have to support this? As stated earlier, MacPherson et al. (40) showed that there was preferential pRBC accumulation in the brains of people dying of CM compared with in non-CM. One way that this might be taking place is that in some malaria infections, there is higher recruitment of pRBC to cerebral vessels due to the increased levels of receptors such as ICAM-1 (77) and the presence of parasites that are able to bind efficiently to these receptors (32). This clearly oversimplifies the potential mechanisms contributing to the preferential recruitment of pRBC in the brain, and there are likely to be several pathways by which this can be achieved. The role of the infecting parasite variant should not be ignored in this equation, and data from the analysis of pRBC in post-mortem tissues have shown the enrichment of specific PfEMP-1 variant types in the brains of children dying of CM (100).

How might the accumulation of pRBC in tissues lead to pathology? A simple explanation might be that localised ischaemia damages the endothelium, leading to disease. However, the histological evidence only partially supports an impact of endothelial cell destruction, and the relative reversibility of SM on treatment would argue against profound tissue damage. pRBC cytoadherence is known to activate the oxidative cascade (stress-activated protein kinase/c-Jun NH2-terminal kinase pathway), which can regulate gene transcription (101), rho-kinase (102), and nuclear factor κB (103) signalling via radical oxygen species to induce local endothelial activation (104).

Trans-endothelial electrical resistance experiments showed that when pRBC adhered to human brain microvascular endothelial cells, the integrity of the human blood–brain barrier (BBB) reduced 3-fold, causing increased permeability (105). The leakage of BBB leads to serum protein penetrating into the central nervous system (106). This influx of foreign substances activates the microglial cells that release pro-inflammatory cytokines, damaging astrocytes and glial cells that are crucial for BBB maintenance (107). It has also been suggested that interaction of serum protein with TGF-β receptors TGFBR1 and TGFBR2 could result in astrocyte dysfunction, followed by seizures and neuronal death (108).

The binding of pRBC to brain endothelial cells has also been reported to induce endothelial cell apoptosis (109,110). Pino et al. (109) have demonstrated pRBC modulation of the expression of endothelial cell genes such as TNF superfamily genes (Fas, Fas L, and DR-g) and apoptosis-related genes (Bad, Bax, Caspase-3, SARP2, DFF45/ICAD, IFN-γ Receptor 2, Bcl-w, Bik, and iNOS). Toure et al. (110) subsequently showed for the first time that clinical isolates could sometimes induce endothelial cell apoptosis, and Herbert et al. (111) showed that the presence of apoptotic cells might upregulate the expression of cellular adhesion molecules, resulting in hyperadhesiveness, leading to a greater accumulation of pRBC and subsequent endothelial cell apoptosis.

How Might We Alleviate the Symptoms of SM by Targeting Cytoadherence?

As described above, cytoadherence, which we believe may lead to some aspects of disease severity, is a process where mature pRBC erythrocytic stages escape from splenic clearance by binding to endothelial cells and promoting parasite growth in a relatively hypoxic environment. Therefore, can we use this information to devise treatments to prevent death or neurological sequelae?

Antiparasite drugs will still be the main treatment of choice to reduce mortality in patients with malaria; preferentially, these should kill the malaria parasite in early stages (in terms of the erythrocytic cycle) as destruction of non-adhesive ring stages will prevent the next wave of pRBC from sequestering. Therefore, artemisinin is a good choice as it kills ring-stage parasites; this might explain the reduced mortality seen in the field studies from South East Asia (24) and Africa (25) that compared artemisinin and quinine (which only kills mature pRBC). However, even with this welcome progress, there is still over 50% of the mortality recorded during first 48 hours after hospital admission that is largely unaffected by the use of ACTs. This may be because the pRBC has already sequestered to the endothelium. Therefore, there is a need for adjunct therapies to support the critically ill patients, to be used in combination with antimalarials such as artemisinin to remove the sequestered pRBC mass or reduce its effects on the host, while the standard drugs kill the parasite effectively.

To date, several compounds have been explored and screened for their potential to improve SM. N-acetylcysteine (NAC) is an antioxidant drug that is widely used in humans for the treatment of paracetamol overdose and has been shown to be able to reverse almost 72% of pRBC binding to CD36 (112). In addition, it also reduced the rigidity of pRBC (113). A pilot clinical trial study in Thailand (114) showed that NAC was able to normalise serum lactate (an indicator of SM) significantly in SM patients. NAC is thought to inhibit TNF release, thereby reducing cytoadherence. It is also a potent scavenger of free oxygen radicals, which are produced in response to TNF, and can mediate some toxic effects. However, despite these encouraging features, NAC has recently been shown to antagonise the action of artesunate (115), and clinical trials have been disappointing (116), with no reduction in TNF release.

Levamisole is an alkaline phosphatase inhibitor that is used as an antihelminthic drug. Using levamisole for treatment of endothelial cells in vitro showed that it was able to reduce the binding of *P. falciparum* pRBC through dephosphorylated ectodomain of CD36 (117,118). A clinical trial of Levamisole in combination with artesunate is currently underway, and so far, treatment with Levamisole has been shown to be safe and to cause the release of mature pRBC into the peripheral circulation (117). Epigalloyl-catechin-gallate, a naturally occurring polyphenol compound from green tea, was identified as being able to inhibit pRBC binding to ICAM-1 by 50% at micromolar concentrations (119) and has been postulated to synergise the effect of artemisimin on malaria by lowering the IC50 from 14 nM to 8.4 nM (120), but unfortunately, this compound does not appear to be able to reverse adhesion. This highlights the need to test potential anti-cytoadherence agents for inhibition and reversal.

Interventions based on adhesion-related pathology are not limited to attempts to modulate direct interactions of pRBC to specific adhesion molecules but include inhibiting endothelial cell dysfunction during cytoadherence. L-arginine is a substrate for nitric oxide (NO) synthesis by NO synthase. The rationale for the use of L-arginine

follows on from a study (121) in SM patients showing low NO production and low plasma arginine. In normal conditions, NO mediates host resistance to a wide variety of infectious microorganisms, and some in vitro studies have shown that it possessed antiparasitic effects by killing pRBC, as well as an anti-adhesion effect. NO is also a potent inhibitor of TNF production and other pro-inflammatory cytokines implicated in malaria immunopathology (122). Therefore, L-arginine is a good candidate to be used as an adjunct therapy for SM by improving endothelial function. Clinical studies measuring reperfusion parameters have been encouraging (123), and further work is needed in this area to provide better understanding of adhesion-related pathology in malaria and to conduct more clinical trials.

Erythropoietin (EPO) is a hormone produced by the kidney that modulates the survival of developing erythroid precursors and the production of new erythrocytes in the bone marrow. In SM patients, low EPO has been detected and correlated with severe anaemia. Injection of high doses of EPO in mice infected with *P. berghei* showed a significant reduction of pro-inflammatory cytokines TNF and IFN-γ (124) and an increased survival rate when used in combination with artesunate (125). Preliminary clinical trials of EPO in combination with quinine in CM children in Mali showed that it was safe and did not show any side effects (126).

As mentioned before, apoptosis is postulated to be one way in which cytoadherence can cause disease. Therefore, the use of anti-apoptotic agents should be advantageous. Fasudil is a Rho kinase inhibitor and widely used in humans for cardio- and neurovascular diseases. An in vitro study using clinical parasite isolates showed that fasudil has the potential to inhibit apoptosis mediated by *P. falciparum* pRBC adhesion to endothelial cells but showed no effect on reversing or inhibiting pRBC cytoadherence (127). It appears to be a promising adjunctive therapeutic approach for reducing neurological sequelae by reversing endothelial permeability through reducing NFκB activation and endothelial apoptosis (102). The use of statins to control blood cholesterol level has also been shown to be able to restore endothelial damage caused by pRBC cytoadherence (128). Atorvastatin appears to improve endothelial function by increasing NO production, protecting endothelial barrier integrity, reducing oxidative stress, and inhibiting inflammatory responses (129) through activated anti-apoptotic Akt cascade. There is also evidence that statins decrease ICAM-1 expression in stimulated endothelial cell and monocytes (130), but as yet, there is no evidence to show that they are able to reverse established pRBC adhesion.

Further work is needed in this area, such as a better understanding of adhesion-related pathology in malaria and more clinical trials. The latter are complicated by the need to record mortality as an outcome, making the number of patients that need to be recruited relatively large. This means that we need to have better measures of clinical success if this development is to be viable.

What Can We Do for the Future?

The use of adjunct treatments to reverse adhesion of sequestered pRBC is a rational approach to reduce disease severity, but the release of large amount of pRBC into the circulation could be damaging. Can the spleen deal with removing the released pRBC or might it lead to side effects such as splenic dysfunction? Better animal models would help to address this and identify and test lead compounds. Efforts are underway to develop humanised animal models and transgenic parasites (containing PfEMP–1 adhesion domains) that could provide a resource to study the pathophysiology of SM in humans. If we are to preserve some of the advantages gained using ACTs, then the design of new antiparasite drugs should incorporate the ability to kill ring stages as well as mature pRBC and gametocytes.

The need for rapid acting adjunct treatments is critical in order to reduce mortality in SM cases. Anti-adhesion therapies form a part of this portfolio, but we need to understand the biology of this interaction and have better tools to test potential therapies prior to clinical trials.

Authors' Contributions

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References

1. Perlmann P, Troye-Blomberg M. Malaria blood-stage infection and its control by the immune system. *Folia Biol* (*Praha*). 2000;**46(6)**:210–218.
2. Sharma A, Khanduri U. How benign is benign tertian malaria? *J Vector Borne Dis*. 2009;**46(2)**:141–144.
3. Siswantoro H, Russell B, Ratcliff A, Prasetyorini B, Chalfein F, Marfurt J, et al. In vivo and in vitro efficacy of chloroquine against *Plasmodium malariae* and *P. ovale* in Papua, Indonesia. *Antimicrob Agents Chemother*. 2011;**55(1)**:197–202.
4. Sutherland CJ, Tanomsing N, Nolder D, Oguike M, Jennison C, Pukrittayakamee S, et al. Two nonrecombining sympatric forms of the human malaria parasite *Plasmodium ovale* occur globally. *J Infect Dis*. 2010;**201(10)**:1544–1550.
5. Sabbatani S, Fiorino S, Manfredi R. The emerging of the fifth malaria parasite (*Plasmodium knowlesi*): A public health concern? *Braz J Infect Dis*. 2010;**14(3)**:299–309.
6. Cox-Singh J. Malaria: What can apes teach humans? *Future Microbiol*. 2010;**5(8)**:1157–1160.
7. Cox-Singh J, Davis TM, Lee KS, Shamsul SS, Matusop A, Ratnam S, et al. *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis*. 2008;**46(2)**:165–171.
8. Cox-Singh J, Hiu J, Lucas SB, Divis PC, Zulkarnaen M, Chandran P, et al. Severe malaria - A case of fatal *Plasmodium knowlesi* infection with post-mortem findings: A case report. *Malar J*. 2010;**9**:10.
9. Cox-Singh J, Singh B. Knowlesi malaria: Newly emergent and of public health importance? *Trends Parasitol*. 2008;**24(9)**:406–410.
10. Anstey NM, Russell B, Yeo TW, Price RN. The pathophysiology of vivax malaria. *Trends Parasitol*. 2009;**25(5)**:220–227.
11. Genton B, D'Acremont V, Rare L, Baea K, Reeder JC, Alpers MP, et al. *Plasmodium vivax* and mixed infections are associated with severe malaria in children: A prospective cohort study from Papua New Guinea. *PLoS Med*. 2008;**5(6)**:e127.
12. Marchiafava E, Bignami A, Mannaberg J. *On summer-autumn malaria fevers*. London (GB): The New Sydenham Society; 1894.
13. Dubos F, Dauriac A, El Mansouf L, Courouble C, Aurel M, Martinot A. Imported malaria in children: Incidence and risk factors for severity. *Diagn Microbiol Infect Dis*. 2010;**66(2)**:169–174.
14. Carvalho BO, Lopes SC, Nogueira PA, Orlandi PP, Bargieri DY, Blanco YC, et al. On the cytoadhesion of *Plasmodium vivax*-infected erythrocytes. *J Infect Dis*. 2010;**202(4)**:638–647.
15. Fatih FA, Siner A, Ahmed A, Woon LC, Craig AG, Singh B, et al. Cytoadherence and virulence - The case of *Plasmodium knowlesi* malaria. *Malar J*. 2012;**11(1)**:33.
16. Pasternak ND, Dzikowski R. PfEMP1: An antigen that plays a key role in the pathogenicity and immune evasion of the malaria parasite *Plasmodium falciparum*. *Int J Biochem Cell Biol*. 2009;**41(7)**:1463–1466.
17. Scherf A, Lopez-Rubio JJ, Riviere L. Antigenic variation in *Plasmodium falciparum*. *Annu Rev Microbiol*. 2008;**62**:445–470.
18. Flick K, Chen Q. *var* genes, PfEMP1 and the human host. *Mol Biochem Parasitol*. 2004;**134(1)**:3–9.
19. Newbold CI, Craig AG, Kyes S, Berendt AR, Snow RW, Peshu N, et al. PfEMP1, polymorphism and pathogenesis. *Ann Trop Med Parasitol*. 1997;**91(5)**:551–557.
20. Newbold C, Craig A, Kyes S, Rowe A, Fernandez-Reyes D, Fagan T. Cytoadherence, pathogenesis and the infected red cell surface in *Plasmodium falciparum*. *Int J Parasitol*. 1999;**29(6)**:927–937.
21. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. *Clin Pharmacokinet*. 1996;**30(4)**:263–299.
22. Zucker JR, Lackritz EM, Ruebush TK 2nd, Hightower AW, Adungosi JE, Were JB, et al. Childhood mortality during and after hospitalization in western Kenya: Effect of malaria treatment regimens. *Am J Trop Med Hyg*. 1996;**55(6)**:655–660.
23. Giha HA, Elbashir MI, A-Elbasit IE, A-Elqadir TM, ElGhazali GE, Mackinnon MJ, et al. Drug resistance-virulence relationship in *Plasmodium falciparum* causing severe malaria in an area of seasonal and unstable transmission. *Acta Trop*. 2006;**97(2)**: 181–187.
24. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: A randomised trial. *Lancet*. 2005;**366(9487)**:717–725.
25. Dondorp AM, Fanello CI, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. *Lancet*. 2010;**376(9753)**: 1647–1657.
26. Hughes KR, Biagini GA, Craig AG. Continued cytoadherence of *Plasmodium falciparum* infected red blood cells after antimalarial treatment. *Mol Biochem Parasitol*. 2010;**169(2)**:71–78.
27. Dondorp AM, Nyanoti M, Kager PA, Mithwani S, Vreeken J, Marsh K. The role of reduced red cell deformability in the pathogenesis of severe falciparum malaria and its restoration by blood transfusion. *Trans R Soc Trop Med Hyg*. 2002;**96(3)**:282–286.
28. Dondorp AM, Kager PA, Vreeken J, White NJ. Abnormal blood flow and red blood cell deformability in severe malaria. *Parasitol Today*. 2000;**16(6)**: 228–232.

29. Dondorp AM, Angus BJ, Chotivanich K, Silamut K, Ruangveerayuth R, Hardeman MR, et al. Red blood cell deformability as a predictor of anemia in severe falciparum malaria. *Am J Trop Med Hyg*. 1999;**60(5)**:733–737.

30. Armah H, Wired EK, Dodoo AK, Adjei AA, Tettey Y, Gyasi R. Cytokines and adhesion molecules expression in the brain in human cerebral malaria. *Int J Environ Res Public Health*. 2005;**2(1)**:123–131.

31. Armah H, Dodoo AK, Wiredu EK, Stiles JK, Adjei AA, Gyasi RK, et al. High-level cerebellar expression of cytokines and adhesion molecules in fatal, paediatric, cerebral malaria. *Ann Trop Med Parasitol*. 2005;**99(7)**:629–647.

32. Ochola LB, Siddondo BR, Ocholla H, Nkya S, Kimani EN, Williams TN, et al. Specific receptor usage in *Plasmodium falciparum* cytoadherence is associated with disease outcome. *PLoS One*. 2011;**6(3)**:e14741.

33. Conroy AL, Phiri H, Hawkes M, Glover S, Mallewa M, Seydel KB, et al. Endothelium-based biomarkers are associated with cerebral malaria in Malawian children: A retrospective case-control study. *PLoS One*. 2010;**5(12)**:e15291.

34. Garcia F, Cebrian M, Dgedge M, Casademont J, Bedini JL, Neves O, et al. Endothelial cell activation in muscle biopsy samples is related to clinical severity in human cerebral malaria. *J Infect Dis*. 1999;**179(2)**:475–483.

35. Chakravorty SJ, Hughes KR, Craig AG. Host response to cytoadherence in *Plasmodium falciparum*. *Biochem Soc Trans*. 2008;**36(Pt 2)**:221–228.

36. Schofield L, Novakovic S, Gerold P, Schwarz RT, McConville MJ, Tachado SD. Glycosylphosphatidylinositol toxin of *Plasmodium* up-regulates intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin expression in vascular endothelial cells and increases leukocyte and parasite cytoadherence via tyrosine kinase-dependent signal transduction. *J Immunol*. 1996;**156(5)**:1886–1896.

37. Francischetti IM. Does activation of the blood coagulation cascade have a role in malaria pathogenesis? *Trends Parasitol*. 2008;**24(6)**: 258–263.

38. Francischetti IM, Seydel KB, Monteiro RQ, Whitten RO, Erexson CR, Noronha AL, et al. *Plasmodium falciparum*-infected erythrocytes induce tissue factor expression in endothelial cells and support the assembly of multimolecular coagulation complexes. *J Thromb Haemost*. 2007;**5(1)**:155–165.

39. Dondorp AM, Pongponratn E, White NJ. Reduced microcirculatory flow in severe falciparum malaria: Pathophysiology and electron-microscopic pathology. *Acta Trop*. 2004;**89(3)**:309–317.

40. MacPherson GG, Warrell MJ, White NJ, Looareesuwan S, Warrell DA. Human cerebral malaria. A quantitative ultrastructural analysis of parasitized erythrocyte sequestration. *Am J Pathol*. 1985;**119(3)**:385–401.

41. Howard RJ, Handunnetti SM, Hasler T, Gilladoga A, de Aguiar JC, Pasloske BL, et al. Surface molecules on *Plasmodium falciparum*-infected erythrocytes involved in adherence. *Am J Trop Med Hyg*. 1990; **43(2 Pt 2)**:15–29.

42. Craig A, Scherf A. Molecules on the surface of the *Plasmodium falciparum* infected erythrocyte and their role in malaria pathogenesis and immune evasion. *Mol Biochem Parasitol*. 2001;**115(2)**: 129–143.

43. Moreno-Perez DA, Mongui A, Soler LN, Sanchez-Ladino M, Patarroyo MA. Identifying and characterizing a member of the RhopH1/Clag family in *Plasmodium vivax*. *Gene*. 2011;**481(1)**:17–23.

44. Biggs BA, Culvenor JG, Ng JS, Kemp DJ, Brown GV. *Plasmodium falciparum*: Cytoadherence of a knobless clone. *Exp Parasitol*. 1989;**69(2)**:189–197.

45. Rug M, Prescott SW, Fernandez KM, Cooke BM, Cowman AF. The role of KAHRP domains in knob formation and cytoadherence of *P. falciparum*-infected human erythrocytes. *Blood*. 2006;**108(1)**:370–378.

46. Chilongola J, Balthazary S, Mpina M, Mhando M, Mbugi E. CD36 deficiency protects against malarial anaemia in children by reducing *Plasmodium falciparum*-infected red blood cell adherence to vascular endothelium. *Trop Med Int Health*. 2009;**14(7)**:810–816.

47. Cojean S, Jafari-Guemouri S, Le Bras J, Durand R. Cytoadherence characteristics to endothelial receptors ICAM-1 and CD36 of *Plasmodium falciparum* populations from severe and uncomplicated malaria cases. *Parasite*. 2008;**15(2)**:163–169.

48. Yipp BG, Anand S, Schollaardt T, Patel KD, Looareesuwan S, Ho M. Synergism of multiple adhesion molecules in mediating cytoadherence of *Plasmodium falciparum*-infected erythrocytes to microvascular endothelial cells under flow. *Blood*. 2000;**96(6)**:2292–2298.

49. Gray C, McCormick C, Turner G, Craig A. ICAM-1 can play a major role in mediating *P. falciparum* adhesion to endothelium under flow. *Mol Biochem Parasitol*. 2003;**128(2)**:187–193.

50. Marsh K, Marsh VM, Brown J, Whittle HC, Greenwood BM. *Plasmodium falciparum:* The behavior of clinical isolates in an in vitro model of infected red blood cell sequestration. *Exp Parasitol*. 1988;**65(2)**:202–208.

51. Ockenhouse CF, Ho M, Tandon NN, Van Seventer GA, Shaw S, White NJ, et al. Molecular basis of sequestration in severe and uncomplicated *Plasmodium falciparum* malaria: differential adhesion of infected erythrocytes to CD36 and ICAM-1. *J Infect Dis*. 1991;**164(1)**:163–169.

52. Ho M, Singh B, Looareesuwan S, Davis TME, Bunnag D, White NJ. Clinical correlates of in vitro *Plasmodium falciparum* cytoadherence. *Infect Immun*. 1991;**59(3)**:873–878.

53. Chaiyaroj SC, Angkasekwinai P, Buranakiti A, Looareesuwan S, Rogerson SJ, Brown GV. Cytoadherence characteristics of *Plasmodium falciparum* isolates from Thailand: Evidence for chondroitin sulfate a as a cytoadherence receptor. *Am J Trop Med Hyg*. 1996;**55(1)**:76-80.

54. Udomsangpetch R, Taylor BJ, Looareesuwan S, White NJ, Elliott JF, Ho M. Receptor specificity of clinical *Plasmodium falciparum* isolates: Nonadherence to cell-bound E-selectin and vascular cell adhesion molecule-1. *Blood*. 1996;**88(7)**:2754–2760.

55. Newbold C, Warn P, Black G, Berendt A, Craig A, Snow B, et al. Receptor-specific adhesion and clinical disease in *Plasmodium falciparum*. *Am J Trop Med Hyg*. 1997;**57(4)**:389–398.

56. Rogerson SJ, Tembenu R, Dobano C, Plitt S, Taylor TE, Molyneux ME. Cytoadherence characteristics of *Plasmodium falciparum*-infected erythrocytes from Malawian children with severe and uncomplicated malaria. *Am J Trop Med Hyg*. 1999;**61(3)**:467–472.

57. Heddini A, Pettersson F, Kai O, Shafi J, Obiero J, Chen Q, et al. Fresh isolates from children with severe *Plasmodium falciparum* malaria bind to multiple receptors. *Infect Immun*. 2001;**69(9)**:5849–5856.

58. Mayor A, Hafiz A, Bassat Q, Rovira-Vallbona E, Sanz S, Machevo S, et al. Association of severe malaria outcomes with platelet-mediated clumping and adhesion to a novel host receptor. *PLoS One*. 2011;**6(4)**:e19422.

59. Fried M, Duffy PE. Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. *Science*. 1996;**272(5267)**:1502–1504.

60. Salanti A, Resende M, Ditlev SB, Pinto VV, Dahlback M, Andersen G, et al. Several domains from VAR2CSA can induce *Plasmodium falciparum* adhesion-blocking antibodies. *Malar J*. 2010;**9(1)**:11.

61. Salanti A, Staalsoe T, Lavstsen T, Jensen AT, Sowa MP, Arnot DE, et al. Selective upregulation of a single distinctly structured var gene in chondroitin sulphate A-adhering *Plasmodium falciparum* involved in pregnancy-associated malaria. *Mol Microbiol*. 2003;**49(1)**:179–191.

62. Schofield L. Rational approaches to developing an anti-disease vaccine against malaria. *Microbes Infect*. 2007;**9(6)**:784–791.

63. Karunaweera ND, Grau GE, Gamage P, Carter R, Mendis KN. Dynamics of fever and serum levels of tumor necrosis factor are closely associated during clinical paroxysms in *Plasmodium vivax* malaria. *Proc Natl Acad Sci U S A*. 1992;**89(8)**:3200–3203.

64. Brown H, Turner G, Rogerson S, Tembo M, Mwenechanya J, Molyneux M, et al. Cytokine expression in the brain in human cerebral malaria. *J Infect Dis*. 1999;**180(5)**:1742–1746.

65. Grau GE, Taylor TE, Molyneux ME, Wirima JJ, Vassalli P, Hommel M, et al. Tumor necrosis factor and disease severity in children with falciparum malaria. *N Engl J Med*. 1989;**320(24)**:1586–1591.

66. Grau GE, Bieler G, Pointaire P, De Kossodo S, Tacchini-Cotier F, Vassalli P, et al. Significance of cytokine production and adhesion molecules in malarial immunopathology. *Immunol Lett*. 1990;**25(1–3)**:189–194.

67. Kwiatkowski D, Molyneux ME, Stephens S, Curtis N, Klein N, Pointaire P, et al. Anti-TNF therapy inhibits fever in cerebral malaria. *Q J Med*. 1993;**86(2)**: 91–98.

68. Van Hensbroek MB, Palmer A, Onyiorah E, Schneider G, Jaffar S, Dolan G, et al. The effect of a monoclonal antibody to tumor necrosis factor on survival from childhood cerebral malaria. *J Infect Dis*. 1996;**174(5)**:1091–1097.

69. Erdman LK, Dhabangi A, Musoke C, Conroy AL, Hawkes M, Higgins S, et al. Combinations of host biomarkers predict mortality among Ugandan children with severe malaria: A retrospective case-control study. *PLoS One*. 2011;**6(2)**:e17440.

70. Day NP, Hien TT, Schollaardt T, Loc PP, Chuong LV, Chau TT, et al. The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. *J Infect Dis*. 1999;**180(4)**:1288–1297.

71. Richards AL. Tumour necrosis factor and associated cytokines in the host's response to malaria. *Int J Parasitol*. 1997;**27(10)**:1251–1263.

72. Serghides L, Smith TG, Patel SN, Kain KC. CD36 and malaria: friends or foes? *Trends Parasitol*. 2003;**19(10)**:461–469.

73. Patel SN, Serghides L, Smith TG, Febbraio M, Silverstein RL, Kurtz TW, et al. CD36 mediates the phagocytosis of *Plasmodium falciparum*-infected erythrocytes by rodent macrophages. *J Infect Dis*. 2004;**189(2)**:204–213.

74. Urban BC, Ferguson DJ, Pain A, Willcox N, Plebanski M, Austyn JM, et al. *Plasmodium falciparum*-infected erythrocytes modulate the maturation of dendritic cells. *Nature*. 1999;**400(6739)**:73–77.

75. Elliott SR, Spurck TP, Dodin JM, Maier AG, Voss TS, Yosaatmadja F, et al. Inhibition of dendritic cell maturation by malaria is dose dependent and does not require *Plasmodium falciparum* erythrocyte membrane protein 1. *Infect Immun*. 2007;**75(7)**: 3621–3632.

76. Wykes MN, Liu XQ, Beattie L, Stanisic DI, Stacey KJ, Smyth MJ, et al. *Plasmodium* strain determines dendritic cell function essential for survival from malaria. *PLoS Pathog*. 2007;**3(7)**:e96.

77. Turner GD, Morrison H, Jones M, Davis TM, Looareesuwan S, Buley ID, et al. An immunohistochemical study of the pathology of fatal malaria. Evidence for widespread endothelial activation and a potential role for intercellular adhesion molecule-1 in cerebral sequestration. *Am J Pathol*. 1994;**145(5)**:1057–1069.

78. Turner GD, Ly VC, Nguyen TH, Tran TH, Nguyen HP, Bethell D, et al. Systemic endothelial activation occurs in both mild and severe malaria. Correlating dermal microvascular endothelial cell phenotype and soluble cell adhesion molecules with disease severity. *Am J Pathol*. 1998;**152(6)**:1477–1487.

79. Van Mourik JA, Romani de Wit T, Voorberg J. Biogenesis and exocytosis of Weibel-Palade bodies. *Histochem Cell Biol*. 2002;**117(2)**:113–122.

80. Beghdadi W, Porcherie A, Schneider BS, Dubayle D, Peronet R, Huerre M, et al. Inhibition of histamine-mediated signaling confers significant protection against severe malaria in mouse models of disease. *J Exp Med*. 2008;**205(2)**:395–408.

81. Bridges DJ, Bunn J, van Mourik JA, Grau G, Preston RJ, Molyneux M, et al. Rapid activation of endothelial cells enables *Plasmodium falciparum* adhesion to platelet-decorated von Willebrand factor strings. *Blood*. 2010;**115(7)**:1472–1474.

82. Hollestelle MJ, Donkor C, Mantey EA, Chakravorty SJ, Craig A, Akoto AO, et al. von Willebrand factor propeptide in malaria: Evidence of acute endothelial cell activation. *Br J Haematol*. 2006;**133(5)**: 562–569.

83. Lowenberg EC, Charunwatthana P, Cohen S, van den Born BJ, Meijers JC, Yunus EB, et al. Severe malaria is associated with a deficiency of von Willebrand factor cleaving protease, ADAMTS13. *Thromb Haemost*. 2010;**103(1)**:181–187.

84. Larkin D, de Laat B, Jenkins PV, Bunn J, Craig AG, Terraube V, et al. Severe *Plasmodium falciparum* malaria is associated with circulating ultra-large von Willebrand multimers and ADAMTS13 inhibition. *PLoS Pathog*. 2009;**5(3)**:e1000349.

85. Tripathi K, Kumar R, Bharti K, Kumar P, Shrivastav R, Sundar S, et al. Adenosine deaminase activity in sera of patients with visceral leishmaniasis in India. *Clin Chim Acta*. 2008;**388(1–2)**:135–138.

86. Udomsangpetch R, Pipitaporn B, Silamut K, Pinches R, Kyes S, Looareesuwan S, et al. Febrile temperatures induce cytoadherence of ring-stage *Plasmodium falciparum*-infected erythrocytes. *Proc Natl Acad Sci U S A*. 2002;**99(18)**:11825–11829.

87. Oakley MS, Kumar S, Anantharaman V, Zheng H, Mahajan B, Haynes JD, et al. Molecular factors and biochemical pathways induced by febrile temperature in intraerythrocytic *Plasmodium falciparum* parasites. *Infect Immun*. 2007;**75(4)**:2012–2025.

88. Pattanapanyasat K, Sratongno P, Chimma P, Chitjamnongchai S, Polsrila K, Chotivanich K. Febrile temperature but not proinflammatory cytokines promotes phosphatidylserine expression on *Plasmodium falciparum* malaria-infected red blood cells during parasite maturation. *Cytometry A*. 2010;**77(6)**:515–523.

89. Sherman IW, Prudhomme J. Phosphatidylserine expression on the surface of malaria-parasitized erythrocytes. *Parasitol Today*. 1996;**12(3)**:122; author reply 122.

90. Sherman IW, Eda S, Winograd E. Cytoadherence and sequestration in *Plasmodium falciparum*: Defining the ties that bind. *Microbes Infect*. 2003;**5(10)**: 897–909.

91. Eda S, Sherman IW. Cytoadherence of malaria-infected red blood cells involves exposure of phosphatidylserine. *Cell Physiol Biochem*. 2002;**12(5–6)**:373–384.

92. Ho M, White NJ. Molecular mechanisms of cytoadherence in malaria. *Am J Physiol*. 1999; **276(6 Pt 1)**:C1231–C1242.

93. Riedel W, Maulik G. Fever: An integrated response of the central nervous system to oxidative stress. *Mol Cell Biochem*. 1999;**196(1–2)**:125–132.

94. Krudsood S, Tangpukdee N, Wilairatana P, Pothipak N, Duangdee C, Warrell DA, et al. Intravenous ibuprofen (IV-ibuprofen) controls fever effectively in adults with acute uncomplicated *Plasmodium falciparum* malaria but prolongs parasitemia. *Am J Trop Med Hyg*. 2010;**83(1)**:51–55.

95. Marinkovic M, Diez-Silva M, Pantic I, Fredberg JJ, Suresh S, Butler JP. Febrile temperature leads to significant stiffening of *Plasmodium falciparum* parasitized erythrocytes. *Am J Physiol Cell Physiol*. 2009;**296(1)**:C59–C64.

96. Dondorp AM, Ince C, Charunwatthana P, Hanson J, van Kuijen A, Faiz MA, et al. Direct in vivo assessment of microcirculatory dysfunction in sever falciparum malaria. *J Infect Dis*. 2008;**197(1)**:79–84.

97. Maude RJ, Beare NA, Abu Sayeed A, Chang CC, Charunwatthana P, Faiz MA, et al. The spectrum of retinopathy in adults with *Plasmodium falciparum* malaria. *Trans R Soc Trop Med Hyg*. 2009;**103(7)**:665–671.

98. Medana IM, Chan-Ling T, Hunt NH. Reactive changes of retinal microglia during fatal murine cerebral malaria: Effects of dexamethasone and experimental permeabilization of the blood-brain barrier. *Am J Pathol*. 2000;**156(3)**:1055–1065.

99. Chang-Ling T, Neill AL, Hunt NH. Early microvascular changes in murine cerebral malaria detected in retinal wholemounts. *Am J Pathol*. 1992;**140(5)**:1121–1130.

100. Janes JH, Wang CP, Levin-Edens E, Vigan-Womas I, Guillotte M, Melcher M, et al. Investigating the host binding signature on the *Plasmodium falciparum* PfEMP1 protein family. *PLoS Pathog*. 2011;**7(5)**:e1002032.

101. Adams S, Brown H, Turner G. Breaking down the blood-brain barrier: Signaling a path to cerebral malaria? *Trends Parasitol*. 2002;**18(8)**:360–366.

102. Taoufiq Z, Gay F, Balvanyos J, Ciceron L, Tefit M, Lechat P, et al. Rho kinase inhibition in severe malaria: Thwarting parasite-induced collateral damage to endothelia. *J Infect Dis*. 2008;**197(7)**:1062–1073.

103. Tripathi AK, Sullivan DJ, Stins MF. *Plasmodium falciparum*-infected erythrocytes increase intercellular adhesion molecule 1 expression on brain endothelium through NF-kappaB. *Infect Immun*. 2006;**74(6)**:3262–3270.

104. Jenkins N, Wu Y, Chakravorty S, Kai O, Marsh K, Craig A. *Plasmodium falciparum* intercellular adhesion molecule-1-based cytoadherence-related signaling in human endothelial cells. *J Infect Dis*. 2007;**196(2)**:321–327.

105. Wassmer SC, Combes V, Candal FJ, Juhan-Vague I, Grau GE. Platelets potentiate brain endothelial alterations induced by *Plasmodium falciparum*. *Infect Immun*. 2006;**74(1)**:645–653.

106. Tripathi AK, Sullivan DJ, Stins MF. *Plasmodium falciparum*-infected erythrocytes decrease the integrity of human blood-brain barrier endothelial cell monolayers. *J Infect Dis*. 2007;**195(7)**:942–950.

107. Medana IM, Turner GD. Human cerebral malaria and the blood-brain barrier. *Int J Parasitol*. 2006;**36(5)**:555–568.

108. Rao A, Kumar MK, Joseph T, Bulusu G. Cerebral malaria: Insights from host-parasite protein-protein interactions. *Malar J*. 2010;**9**:155.

109. Pino P, Vouldoukis I, Kolb JP, Mahmoudi N, Desportes-Livage I, Bricaire F, et al. *Plasmodium falciparum*–infected erythrocyte adhesion induces caspase activation and apoptosis in human endothelial cells. *J Infect Dis*. 2003;**187(8)**:1283–1290.

110. Toure FS, Ouwe-Missi-Oukem-Boyer O, Bisvigou U, Moussa O, Rogier C, Pino P, et al. Apoptosis: A potential triggering mechanism of neurological manifestation in *Plasmodium falciparum* malaria. *Parasite Immunol*. 2008;**30(1)**:47–51.

111. Hebert MJ, Gullans SR, Mackenzie HS, Brady HR. Apoptosis of endothelial cells is associated with paracrine induction of adhesion molecules: Evidence for an interleukin-1beta-dependent paracrine loop. *Am J Pathol*. 1998;**152(2)**:523–532.

112. Treeprasertsuk S, Krudsood S, Tosukhowong T, Maek-A-Nantawat W, Vannaphan S, Saengnetswang T, et al. N-acetylcysteine in severe falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health*. 2003;**34(1)**:37–42.

113. Nuchsongsin F, Chotivanich K, Charunwatthana P, Omodeo-Sale F, Taramelli D, Day NP, et al. Effects of malaria heme products on red blood cell deformability. *Am J Trop Med Hyg*. 2007;**77(4)**:617–622.

114. Watt G, Jongsakul K, Ruangvirayuth R. A pilot study of N-acetylcysteine as adjunctive therapy for severe malaria. *QJM*. 2002;**95(5)**:285–290.

115. Arreesrisom P, Dondorp AM, Looareesuwan S, Udomsangpetch R. Suppressive effects of the anti-oxidant N-acetylcysteine on the anti-malarial activity of artesunate. *Parasitol Int*. 2007;**56(3)**:221–226.

116. Charunwatthana P, Abul Faiz M, Ruangveerayut R, Maude RJ, Rahman MR, Roberts LJ 2nd, et al. N-acetylcysteine as adjunctive treatment in severe malaria: Arandomized, double-blinded placebo-controlled clinical trial. *Crit Care Med*. 2009;**37(2)**:516–522.

117. Dondorp AM, Silamut K, Charunwatthana P, Chuasuwanchai S, Ruangveerayut R, Krintratun S, et al. Levamisole inhibits sequestration of infected red blood cells in patients with falciparum malaria. *J Infect Dis*. 2007;**196(3)**:460–466.

118. Ho M, Hoang HL, Lee KM, Liu N, MacRae T, Montes L, et al. Ectophosphorylation of CD36 regulates cytoadherence of *Plasmodium falciparum* to microvascular endothelium under flow conditions. *Infect Immun*. 2005;**73(12)**:8179–8187.

119. Dormeyer M, Adams Y, Kramer B, Chakravorty S, Tse MT, Pegoraro S, et al. Rational design of anticytoadherence inhibitors for *Plasmodium falciparum* based on the crystal structure of human intercellular adhesion molecule 1. *Antimicrob Agents Chemother*. 2006;**50(2)**:724–730.

120. Sannella AR, Messori L, Casini A, Francesco Vincieri F, Bilia AR, Majori G, et al. Antimalarial properties of green tea. *Biochem Biophys Res Commun*. 2007;**353(1)**:177–181.

121. Lopansri BK, Anstey NM, Weinberg JB, Stoddard GJ, Hobbs MR, Levesque MC, et al. Low plasma arginine concentrations in children with cerebral malaria and decreased nitric oxide production. *Lancet*. 2003;**361(9358)**:676–678.

122. John CC, Kutamba E, Mugarura K, Opoka RO. Adjunctive therapy for cerebral malaria and other severe forms of *Plasmodium falciparum* malaria. *Expert Rev Anti Infect Ther*. 2010;**8(9)**:997–1008.

123. Yeo TW, Rooslamiati I, Gitawati R, Tjitra E, Lampah DA, Kenangalem E, et al. Pharmacokinetics of L-arginine in adults with moderately severe malaria. *Antimicrob Agents Chemother*. 2008;**52(12)**: 4381–4387.

124. Kaiser K, Texier A, Ferrandiz J, Buguet A, Meiller A, Latour C, et al. Recombinant human erythropoietin prevents the death of mice during cerebral malaria. *J Infect Dis*. 2006;**193(7)**:987–995.

125. Bienvenu AL, Ferrandiz J, Kaiser K, Latour C, Picot S. Artesunate-erythropoietin combination for murine cerebral malaria treatment. *Acta Trop*. 2008;**106(2)**:104–108.

126. Picot S, Bienvenu AL, Konate S, Sissoko S, Barry A, Diarra E, et al. Safety of epoietin beta-quinine drug combination in children with cerebral malaria in Mali. *Malar J*. 2009;**8**:169.

127. Zang-Edou ES, Bisvigou U, Taoufiq Z, Lekoulou F, Lekana-Douki JB, Traore Y, et al. Inhibition of *Plasmodium falciparum* field isolates-mediated endothelial cell apoptosis by Fasudil: Therapeutic implications for severe malaria. *PLoS One*. 2010;**5(10)**:e13221.

128. Taoufiq Z, Pino P, N'dilimabaka N, Arrouss I, Assi S, Soubrier F, et al. Atorvastatin prevents *Plasmodium falciparum* cytoadherence and endothelial damage. *Malar J*. 2011;**10**:52.

129. Laufs U. Beyond lipid-lowering: Effects of statins on endothelial nitric oxide. *Eur J Clin Pharmacol*. 2003;**58(11)**:719–731.

130. Romano M, Mezzetti A, Marulli C, Ciabattoni G, Febo F, Di Ienno S, et al. Fluvastatin reduces soluble P-selectin and ICAM-1 levels in hypercholesterolemic patients: Role of nitric oxide. *J Investig Med*. 2000;**48(3)**:183–189.

Original Article

Comparison of Job Satisfaction among Eight Health Care Professions in Private (Non-Government) Settings

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Abstract

Background: **A comparison of the job satisfaction of health care professionals has not been well studied in Malaysia. This study aimed to compare the job satisfaction level among 8 groups of health care professionals in private settings, using the Job Satisfaction Survey (JSS).**

Methods: **A total of 81 health care professionals, including nurses, physiotherapists, occupational therapists, medical laboratory technologists, dieticians, medical imaging practitioners, environmental health officers, and optometrists in private (non-government) settings in the Klang Valley, were interviewed using the Job Satisfaction Survey scale invented by Dr Paul E Spector. Their job satisfaction scores were calculated and determined.**

Results: **In the demographic data, the majority of the subjects were 20–30 years old (81.5%), were female (72.8%), had a basic degree (98.8%), were single (64.2%), and had 1–5 years of working experience (83.9%). A Kruskal–Wallis analysis showed significant differences ($P < 0.05$) in promotion, supervision, operating conditions, co-workers, nature of the work, and communication, but there were no significant differences ($P > 0.05$) in pay, fringe benefits, and contingent rewards in JSS score among the 8 health care professions. The Friedman Test showed a significant difference of overall JSS scores ($\chi^2 = 526.418$, $P < 0.001$) among the 8 health care professions.**

Conclusion: **The overall job satisfaction levels are different among health care professionals in private settings, especially regarding promotion, supervision, operating conditions, co-workers, the nature of the work, and communication.**

Keywords: *job satisfaction, health care, non-governmental organizations, private sector*

Introduction

Job satisfaction (JS) designates how people feel towards their jobs, whether they like (satisfaction) or dislike (dissatisfaction) their jobs (1). Factors that influence JS comprise several aspects pertaining to the job situation, such as salary, career development, the nature of the work, the policies and procedures of an organisation, working conditions, relationships with colleagues and management, and individual needs (2). JS trends can affect labour market behaviour and influence work productivity, work effort, employee absenteeism, and staff turnover. Moreover, JS is considered a strong predictor of overall individual well-being and a good predictor of the intentions or decisions of employees to leave a job (3,4).

Among health care professions, similar factors have been reported to contribute to JS, including competitive pay, adequate staffing, flexible scheduling, feeling of worthwhile accomplishment from their job, opportunities for personal and professional growth, recognition, noticeable progress of patients, positive relationships with co-workers, autonomy on the job, a pleasant working environment, a reasonable workload, the nature of the work, supervision, communication, benefits, job security, career advancement and contingent rewards (5–18).

A comparison of the JS of health care professionals has not been well studied in Malaysia. Therefore, this study aimed to determine the overall JS among health care professionals in the private (non-government) sectors in the Klang Valley. An established Job Satisfaction Survey (JSS) scale was chosen as the instrument to measure the JS level among the health care professionals.

Subjects and Methods

This study was conducted using a descriptive survey-designed method based on convenient sampling. A total of 81 health care professionals, including nurses, physiotherapists, occupational therapists, medical laboratory technologists, dieticians, medical imaging practitioners, environmental health officers, and optometrists at private (non-government) settings in the Klang

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Valley, participated in this study. A sample size of approximately 80 was targeted due to limited resources, such as the difficulty of obtaining approval from employers to conduct the study in the private sector, a limited amount of time, and budget constraints barring extension of the study to other states. The JSS was sent by hand to the human resource assistants of each non-government/private hospital in the Klang Valley that allowed this study to be conducted among their employees; the human resource assistants then distributed the questionnaires to the health care professionals from 8 groups of interest. This project adhered to the ethical considerations in the Declaration of Helsinki and obtained approval from the Ethical Committee of the Faculty of Health Sciences, Universiti Teknologi MARA.

Demographic information, including age, gender, marital status, educational level, and years of experience, was recorded before administration of the JSS. The JSS, invented by Dr Paul E Spector (1), recognises 9 facets of JS using attitude scale construction techniques for summated (Likert) rating scales. The scales include satisfaction with pay, promotional opportunities, fringe benefits, contingent rewards, supervision, co-workers, the nature of the work, communication, and working conditions. Each item uses a 6-point Likert scale that measures the degree of agreement with the statement. Four-subscale questions with positively and negatively worded statements in 9 facets of the job are evaluated in JSS. The scores of the negatively worded items are added to the positively worded items to obtain the total scores. The overall JSS score is classified as dissatisfaction, moderate, and satisfaction, with total scores of 36–108, 109–144, and 145–216, respectively (1). The JSS for each facet score is classified as dissatisfaction, moderate, and satisfaction with respect to scores of 4–12, 13–15, and 16–24 (1).

With acceptable reliability and validity, JSS has been widely used in many studies on various fields (19). The internal consistency of reliability ranges from 0.60 for co-workers at the sub-scale to 0.91 for the total scale. The widely accepted minimum standard for internal consistency is 0.70 (20). The test–retest reliability ranges from 0.37 to 0.74. A good correlation of sub-scales between the JSS and corresponding sub-scales of the Job Descriptive Index, which is considered to be the most carefully validated scale of JS, ranges from 0.61 for co-workers to 0.80 for supervision (21).

To bolster confidence in the suitability of the JSS in Malaysian health care professionals, a Rasch analysis was performed to analyse the reliability of the JSS in terms of the questionnaire (measured items) itself and the target groups (measured persons).

For the questionnaire (Table 1), the expected mean square value was found to be 1.00 and within the expected range of $0.5 < x < 1.5$, while the outfit z-standard value for normality was found to be −0.1, which is very close to the expected value of zero and within the normality range of $-2 < z < 2$. The questionnaire has excellent fit with the item reliability of 0.96 (22). The high item reliability of 0.96 indicates that the replicability of the items could occur if these items are to be given to another sample of the same size (23).

In determining the suitability of the questionnaire for Malaysian health care professionals, the person reliability value was found to be poor (0.67) when all 8 health care professional groups were combined. However, the means for the item and for the person were found to be at a similar level on the Items MAP of Persons (Figure 1), which indicates that the difficulty level of the questionnaire was not above or below the ability of the respondents. The mean value is 0.40 and 0.00 for Person and Item, respectively, which is near zero (Table 1). With further analysis of the person reliability for each health care profession, we found out that only the medical laboratory technologist group was problematic regarding separation and reliability values at zero. After re-examining the questionnaire and re-analysing the nature of the work demands, we noticed that the medical laboratory technologists were the only group of the 8 health care professions who do not have direct contact with patients, as their work is laboratory-based. Thus, this questionnaire may not be suitable for use by this group of professionals. When we excluded the group, the person reliability became fairly reliable (0.69). We can confidently conclude that the JSS is reliable for use with Malaysian health care professionals.

Results

A total of 100 questionnaires were distributed in this study, and the response rate was 81.0% (Table 2). In the demographic data of the respondents (Table 3), the highest percentage is from the group aged 20 to 30 (81.5%). More females (72.8%) responded than males. The majority of the respondents have basic degrees (98.8%). Most of the respondents are single (64.2%), and most have 1–5 years of working experience (83.9%).

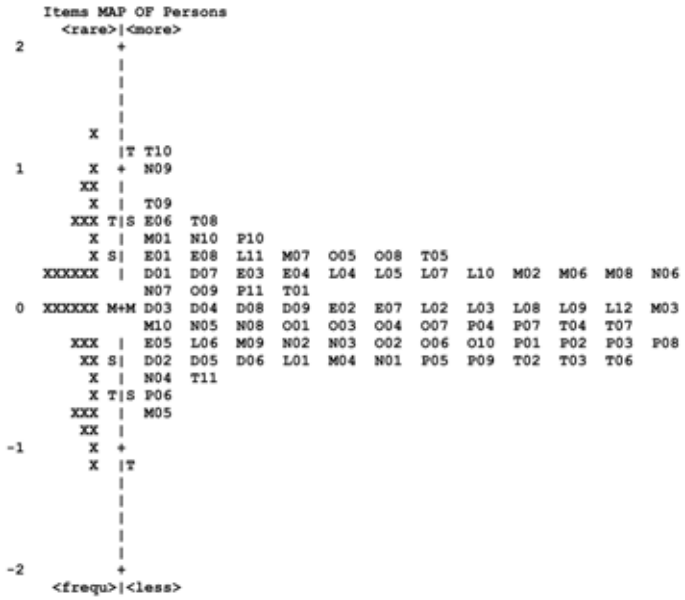

Figure 1: Rasch analysis: Items MAP of Persons

Table 1a: Rasch analysis reliability table for 81 measured persons

	Raw score	Count	Measure	Model error	Infit		Outfit	
					MNSQ	ZSTD	MNSQ	ZSTD
Mean	131.7	36.0	0.04	0.16	1.00	−0.4	1.00	−0.4
SD	11.4	0.0	0.29	0.01	0.59	2.4	0.58	2.3
Max	170.0	36.0	1.12	0.19	3.41	7.3	3.39	7.1
Min	102.0	36.0	−0.68	0.15	0.25	−5.0	0.25	−4.9
Real RMSE	0.18	Adj. SD	0.23	Separation	1.34	Person reliability		0.64
Model RMSE	0.16	Adj. SD	0.25	Separation	1.55	Person reliability		0.71
SE of Person mean = 0.03								

Person raw score-to-measure correlation = 1.00
Cronbach alpha (kr-20) person raw score reliability = 0.68

Table 1b: Rasch analysis reliability table for 36 measured items

	Raw score	Count	Measure	Model error	Infit		Outfit	
					MNSQ	ZSTD	MNSQ	ZSTD
Mean	296.4	81.0	0.00	0.11	0.99	−0.1	1.00	−0.1
SD	53.0	0.0	0.58	0.01	0.23	1.6	0.24	1.6
Max	388.0	81.0	1.25	0.13	1.54	3.3	1.56	3.5
Min	178.0	81.0	−1.12	0.10	0.60	−2.8	0.62	−2.9
Real RMSE	0.11	Adj. SD	0.57	Separation	5.14	Person reliability		0.96
Model RMSE	0.11	Adj. SD	0.57	Separation	5.37	Person reliability		0.97
SE of Item mean = 0.10								

Umean = 0.000 uscale = 1.000
Item raw score-to-measure correlation = −1.00
2916 data points. Approximate log-likelihood chi-square: 8390.88

Table 2: Number of respondents from each health care profession

Profession	*n*
Optometrist	10
Nurse	10
Physiotherapist	11
Occupational therapist	11
Medical imaging practitioner	10
Medical laboratory technologist	12
Environmental health officer	8
Nutritionist and dietician	9
Total	**81**

Table 3: Distribution of demographic data

Parameter	*n*	%
Age		
Not stated	2	2.5
20–30 years	66	81.5
31–40 years	10	12.4
41–50 years	1	1.2
51–60 years	2	2.4
Gender		
Male	22	27.2
Female	59	72.8
Educational level		
Diploma	37	45.7
Bachelor	43	53.1
Master	1	1.2
PhD	0	0.0
Marital status		
Single	52	64.2
Married	29	35.8
Divorced	0	0.0
Widowed	0	0.0
Year(s) of experience		
1–5 year(s)	68	83.9
6–10 years	6	7.4
11–15 years	7	8.7

The descriptive statistics are presented in Table 4 in terms of median, interquartile range, and minimum and maximum scores. A Kruskal–Wallis analysis was used to compare the 8 health care professions for each facet. There are significant differences ($P < 0.05$) in 6 (promotion, supervision, operating conditions, co-workers, nature of the work, and communication) of the 9 facets in the JSS among the 8 health care professions. There is no significant difference ($P > 0.05$) in 3 (pay, fringe benefit, and contingent reward) out of the 9 facets. The Friedman Test showed a significant difference in the overall JS scores ($\chi^2 = 526.418$, $P < 0.001$) among the 8 health care professions. The median was 140 (interquartile range = 22), with a minimum of 107 and a maximum of 170.

This study reveals an interesting trend in JS when the data are viewed differently by matching the JSS classification based on the mean score for each facet (Table 5). This trend is outlined as follows:

Pay facet

All eight health care profession groups are moderately satisfied.

Promotion facet

Most of the groups were moderately satisfied (optometrists, nurses, occupational therapists, and medical imaging practitioners), 2 were satisfied (medical laboratory technologists and environmental health officers), and 2 were dissatisfied (physiotherapists and dieticians).

Supervision facet

All 8 groups were satisfied.

Fringe benefit facet

Most of the groups were moderately satisfied, except physiotherapists and medical laboratory technologists (dissatisfied).

Contingent reward facet

All 8 groups were moderately satisfied.

Operating condition facet

Most of the groups were moderately satisfied, except nurses, occupational therapists, and environmental health officers (dissatisfied).

Co-workers facet

Most groups were satisfied, except nurses and occupational therapists (moderately satisfied).

Nature of the work facet

All 8 health care groups were satisfied.

Communication facet

Most of the groups were satisfied, except occupational therapists, medical imaging practitioners, and environmental health & safety officers (moderately satisfied).

Table 4: Descriptive statistics of the comparisons of 9 facets in Job Satisfaction Survey among 8 health care professions

Facets	Median	Interquartile Range	Minimum	Maximum	Kruskal – Wallis chi-square (df = 7)	*P* value
Pay	15	3	6	20	9.223	0.237
Promotion	15	3	7	20	17.024	0.017
Supervision	18	4	12	24	15.078	0.035
Fringe benefits	14	4	6	22	9.977	0.190
Contingent rewards	15	4	5	19	9.480	0.220
Operating condition	13	3	7	20	18.293	0.011
Co-workers	17	4	10	23	21.882	0.003
Nature of work	18	3	11	24	22.243	0.002
Communication	17	4	11	24	19.855	0.006

Discussion

The level of job satisfaction is different among health care professionals in private settings, especially regarding promotion, supervision, operating conditions, co-workers, the nature of the work, and communication, but not regarding pay, fringe benefits, or contingent rewards.

In previous studies (5–8), nurses identified tremendous workloads as the leading cause of dissatisfaction with their job, followed by poor staff cohesiveness, poor staffing, and poor working relationships with administrators. Our study reveals that, overall, nurses displayed moderate JS; they were relatively more satisfied in terms of supervision, the nature of the work, and communication, but were less satisfied with operating conditions among the 9 facets of the JSS considered within the profession.

In previous studies (6,10,11), unrealistic workload, non-competitive pay, inadequate staffing, and inflexible scheduling were common factors in job dissatisfaction for occupational therapists and physiotherapists, whereas factors contributing to JS included the noticeable progress of patients, positive relationships with co-workers, autonomy on the job, and a pleasant working environment. Our study reveals that physiotherapists were moderately satisfied with their overall JS; they were relatively more satisfied in terms of supervision, co-workers, the nature of the work, and communication, but were less satisfied with promotion and fringe benefits among the 9 facets of the JSS considered within the profession. Our study also reveals that occupational therapists were moderately satisfied with their jobs; they were relatively more satisfied in terms of supervision and the nature of the work, but were less satisfied with operating conditions among the 9 facets of the JSS considered within the profession.

Opportunities for autonomy, upward mobility, promotions, and self-esteem were found to be important contributors to JS among medical laboratory technologists in a previous study (11). Our study reveals that medical laboratory technologists were satisfied with their jobs and were relatively more satisfied in terms of promotions, supervision, co-workers, communication, and the nature of the work, but were less satisfied with fringe benefits among the 9 facets of the JSS considered within the profession.

JS among dieticians was reported to be moderate in previous studies (12–14), and they were satisfied with the nature of the work, supervision, communication, benefits, and contingent rewards, but were less satisfied with salary and promotion. Our study also reveals that dieticians were moderately satisfied with their jobs, being relatively more satisfied in terms of supervision, co-workers, communication, and the nature of the work, but less satisfied with promotion among the 9 facets of the JSS considered within the profession.

In a previous study (15), medical imaging practitioners were satisfied with their with their jobs. Our study reveals that medical imaging practitioners were only moderately satisfied

Table 5: Comparisons of job satisfaction based on Job Satisfaction Survey among 8 professions

Facets	OPT	NRS	PST	OCT	MIP	MLT	EHO	DTC
Pay	15.70 (2.26) M	14.50 (3.27) M	13.45 (2.95) M	14.45 (1.57) M	13.10 (2.89) M	14.42 (3.18) M	15.00 (3.29) M	15.89 (1.76) M
Promotion	14.20 (1.39) M	15.40 (1.78) M	12.55 (3.27) D	14.73 (3.47) M	14.10 (2.38) M	16.67 (1.97) S	16.88 (2.17) S	12.67 (3.54) D
Supervision	19.00 (3.74) S	18.40 (2.41) S	17.45 (1.57) S	16.18 (2.44) S	18.60 (1.96) S	19.67 (2.35) S	18.38 (2.67) S	17.33 (1.50) S
Fringe benefits	13.70 (3.09) M	14.40 (1.71) M	12.36 (5.37) D	13.27 (1.42) M	13.30 (2.16) M	12.92 (4.01) D	14.00 (2.67) M	15.67 (1.23) M
Contingent rewards	13.90 (4.15) M	13.60 (3.69) M	13.45 (2.73) M	13.36 (1.69) M	13.40 (1.95) M	15.25 (2.45) M	15.25 (1.91) M	15.78 (1.86) M
Operating condition	14.80 (1.93) M	11.40 (2.46) D	13.73 (1.95) M	12.91 (2.02) D	15.10 (1.97) M	13.83 (3.43) M	11.25 (2.82) D	13.44 (3.09) M
Co-workers	17.20 (2.15) S	15.40 (2.46) M	20.55 (2.81) S	14.91 (1.92) M	16.20 (2.53) S	17.92 (3.26) S	16.13 (2.98) S	16.89 (2.71) S
Nature of work	19.50 (2.12) S	18.50 (3.17) S	19.00 (2.98) S	18.00 (2.93) S	16.00 (2.82) S	19.50 (1.93) S	22.00 (2.25) S	18.00 (1.32) S
Communication	17.80 (3.16) S	17.20 (2.44) S	17.64 (2.77) S	14.64 (2.77) M	14.70 (2.58) M	19.17 (2.76) S	15.75 (2.49) M	16.22 (1.86) S
Overall	145.90 (14.44) S	139.00 (13.09) M	138.82 (19.63) M	131.27 (9.85) M	134.70 (10.13) M	149.33 (13.21) S	143.88 (12.42) M	141.56 (7.83) M

The Job Satisfaction Survey scores are expressed in mean (SD) and classified as dissatisfaction (D), moderate (M), and satisfaction (S) based on the mean values. Abbreviation: OPT = optometrist, NRS = nurse, PST = physiotherapist, OCT = occupational therapist, MIP = medical imaging practitioner, MLT = medical laboratory technologist, EHO = environmental health officers, DTC = dietician.

with their jobs. This group was relatively more satisfied in terms of supervision, co-workers, and the nature of the work among the 9 facets of the JSS considered within the profession.

In previous studies (16–18), environmental health officers were only moderately satisfied with the organisation or supervision. Our study reveals that environmental health officers were moderately satisfied with their jobs. This group was relatively more satisfied in terms of promotion, supervision, co-workers, and the nature of the work, but was less satisfied with operating conditions among the nine facets of the JSS considered within the profession.

In a previous study (9), optometrists were dissatisfied with payment, co-workers, job security, working hours, supervision, and variety in the job. Our study reveals the second-highest scores in JS for optometrists compared with 7 other professions in terms of payment, co-workers, and supervision. Meanwhile, optometrists were relatively more satisfied in terms of supervision, co-workers, the nature of the work and communication among the 9 facets of JSS considered within the profession.

All of these findings might be due to country-specific and policy differences in organisations compared with previous studies. Spector (1)

also stated that country-specific differences indeed influence the JS level, based on his study comparing the global JS level measured using the JSS in 4 different countries: the Dominican Republic, Hong Kong, Singapore, and the United States. He found that the pattern of overall JS and the 9 facets considered in the JSS varied in all 4 countries. Under the 10th Malaysia Plan, allocation is emphasised for the construction of hospitals and clinics around Malaysia to ensure that citizens can access health care services. Our study may provide important information regarding JS among health care professionals, which could be an important factor contributing to a better understanding of high-quality health care delivery for health care policy makers, institutes of higher education, and potential candidates who would choose health care as their career in Malaysia.

One major limitation of the study was obtaining approval for organisational participation because JS among workers was perceived as a sensitive issue in organisations. Thus, much time and effort were invested in explaining the purpose of this study and convincing the relevant parties that the data given by the respondents about their JS would be kept confidential. Furthermore, there were private organisations that strictly prohibited this study from being conducted on their employees because of the sensitive issues in JS itself as well as interference with their workflow. One of the limitations in this study is that our sample size of 81 was relatively small due to the limited resources available. A larger sample size in future research might draw a more conclusive comparison of JS.

Conclusion

The JS levels were different among health care professionals in private (non-government) settings in the Klang Valley. Differences in JS were found in terms of promotion, supervision, operating conditions, co-workers, the nature of the work, and communication, but not in terms of pay, fringe benefits, and contingent rewards among the 8 health care professions. It is recommended that all organisations providing health care services in Malaysia be encouraged to conduct JS surveys among their health care professionals to improve the services provided to patients by early intervention in any dissatisfaction expressed towards various facets of the job.

Authors' Contributions

Conception and design, analysis and interpretation of the data, drafting and final approval of the article: AHC, SNJ, ARMN
Obtaining of funding, provision of study materials, statistical expertise, administrative, technical, or logistic support: AHC
Collection and assembly of the data: SNJ
Critical revision of the article: AHC

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References

1. Spector PE. *Job satisfaction: Application, assessment, causes, and consequences*. London (GB): Sage Publication, Inc.; 1997.

2. Moorhead G, Griffin RW. *Organizational behavior*: *Managing people and organizations*. 2nd ed. Boston (MA): Houghton Mifflin; 1989.

3. Diaz-Serrano L, Cabral Vieira JA. Low pay, higher pay and job satisfaction within the European Union: Empirical evidence from fourteen countries. Boon (DE): Institute for the Study of Labor (IZA); 2005. IZA discussion paper no. 1558.

4. Gazioglu S, Tansel A. Job satisfaction in Britain: Individual and job-related factors. *Appl Econ*. 2002;**38(10)**;1163-1171.

5. Pillay R. Work satisfaction of professional nurses in South Africa: A comparative analysis of the public and private sectors. *Hum Resour Health*. 2009;7:15.

6. Lyons KJ, Lapin J, Young B. A study of job satisfaction of nursing and allied health graduates from a Mid-Atlantic university. *J Allied Health*. 2003;**32(1)**: 10-17.

7. Adams A, Bond S. Hospital nurses' job satisfaction, individual and organizational characteristics. *J Adv Nurs*. 2000;**32(3)**:536-543.

8. Kaplan RA, Boshoff AB, Kellerman AM. Job involvement and job satisfaction of South African nurses compared with other professions. *Curationis*. 1991;**14(1)**: 3-7.

9. Freeborn DK, Hooker RS. Satisfaction of physician assistants and other nonphysician providers in a managed care setting. *Public Health Rep*. 1995;**110(6)**:714-719.

10. Eker L, Tuzun EH, Daskapan A, Surenkok O. Predictors of job satisfaction among physiotherapists in Turkey. *J Occup Health*. 2004;**46(6)**;500-505.

11. Broski DC, Cook S. The job satisfaction of allied health professionals. *J Allied Health*. 1978;**7(4)**:281-287.

12. Pratt PE, Kwon J, Rew ML. Perceived job importance and job performance satisfaction of selected clinical nutrition management responsibilities. *J Am Diet Assoc*. 2005;**105(7)**:1128-1133.

13. Sauer K, Shanklin C, Canter D, Angell K. Development of a proposed methodology for assessing career development of registered dieticians. *J Am Diet Assoc*. 2007; **107(8 Suppl)**:A15.

14. Stone PK, Vaden AG, Vaden RE. Dietitians in the early establishment stage of their careers. II. Correlates of career motivation and satisfaction. *J Am Diet Assoc*. 1981;**79(1)**:37-44.

15. Crawford J, Gressley D. Job satisfaction in the medical imaging profession: Alleviating the shortage of personnel. *Radiol Manage*. 1993;**15(2)**:35-40.

16. Lambeth JD. A study of the job satisfaction of public health sanitarians in six southern states. *J Environ Health*. 1987;**49(5)**:270-273.

17. Oleckno WA, Blacconiere M. Job satisfaction among environmental health professionals: An examination of descriptors, correlates and predictors. *J Environ Health*. 1993;**55(4)**;10-15.

18. Zontek TL, DuVernois CC, Ogle BR. Job satisfaction and issues related to the retention of environmental health professionals in North Carolina. *J Environ Health*. 2009;**72(3)**;10-15.

19. Van Saane N, Sluiter JK, Verbeek JH, Frings-Dresen MH. Reliability and validity of instruments measuring job satisfaction—A systematic review. *Occup Med (Lond)*. 2003;**53(3)**:191-200.

20. Nunnally JC. *Psychometric theory*. 2nd ed. New York (NY): McGraw-Hill; 1978.

21. Smith PC, Kendall LM, Hulin CL. *The measurement of satisfaction in work and retirement: A strategy for the study of attitudes*. Chicago (IL): Rand McNally; 1969.

22. Fisher WP Jr. Rating scale instrument quality criteria. *Rasch Meas Trans*. 2007;**21(1)**:1095.

23. Bond TG, Fox CM. *Applying the Rasch model. Fundamental measurement in the human sciences*. 1st ed. Mahwah (NJ): Lawrence Erlbaum Associates; 2001.

Original Article

The Prevalence of Cardiovascular Risk Factors in the Young and Middle-Aged Rural Population in Sarawak, Malaysia

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Abstract

***Background*: Coronary heart disease (CHD) was the second leading cause of death in Malaysia in 2006. CHD has known risk factors including hypertension, diabetes mellitus, and obesity.**

***Methods:* This cross-sectional study examined the prevalence of cardiovascular risk factors among 260 participants aged 20 to 65 years in a rural community in Sarawak.**

***Results:* The prevalences of overweight and obesity in this study were 39.6% and 11.9%, respectively. Approximately 13% of participants had hypertension, and 1.5% had a random blood sugar greater than 11.1 mmol/L. Chi-square tests showed significant associations between obesity and gender (P = 0.007), low high-density lipoprotein cholesterol and race (P = 0.05), high total cholesterol and age (P = 0.007), age and hypertension (P = 0.011), smoking and gender (P < 0.001), and smoking and income (P = 0.050). Age-adjusted logistic regression showed that women were 0.246 times more likely to be obese, that older participants (> 45 years) were 0.395 times more likely to have high cholesterol and that those with a higher monthly household income (> RM830) were 2.471 times more likely to smoke.**

***Conclusion:* These findings indicate that we should be concerned about the high rates of overweight in this rural community to prevent obesity.**

Keywords: *adult, cardiovascular diseases, epidemiology, obesity, prevalence, risk factors*

Introduction

The World Health Organisation (WHO) reported that cardiovascular diseases (CVD) caused 17.1 million deaths globally in 2004 and that 82% of these deaths took place in low- and middle-income countries (1). Of these deaths, 7.2 million were due to coronary heart disease (CHD), and another 5.7 million were due to stroke. The WHO also projected that Southeast Asia would have the largest percentage increase in CVD-related deaths by 2030 (1). CVD continues to exact a heavy burden in Malaysia. A study in one rural community in Peninsular Malaysia found that 26.3% of participants aged 15 years and older had hypertension (2). In another study, the prevalence of obesity was found to be 11.4% (3). Chia and Pengal (4) found that among 1417 participants aged 55 years and older in a semirural community in Malaysia, 34.9% were smokers, 18.8% had hypertension, 10.7% had diabetes mellitus, and 63.1% had total serum cholesterol levels greater than the desired upper limit of 5.2 mmol/L.

Hypertension, hypercholesterolaemia, and obesity are known risk factors for CHD. Rampal et al. (5) found a significant association between obesity and age, gender, ethnicity, urban/rural status, and smoking status. In urban China, being married was associated with the number of cigarettes smoked, while those with more education smoked significantly fewer cigarettes. In addition, participants with higher total family financial assets smoked less than participants with an average income did (6).

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(NCD) Surveillance 2005/2006 (7) reported that the prevalence of physical inactivity was 60.1%; smoking, 25.5%; obesity, 16.3%; central obesity, 48.6%; hypertension, 25.7%; elevated blood glucose (including cases of known diabetes mellitus and high fasting plasma glucose), 11%; and hypercholesterolaemia, 53.5%. Heart disease was the second leading cause of death in 2006, accounting for 15.5% of individuals who died in Malaysian government hospitals (8). Although CVD can be prevented and treated, an estimated 17 million people die of it every year around the world (9).

There is information about CVD in Malaysia, and studies have shown that CVD risk factors are seen in rural (2) and semirural communities (4). However, there is a relative lack of published information on this issue in Sarawak, especially among the major native groups in the rural community. The objective of this study was to determine the prevalence of CVD and CVD risk factors in the rural community of Sarawak.

Subjects and Methods

This study was conducted in a rural community of the Serian district of Sarawak. Sarawak is one of the states of Malaysia, situated on the Borneo Island. The Serian district is 1 of the 3 districts of the Samarahan division, which has 203 villages with a total population of 80 200. The highest proportion of the population comprises the Bidayuh group, followed by the Iban, the Chinese, the Malays, and other races (10). The primary focus of this study was the major native groups, as they are considered to have similar socio-economic characteristics. Thus, Chinese individuals and other races were excluded. This was a cross-sectional study using stratified proportionate fixed random sampling. This study was approved by the Ethics Committee of Universiti Malaysia Sarawak and and conformed to the requirements for ethical procedures for research in Malaysia.

Eight villages, including 3 Bidayuh, 3 Iban, and 2 Malay villages, were randomly selected. The total number of households was similar for each ethnic group. Therefore, two Malay villages were included (n = 1075). Once the villages were selected, a preparatory meeting was held with each village headman to obtain permission and to provide information about the survey. Every 4th house of each village was visited, and all eligible occupants of the household present at the time of the visit were interviewed. If the selected house was not occupied, the 3rd or the 5th house was included in the study. A total of 304 participants from 269 households were interviewed.

The age of the participants ranged from 20 to 65 years. Participants were included if they had not been diagnosed with hypertension, myocardial infarction, or angina pectoris. After informed consent was obtained, a trained research assistant (a trained nurse) used a pre-tested and structured questionnaire to interview the participants. The questionnaire asked for sociodemographic data, blood pressure (BP) measurements, smoking status, height, and weight. BP, weight, and height were measured by trained nurses. All anthropometric measurements, BP measurements, and blood specimens were obtained at the village community halls at a pre-arranged date and time. We collected random, rather than fasting, blood sugar because asking the participants to fast was deemed inappropriate; some of the villages were remote and road conditions were poor, so it was hard to ascertain the time of arrival of the research team.

BP was measured using an Accoson mercury sphygmomanometer (AC Cossor & Son [Surgical] Ltd, Essex, GB) while the participant was seated. The Malaysian Hypertension Consensus Guidelines (11) on the measurement of BP were used. The average of 2 BP measurements was used in the statistical analysis. Height was measured using a Seca body meter (Seca, JP), which was suspended upright against a straight wall. Each participant stood underneath the body meter, and the measuring beam was pushed down to rest on top of the participant's head. The visual display recorded the height to the nearest 0.1 cm. Participants were weighed in their street clothing without shoes using a calibrated Seca weighing scale (Seca, JP). Weight was recorded to the nearest 0.1 kg.

Blood samples were collected by a trained laboratory assistant; 5 mL of blood for cholesterol tests and 2 mL of blood for random blood sugar testing were drawn from the median cubital vein. All of the blood tests were conducted in the medical laboratory of Universiti Malaysia Sarawak. The blood was spun in a centrifuge at 1370 g for 5 minutes to obtain the serum, and total cholesterol, high-density lipoprotein cholesterol (HDL), and glucose were measured using a Hitachi 902 Automatic Analyser (Boehringer Mannheim Diagnostics, Indianapolis, IN, US).

Participants who had smoked in the last month were considered current smokers (4).

Hypertension was defined as BP ≥ 140/90 mmHg (11). Hypercholesterolaemia was defined as total cholesterol ≥ 5.2 mmol/L, and low HDL as HDL < 1.04 mmol/L (12). Impaired plasma glucose was defined as random plasma glucose ≥ 11.1 mmol/L (13). Participants with a body mass index (BMI) of 25 to 29.9 kg/m² were considered overweight, and those with a BMI of ≥ 30 kg/m² were considered obese (14). SPSS version 17 (SPSS Inc., Chicago, IL, US) was used to analyse the data. Between-group comparisons of categorical variables were performed using chi-square tests. Binary logistic regression analyses were performed to identify factors associated with high total cholesterol, low HDL, and obesity.

Results

A total of 304 participants provided consent and participated in the interview. However, 44 did not show up for blood tests and anthropometric and BP measurements; therefore, the final analysis was based on 260 (85.5%) participants. The sociodemographic data for the 44 excluded participants were similar to those of the participants included in the final analysis. Of the 260 participants, 34.6% (n = 90) were male and 65.4% (n = 170) were female. There were almost equal numbers of participants from the 3 indigenous groups (Malay, 32.3%, n = 50; Bidayuh, 33.1%, n = 65; Iban, 34.6%, n = 74). The mean age was 44.3 years (SD 9.8) and ranged from 20 to 65 years. More than 30% (n = 98) of the participants were farmers, 11.9% (n = 31) were labourers, 29.6% (n = 77) were housewives, and the rest were government employees or employed in some other occupation. Examining each indigenous group, 60% of Iban participants, 43% of Bidayuh participants, and 8.3% of Malay participants were farmers. The mean reported household income was RM643 with a standard deviation of RM559.1 (USD196, SD 170.3). Based on the poverty line index (PLI) of RM830 in Sarawak (15), 72.7% (n = 189) of the participants lived below the PLI. A higher percentage of Iban participants (82.2%) lived below the PLI compared with Bidayuh (75.6%) and Malay participants (59.5%). The male participants were slightly older than the female participants (mean age 47.0 years, SD 9.8, compared with 42.9 years, SD 9.2), but all of the other risk factors were comparable between the genders in this study.

Table 1 shows the demographic characteristics and means of some CVD risk factors of the participants.

Using the World Health Organization's cut-off points (14), 48.5% (n = 126) of participants were of normal weight, 39.6% (n = 103) were overweight, and 11.9% (n = 31) were obese. The percentage of participants with hypertension was 13.6% (n = 36), and 15.4% (n = 40) of the participants were current smokers. More than 26% (26.5%, n = 69) had a total cholesterol ≥ 5.2 mmol/L, 37.3% (n = 97) had low HDL cholesterol (≤ 1.04 mmol/L), and only 1.5% of participants had a random blood sugar higher than 11.1 mmol/L.

The associations between sociodemographic characteristics and hypertension, BMI, total cholesterol, high-density lipoprotein, and smoking status were analysed using chi-square tests. The results showed significant differences in the rates of obesity according to gender (χ^2 = 7.33, df = 1, P = 0.007), in the rates of hypertension (χ^2 = 6.54, df = 1, P = 0.01) and levels of total cholesterol (χ^2 = 7.34, df = 1, P = 0.07) according to age, as well as in the rates of low HDL according to race (χ^2 = 6.01, df = 1, P < 0.05) (Table 2).

Table 1: Means of cardiovascular disease risk factors

Parameter	All (n = 260)		Males (n = 90)		Females (n = 170)	
Age (years)	44.3	(9.8)	47.0	(9.2)	42.9	(9.8)
Systolic blood pressure (mmHg)	118.7	(16.5)	118.6	(11.9)	118.7	(18.5)
Diastolic blood pressure (mmHg)	76.3	(10.1)	76.9	(9.0)	75.9	(10.6)
Total cholesterol (mmol/L)	4.8	(1.2)	4.7	(1.0)	4.9	(1.3)
HDL cholesterol (mmol/L)	1.3	(0.9)	1.20	(0.7)	1.3	(1.0)
Random blood sugar (mmol/L)	4.1	(1.5)	4.3	(1.9)	3.9	(1.2)
Body mass index (kg/m²)	25.1	(4.1)	25.3	(4.5)	24.4	(3.1)
Waist circumference (cm)	81.7	(11.4)	81.1	(10.9)	83.0	(12.3)

Data are expressed in mean (SD).

Logistic regression was undertaken to examine the impact of gender, race, and income on each of the cardiovascular risk factors: obesity, low HDL, high total cholesterol, and smoking status. Table 3 shows the results of this analysis. After adjusting for age, only 3 models containing all predictors were statistically significant—obesity, χ^2 (5, 260) = 10.303, P = 0.05; high total cholesterol, χ^2 (5, 260) = 13.824, P = 0.017; and smoking status, χ^2 (5, 260) = 8.891; P < 0.001—indicating that these models were able to distinguish participants who had the risk factors from those who did not.

Table 3 shows that gender was significantly associated with obesity. The odds ratio or Exp (B) value for gender was 0.246, indicating that female participants were 0.246 times more likely to be obese than male participants. Participants older than 45 years were 0.395 times more likely to have high total cholesterol than participants younger than 45 years old were. This study also found that participants who earned a monthly income of more than RM830 were 2.471 times more likely to be current smokers than those with a lower income.

Table 2: Association of sociodemographic characteristics and hypertension, obesity, high total cholesterol, low high-density lipoprotein (HDL), and smoking

Parameter	*n*	Hypertension	Obesity	High total cholesterol	Low HDL	Smoking
Gender						
Male	90	12.2 (5.3–19.1)	4.0 (0.1–8.8)	21.1 (12.5–29.7)	38.9 (28.6–49.2)	15.8 (14.9–16.9)
Female	170	14.7 (9.3–20.1)	15.9 (10.3–21.4)	29.4 (22.5–36.3)	36.7 (29.2–43.8)	19.0 (19.6–20.0)
P value		0.581	0.007 [a]	0.149	0.701	< 0.001 [a]
Race						
Malay	84	10.7 (4.0–17.5)	14.3 (6.7–21.9)	30.6 (20.9–41.1)	31.0 (20.9–41.1)	18.8 (18.1–19.5)
Iban	90	17.8 (9.7–25.8)	10.0 (3.7–16.3)	22.2 (13.4–31.0)	33.3 (23.4–43.3)	17.9 (17.0–18.7)
Bidayuh	86	12.8 (5.6–20.0)	11.6 (4.7–18.5)	26.7 (17.2–36.3)	47.7 (36.9–58.4)	18.7 (18.0–19.4)
P value		0.380	0.680	0.427	0.050 [a]	0.174
Age						
≤ 45 years	138	8.7 (3.9–13.5)	13.8 (8.0–19.6)	11.9 (11.2–12.6)	16.3 (15.6–17.2)	18.5 (17.9–19.1)
≥ 46 years	122	19.6 (12.5–26.8)	9.8 (4.5–15.2)	13.4 (12.6–14.3)	16.1 (15.3–17.0)	18.3 (17.7–19.0)
P value		0.011 [a]	0.329	0.007 [a]	0.703	0.672
Income						
≤ RM830	189	13.7 (8.8–18.7)	10.6 (6.2–15.0)	27.0 (20.5–33.4)	39.7 (32.6–46.7)	18.7 (18.2–19.2)
> RM830	71	14.1 (5.8–22.4)	15.5 (6.9–24.1)	25.4 (15.0–35.7)	40.0 (20.0–42.0)	17.7 (16.8–18.7)
P value		0.946	0.276	0.791	0.196	0.050 [a]

Data are expressed in percentage (95% confidence interval). High total cholesterol was defined as total cholesterol ≥ 5.1 mmol/L. Low HDL was defined as HDL ≤ 1.4 mmol/L.
[a] Significant different (P < 0.05) by chi-square test.

Table 3: Binary logistics regression analysis for cardiovascular risk factors

Variable	*n*	Obesity [a]		Low HDL [b]		High total cholesterol [c]		Smoking [d]	
		%	OR (95% CI, *P* value)	%	OR (95% CI, *P* value)	%	OR (95% CI, *P* value)	%	OR (95% CI, *P* value)
Gender									
Male	90	51.1	1.0	38.9	1.0	21.1	1.0	41.6	–
Female	170	32.4	0.246 (0.082–0.740, 0.013 [e])	36.7	1.014 (0.581–1.770, 0.923)	29.4	0.557 (0.293–1.057, 0.073)	1.8	–
Race									
Malay	84	46.4	1.0	31.0	1.0	30.6	1.0	11.9	1.0
Iban	90	46.3	0.928 (0.364–2.365, 0.875)	33.3	0.516 (0.270–0.985, < 0.05 [e])	22.2	1.133 (0.561–2.288, 0.727)	21.1	1.272 (0.499–3.245, 0.615)
Bidayuh	86	23.3	0.775 (0.289–2.075, 0.611)	47.7	0.524 (0.281–0.978, < 0.05 [e])	26.7	0. 615 (0.298–1.270, 0.189)	12.8	0.510 (0.223–1.167, 0.111)
Age									
≤ 45 years	138	50.7	1	36.2	1.0	19.6	1.0	14.5	1.0
≥ 46 years	122	52.5	1.235 (0.560–2.772, 0.601)	38.5	0.894 (0.530–1.508, 0.674)	34.4	0.395 (0.220–0.712, < 0.05 [e])	16.4	0.827 (0.348–1.968, 0.667)
Income									
≤ RM830	189	34.9	1.0	39.7	1.0	27.0	1.0	12.7	1.0
> RM830	71	49.3	0.655 (0.286–1.498, 0.316)	40.0	1.411 (0.773–2.574, 0.262)	25.4	1.146 (0.589–2.229, 0.689)	22.5	2.471 (1.171–5.218, 0.018 [e])

Obesity was defined as BMI ≥ 30 kg/m². High total cholesterol was defined as total cholesterol ≥ 5.1 mmol/L. Low HDL was defined as HDL ≤ 1.4 mmol/L.

[a] After adjusting for age, X^2 (5, 260) = 10.303, P = 0.05, Cox and Snell R square = 0.039, Nagelkerke R squared = 0.075, able to classify 88.1% of the cases.

[b] After adjusting for age, X^2 (5, 260) = 7.47, P = 0.188, Cox and Snell R square = 0.028, Nagelkerke R squared = 0.039, able to classify 63.1% of the cases.

[c] After adjusting for age, X^2 (5, 260) = 13.824, P = 0.017, Cox and Snell R square = 0.052, Nagelkerke R squared = 0.076, able to classify 73.5% of the cases.

[d] After adjusting for age, X^2 (5, 260) = 8.891, P < 0.001, Cox and Snell R square = 0.34, Nagelkerke R squared = 0.58, able to classify 84.6% of the cases.

[e] Significant (P < 0.05) by binary logistic regression test.

Discussion

The prevalence of hypertension in this study was 13.5%. This finding was low compared with the rate of 25.7% found in the Malaysian NCD Surveillance report 2005/2006 (5) and the rate found in another study in a rural community in Selangor, West Malaysia (3). The prevalence of hypertension in this study was also lower than in studies conducted in rural communities in other Asian countries and China (16,17). This difference could be related to differences in lifestyle, diet, and genetic composition of the indigenous people in the rural communities of Sarawak. Further studies are needed to explore this finding.

Women, participants who belonged to the Iban ethnic group, and participants older than 45 years of age were found to have higher rates of hypertension in this study. Other studies in Malaysia and other Asian countries also reported that the prevalence of hypertension increased

with age (3,16–18). Our finding that women were more likely to have hypertension was inconsistent with a national study from Malaysia (18) and some studies in other Asian countries (16,17); however, another study (3) showed a higher prevalence of hypertension in women. The 13.5% of participants who were found to have hypertension reported that they were unaware of their condition. This finding is concerning, and future studies need to be conducted to investigate the detection of hypertension in rural communities.

Obesity is a well-documented risk factor for hypertension, cardiovascular disease, type 2 diabetes mellitus, cerebrovascular accidents, and the development of numerous types of cancer (14). In this study, 11.9% of the participants were obese, and 39.6% were overweight. Overweight and obese individuals are found equally in urban and rural populations at pervasive rates (19). Two studies found that rural populations in Malaysia were affected by overweight and obesity (20,21). Ng et al. (20) found that 23.5% of men and 46.0% of women were overweight, suggesting that the mild to moderate forms of obesity have reached alarming proportions in rural adult populations. In another study of 4600 rural villagers throughout Peninsular Malaysia, Khor et al. (21) found that 19.8% of men and 28.0% of women were overweight and that 4.2% of men and 11.1% of women were obese. The rate of overweight in this study was higher than in rural studies in other Asian countries including China and India (16,22).

This study found a significant association between BMI and gender. More females than males were obese. Although more Malays and adults 45 years and older were obese, the associations between race, age, and BMI were not statistically significant. This finding was consistent with other local studies (3,23) in which women were found to have a higher prevalence of obesity than that of men. One possible reason could be that women tend to gain weight during the childbearing years (23). Another possibility is that women tend to consume cheaper and less nutritious (more calorie dense) food (24). The higher rate of obesity in Malays may be related to their diet, lifestyle, or genetic factors, and further studies are needed to explore this finding.

The prevalences of smoking (15.4%), hypercholesterolaemia (22.6%), and obesity (11.9%) were all lower than the prevalences reported in the NCD surveillance (smoking, 25.5%; hypercholesterolaemia, 53.5%; obesity, 16.3%) (5). The NCD surveillance included participants from urban areas where the rates of cardiovascular risk factors were higher, and this difference could explain the different prevalences found. In comparison to a rural study in China (16), the current study also found lower rates of cardiovascular risk factors, except for overweight.

This study found that female gender was a predictor for obesity, but this conclusion was not supported by another study (25). Among the Bidayuh and Iban participants in this study, 43% and 60%, respectively, were farmers and were physically active most of the day. However, both groups were at risk of having low HDL. This finding is consistent with another study (26), which showed that increased exercise did not increase HDL. Age greater than 45 years was a predictor for high cholesterol, a finding that was somewhat expected. It has been proposed that aging disrupts lipid homeostasis. In particular, aging affects 3-hydroxy-3-methylglutaryl co-enzyme A reductase, the key rate-limiting enzyme in the cholesterol biosynthetic pathway (27). Gender was excluded from the smoker model because the percentage of female smokers was too small.

This was a preliminary study to explore the prevalence of some modifiable CVD risk factors. This study was carried out in selected villages in the rural areas of the Serian district in Sarawak, so one should only generalise these results to other sites with similar sociodemographic characteristics. We measured random, rather than fasting, cholesterol and glucose as a preliminary screen that only provided initial information about the participants. Further comprehensive diagnostic measures would be needed to confirm elevated blood glucose in the participants if the results obtained were above the recommended range.

Conclusion

The prevalence of some cardiovascular risk factors such as smoking, hypercholesterolaemia, elevated blood glucose, and hypertension were lower in this rural community, but the prevalence of overweight was rather high. Being female, belonging to the Iban and Bidayuh groups, and being older than 45 years were predictors for obesity, low HDL, and high total cholesterol, respectively. Individuals who were not extremely poor were more likely to smoke. Health promotion, increased public health capacity, and improved infrastructure are needed in rural areas to provide adequate surveillance and continuous monitoring of the health status of rural villagers and to promote healthy lifestyle practices.

Further longitudinal studies will be needed to obtain an accurate picture of the risk factors for cardiovascular disease.

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Authors' Contributions

Conception and design, obtaining of funding, provision of study materials, collection and assembly of the data, statistical expertise, administrative, technical, or logistic support: CTC Analysis and interpretation of the data, drafting, critical revision, and final approval of the article: CTC, PYL, WLC

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References

1. *Cardiovascular diseases (CVDs)* [Internet]. Geneva (CH): World Health Organization: 2009 [cited 15 Sep 2010]. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/index.html.
2. Yussof K. Defining risks and their implications. *Med J Malaysia*. 1996;**51(3)**:305–306.
3. Mohd Yunus A, Sherina MS, Nor Afiah MZ, Rampal L, Tiew KH. Prevalence of cardiovascular risk factors in rural community in Mukim Dengkil, Selangor. *Mal J Nutr*. 2004;**10(1)**:5–11.
4. Chia YC, Pengal S. Cardiovascular disease risk in a semirural community in Malaysia. *Asia-Pacific J Public Health*. 2009:**21(4)**:410–420.
5. Rampal L, Rampal S, Khor GL, Zain AM, Ooyub SB, Rahmat RB, et al. A national study on the prevalence of obesity among 16,127 Malaysians. *Asia Pac J Clin Nutr*. 2007;**16(3)**:561–566.
6. Pan Z. Socioeconomic predictors of smoking and smoking frequency in urban China: Evidence of smoking as a social function. *Health Promot Int*. 2004;**19(3)**:309–315.
7. Disease Control Division, Ministry of Health Malaysia. *Overview NCD risk factors in Malaysia*. Kuala Lumpur (MY): Ministry of Health Malaysia; 2006.
8. Rise in heart disease a worry. *New Strait Times* [Internet]. 2008 Apr 5 [cited 2010 Jul 10]; Main Section, p 18. Available from: http://www.nib.com.my/.
9. Mackay J, Mensah G. *The atlas of heart disease and stroke* [Internet]. Geneva (CH): World Health Organization; 2004 [cited 2010 Jul 10]. Available from http://www.who.int/cardiovascular_diseases/resources/atlas/en/.
10. Serian District Council [Internet]. Sarawak (MY): Serian District Council; 2010 [cited 2010 Jul 10]. Available from: http://www.seriandc.sarawak.gov.my/.
11. Hypertension Guideline Working Group. *Clinical practice guidelines: Management of hypertension*. 3rd ed. Kuala Lumpur (MY): Ministry of Health Malaysia; 2008.
12. National Cholesterol Education Programme Adult Treatment Panel III. *Report of the expert panel on the detection, evaluation and treatment of high cholesterol in adults*. Kuala Lumpur (MY): National Institute of Health; 2001.
13. Clinical Practice Guideline Task Force. *Clinical practice guidelines: Management of type II diabetes mellitus*. 4th ed. Kuala Lumpur (MY): Ministry of Health Malaysia; 2009.
14. *Obesity and overweight* [Internet]. Geneva (CH): World Health Organization; 2009 [cited 2009 Jul 16]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html.
15. Mat Zin R. Understanding the formulation of the revised poverty line in Malaysia. *Akademika*. 2007; **70(1)**:21–39.
16. Hoang VM, Soonthornthada K, Ng N, Juvekar S, Abdur Razzaque, Ashraf A, et al. Blood pressure in adult rural INDEPTH population in Asia. *Glob Health Action*. 2009:**2**;60–67.
17. Gu D, Gupta A, Muntner P, Hu S, Duan X, Chen J, et al. Prevalence of cardiovascular disease risk factor clustering among the adult population of China: Results from the International Collaborative Study of Cardiovascular Disease in Asia (InterAsia). *Circulation*. 2005;**112(5)**:658–665.
18. Rampal L, Rampal S, Azhar MZ, Rahman AR. Prevalence, awareness, treatment and control of hypertension in Malaysia: A national study of 16,440 subjects. *Public Health*. 2008;**122(1)**:11–18.
19. Lim TO, Ding LM, Zaki M, Suleiman AB, Fatimah S, Siti S, et al. Distribution of body weight, height and body mass index in a national sample of Malaysian adults. *Med J Malaysia*. 2000;**55(1)**:108–128.
20. Ng KWT, Tee ES, Rosman A. Rural communities in nutritional transition: Emergence of obesity, hypertension and hypercholesterolemia as public health problems in three kampungs in Bagan Datoh, Perak. *Malaysia J Nutr*. 1995;**1(2)**:129–139.

21. Khor GL, Azmi MY, Tee ES, Kandiah M, Huang MSL. Prevalence of overweight among Malaysian adults from rural communities. *Asia Pacific J Clin Nutr*. 1999;**8(4)**:272–279.

22. Chow C, Cardona M, Raju PK, Iyengar S, Sukumar A, Raju R, et al. Cardiovascular disease and risk factors among 345 adults in rural India—The Andhra Pradesh Rural Health Initiative. *Int J Cardiol*. 2007;**116(2)**:180–185.

23. Ministry of Health Malaysia. *Report of the Third National Health and Morbidity Survey*. Kuala Lumpur (MY): Institute for Public Health, Ministry of Health Malaysia; 2006.

24. Siega-Riz AM, Evenson KR, Dole N. Pregnancy-related weight gain—A link to obesity? *Nutr Rev*. 2004;**62(7 Pt 2)**: S105–S111.

25. Shahwan-Akl L. Cardiovascular disease risk factors among adult Australian-Lebanese in Melbourne. *Int J Res Nursing*. 2010;**6(1)**: 1–7.

26. Thompson PD, Rader DJ. Does exercise increase HDL cholesterol in those who need it the most? *Arterioscler Thromb Vasc Biol*. 2010;**21(7)**:1097–1098.

27. Laura Trapani L, Pallottini V. Age-related hypercholesterolemia and HMG-CoA reductase dysregulation: Sex does matter (a gender perspective). *Curr Gerontol Geriatr Res*. 2010:420139.

Original Article

Perceived Effects of the Malaysian National Tobacco Control Programme on Adolescent Smoking Cessation: A Qualitative Study

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Abstract

Background: **The prevalence of teenage smoking has decreased over the past decade following the implementation of the national tobacco control programme. However, the effect of the programme on smoking cessation in teenagers has not been determined.**

Methods: **Twenty-eight participants (12 teenagers, 8 teachers, and 8 doctors) were interviewed using 5 in-depth interviews and 3 group discussions. Social cognitive theory (SCT) was applied as the theoretical framework. Semi-structured interview protocols were used, and thematic analysis and analytic generalisation utilising SCT were performed.**

Results: **The current national tobacco control programme was found to be ineffective in promoting smoking cessation among teenagers. The participants attributed the ineffective campaign to the followings: inadequacy of message content, lack of exposure to the programme, and poor presentation and execution. In addition, the participants perceived the developed tobacco control policies to be a failure based on poor law enforcement, failure of retailers to comply with the law, social availability of cigarettes to teenagers, and easy availability of cheap, smuggled cigarettes. This study highlighted that the programme-related problems (environmental factors) were not the only factors contributing to its perceived ineffectiveness. The cunning behaviour of the teenagers (personal factor) and poor self-efficacy to overcome nicotine addiction (behavioural factor) were also found to hinder cessation.**

Conclusion: **Tobacco control programmes should include strategies beyond educating teenagers about smoking and restricting their access to cigarettes. Strategies to manage the cunning behaviour of teenagers and strategies to improve their self-efficacy should also be implemented. These comprehensive programmes should have a foundation in SCT, as this theory demonstrates the complex interactions among the environmental, personal, and behavioural factors that influence teenage smoking.**

Keywords: *adolescent, health campaigns, qualitative research, tobacco cessation, tobacco smoking*

Introduction

In the last decade, the prevalences of teenage smoking in developed countries, such as the United States, England, and Australia, have decreased. The prevalences, however, have remained stable for the past few years (1–3). The decline in teenage smoking that has been observed over the last decade can be attributed to the implementation of comprehensive national tobacco control programmes in these countries (2–4).

These comprehensive programmes are characterised by an optimal combination of evidence-based and state-wide strategies. These strategies work effectively and synergistically to create smoke-free social norms, promote and assist smoking cessation, and prevent smoking initiation (5). These strategies include increasing the tobacco duty, enforcing policies that prevent youth from accessing tobacco, banning smoking advertisements, developing smoking restrictions in public places, creating effective media campaigns, and formulating other specific prevention and cessation programmes (4,5). A review by Wakefield and Chaloupka (4) showed reductions in teenage smoking in Massachusetts, Oregon, and Florida in the late 1990s as a result

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of these comprehensive programmes. These findings were further supported by Nelson et al. (6), as they found a decrease in the prevalence of teenage smoking from 2003 to 2004 in the United States that coincided with the increase in the price of tobacco and the increase of anti-smoking advertisements directed at teenagers. In addition to the decrease in the prevalence of teenage smoking, public awareness of the danger of smoking has increased due to these programmes, and societal norms regarding cigarette smoking have also changed (4).

A similar decrease in the prevalence of teenage smoking has been observed in Malaysia through several national surveys in the past decade. In 2003, 19.9% of teenagers aged 13 to 15 years old were smokers (7). According to the latest National Health and Morbidity Survey III (NHMS III) in 2006, this percentage declined by more than half, as only 8.7% of teenagers aged 13 to 18 years old were smokers (8). This lower prevalence rate is inconsistent with a number of local studies conducted between 2000 and 2008 that demonstrated the prevalence of smokers to be between 14%–37% (9–16).

In Malaysia, a comprehensive tobacco control programme has existed since 1993 (17,18). This programme includes the Control of Tobacco Product Regulations and its enforcement, the tobacco duty, the national anti-tobacco campaign, school-based programmes, and the quit-smoking clinics. The tobacco control regulations are similar to those in developed countries and include the restriction of smoking in public places, advertisement regulations, display of health warnings on cigarette packs, provision of the tar and nicotine content, and regulation of the sale of tobacco products (17,18). Individuals younger than 18 years old are prohibited from smoking, chewing, buying, or possessing any tobacco products (19). In addition to this regulation, the Malaysian government has also increased the tobacco duty (18). In 2004, the largest national anti-smoking campaign, *Tak Nak* (Say No), was launched. The campaign aimed to educate the nation, especially the younger generation, on the health hazards of smoking through an integrated media approach using television, radio, billboards, and poster advertisements. The Ministry of Education Malaysia plays an important role in executing school-based programmes. These school-based programmes consist of health talks, exhibitions, activities, a peer counselling programme, and more. Despite these initiatives, studies examining their effectiveness in curbing teenage smoking and promoting complete abstinence are still lacking in Malaysia. However, the lower prevalence of teenage smoking reported by the NHMS III was postulated to be due to the effectiveness of the current programmes.

The development of comprehensive tobacco control programmes has been based on various models of health behaviour, such as social cognitive theory (SCT), the health belief model, theory of reasoned action, and theory of planned behaviour (5,20). Many of these models have overlapping constructs or variables that are called different names (21). Among these models, SCT is the most comprehensive model; it describes the importance of how multiple factors (personal or cognitive, behavioural, and social) influence human health behaviour (Figure 1) (21,22). According to SCT, our motivations and actions are pre-conditioned by our cognition (knowledge, perception, and beliefs) (21,22). Therefore, in the context of smoking behaviour, smokers' motivations to quit are determined by their knowledge regarding the dangers of smoking, the perceived benefits of quitting, and their belief in their ability to overcome the barriers to quitting (Figure 1). SCT also explains that our cognition is highly influenced by social structural impediments (barriers) and facilitators, particularly through vicarious or observational learning (20–22). Thus, social factors such as the easy availability of cigarettes, the societal norms of smoking, and the approval of smoking among peers could influence smokers' intention and attempts to quit. Concurrently, perceived self-efficacy and adaptive skills for overcoming barriers are posited as the central factors of behavioural change (21,22). All of these factors reciprocally interact with each other (20,22).

In recent years, there have been many international studies on smoking cessation that have applied SCT as their theoretical framework (23). This suggests that SCT has become a fundamental resource for the development of interventions to curb teenage smoking. Therefore, the current study adopted SCT as its framework to help researchers accomplish the objectives of the study.

The purpose of our study was to determine whether teenagers (smokers and ex-smokers) and adults who were involved in the execution of anti-tobacco strategies (doctors and teachers) found these programmes to be effective for smoking cessation among teenagers. The study also examined the potential limitations of strategies that could hamper their effectiveness. Thus, strategies to improve the programmes could be developed.

Subjects and Methods

Overview of the design

The design of this qualitative research was multiple-case study. According to Yin (24), a case study is a comprehensive research inquiry that incorporates specific methods of data collection (theory-based with multiple sources of evidence) and explicit analysis (cross-case conclusion and analytic generalisation) (24,25). Thus, Yin (24) defines a case study as a systematic research strategy to investigate "a phenomena within its real-life context" rather than an individual object (25). When 2 or more cases are included within the same study, the design is called multiple-case study. In our multiple-case study design, 3 cases (teenagers, teachers, and doctors) were selected based on their roles within the smoking cessation strategies. The teenagers were meant to benefit from the strategies, and the teachers and doctors executed the strategies. The phenomenon of teenage smoking was studied in our research, with the specific context of smoking cessation strategies. In reality, strategies that ensure smoking cessation are not clearly distinguished from the equally important strategies for smoking prevention. Due to these unclear boundaries, a case study inquiry is suitable to obtain informative, in-depth, comprehensive findings.

This study was performed on 28 participants (12 teenagers, 8 teachers, and 8 doctors). The participants were interviewed between January 2008 and August 2009 through 5 in-depth interviews (IDI) and 3 group discussions.

Theoretical framework

SCT was chosen for this study's theoretical framework because of the theory's ability to describe the complex phenomenon of teenage smoking (22). The theory guided researchers in the selection of cases to be studied and in the creation of codes during data analysis (24). For example, during the selection of participants, adults who executed the anti-smoking strategies (acted as facilitators of the behavioural change) were recruited because SCT emphasises the important role of social and structural facilitators in influencing one's behaviour.

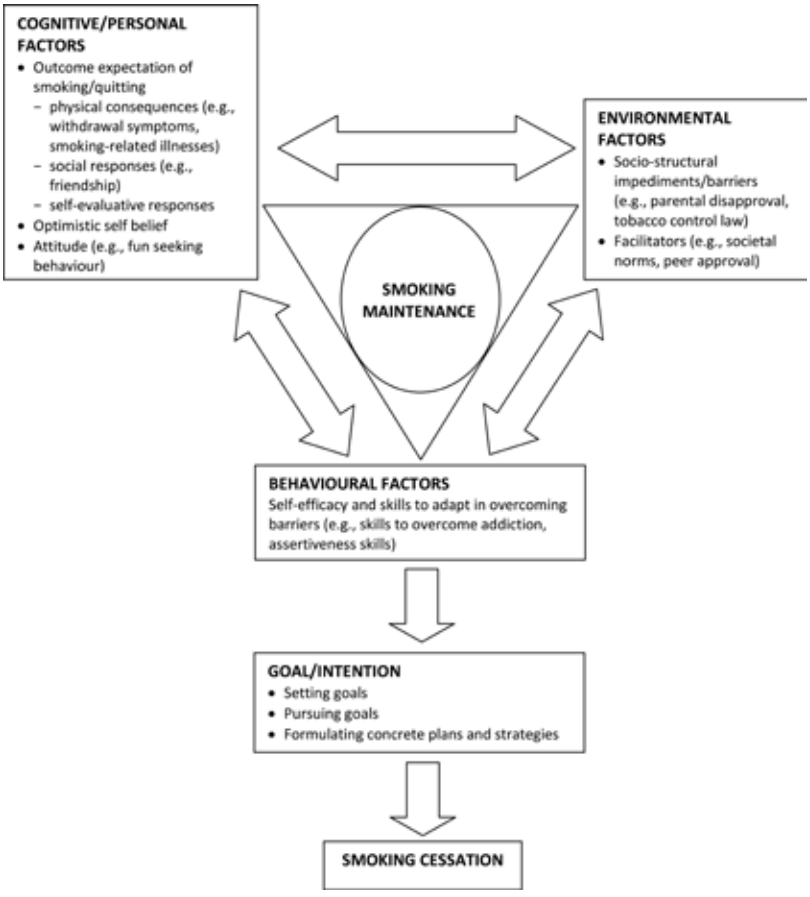

Figure 1: Smoking cessation framework based on social cognitive theory (20–22).

In addition, SCT was used as a template for analytic generalisation. This is a process of comparing the findings of case studies to a developed theory to either confirm replication or to show the need to modify the theory (24).

Sampling procedure

Based on pre-determined criteria, 12 teenagers, 8 doctors, and a school counsellor were selected through purposive sampling, and 7 teachers were recruited through snowball sampling (Table 1). The pre-determined criteria of the participants were teenagers who smoked or had experienced quitting (thus, they were more likely to know which strategies were useful based on their personal experience) (26) and adults (teachers and doctors) who had been involved in promoting strategies to help teenagers quit smoking. These criteria ensured comprehensive, in-depth, and holistic data related to the phenomenon in question.

Because teachers are involved in school-based anti-smoking activities and may have experience in dealing with students who are smokers, 8 teachers from a secondary school in Kuala Lumpur were selected. One of them was a school counsellor who provided counselling to problematic students, including those who smoked.

Similarly, because doctors in community health services commonly address adolescent patients who smoke, 7 primary care doctors from the Universiti Kebangsaan Malaysia Medical Centre were recruited. We thought that their experience in managing these teenagers and their training in general adolescent health would provide different points of view, thus enriching the findings of our study. Another doctor from the Tobacco Unit, Ministry of Health Malaysia, was purposely sampled because of her involvement in developing and implementing the National Tobacco Control Programme in Malaysia.

Twelve 16-year-old students (9 smokers and 3 former smokers) were recruited from the same school where the participating teachers worked. The school was selected due to the high level of anti-smoking activities that had been conducted there in recent years.

The school counsellor who participated in this study was appointed by the school's headmistress. He was recruited during an informal meeting with the main researcher in the study. During this meeting, the purpose of the study was explained, and consent was obtained. The school counsellor was also asked to enlist potential teachers and teenagers who met the pre-determined criteria. The school counsellor distributed letters to the teachers inviting them to participate in the study and to attend a scheduled group discussion. Seven teachers with varying smoking statuses and teaching experience came to the group discussion. This heterogeneity maximised the different perspectives within this group (27).

An informal meeting with the teenagers was subsequently arranged by the school counsellor to brief the students on the study. The main researcher assessed the suitability of the students in participating in the group discussion and IDI. The students were also given packages for their parents that included an acknowledgement letter, an information sheet, and a parental consent form. The parental consent forms were collected prior to the actual interviews.

All of the doctors were enrolled through invitational letters. However, the doctor from the Tobacco Unit, Ministry of Health Malaysia, was initially approached via telephone. Once verbal consent was obtained, a formal invitational letter was mailed to her, and a meeting was scheduled.

Data collection

Before each interview, participants completed written consents and self-administered questionnaires regarding sociodemographic variables. The interviews were guided by a semi-structured interview protocol (Table 2) and conducted mainly in Malay, depending on the comfort level of the participants. Each interview lasted less than 2 hours and was recorded using digital audio recorders. Visual recording was added in the group discussions to identify participants' voices in the audio recordings.

Table 1: The participants' type of interview and method of sampling

Parameter	Doctors		Teachers		Students	
	GD	IDI	GD	IDI	GD	IDI
Number of interviews	1	1	1	1	1	3
Number of participants	7	1	7	1	9	3
Method of sampling	Purposive	Purposive	Snowball	Purposive	Purposive	Purposive

Abbreviation: GD = group discussion, IDI = in-depth interview.

Data analysis

The audio recordings were transcribed into text. All transcripts were cross-checked against the recordings several times to maintain accuracy (24). Thematic analysis of the transcripts was performed using NVIVO 7 (QSR International Pty Ltd, Victoria, AU). The coding was subsequently reviewed by 2 experts in adolescent health to ensure the reliability of the process. The kappa value of agreement in the coding was also calculated using the Cohen kappa formula. The reliability index was maintained above 0.8. A cross-case conclusion was then drawn between the analyses of the cases. After the 7th interview, data saturation was reached. An analytic generalisation, which was performed by mapping the final pattern of findings against SCT, was also performed.

Ethical issues, reliability, and validity

Approval was obtained from the Research and Ethic Committee of the Universiti Kebangsaan Malaysia and the Ministry of Education Malaysia. Permission from the school authority figure was sought before interviewing the teachers and teenagers. In addition, all participants were required to provide written consent before the interviews. Parental consents were also obtained for the teenagers. The teenagers' smoking statuses were kept confidential.

Because converging evidence that was found through triangulation could verify the significance of the detected themes, 2 types of triangulation were performed in this study to increase the validity of the findings (24,25). Triangulation of the multiple sources of data (teenagers, teachers, and doctors) and triangulation of the different methods of data collection (questionnaire, group discussions, and IDIs) were performed. Other means to improve validity and reliability in this study included self-reflection, procedural validity, and good inter-coder agreement (reliability index of above 0.8). Self-reflection allowed the researchers to acknowledge that their own beliefs, perceptions, and past experiences could influence various aspects of the study and result in biases. Therefore, the researchers wrote down their reflections in a journal (28) to help them remain objective throughout the study. Meanwhile, the procedural validity was an interviewing process that ensured rich and unbiased answers from the participants through the intermittent rephrasing of questions, the clarification of statements, and minimal prompting, as necessary (28).

Results

Sociodemographic characteristics of the participants

Twelve students, 8 teachers and 8 doctors were interviewed. Every student was Malay and was 16 years old (Table 3). Nine of the students were male, and 3 were female. Two of the male students and 1 female student were former smokers. The other 9 students were smokers at the time of the study.

Seven of the teachers were Malay, and 1 teacher was Chinese. The teachers were between 23 and 54 years old (Table 3). All of them were male except for 1 female. Four of the teachers,

Table 2: Interview protocol used in the in-depth interviews and group discussions

INTERVIEW PROTOCOL
GOVERNMENT STRATEGIES
1. "What do you think our government has done to make teenagers to stop smoking?"
Discuss the following strategies separately:
a. campaign
b. law and enforcement of law
c. tobacco duty
d. school-based programmes, etc.
2. "Do you think they are effective (to make teenagers to stop smoking)?"
3. "Why are they effective/not effective?"
a. "If they are not effective, what are the problems?"
Explore any issues/ problems raised by the participants in detail
4. "Is there anything else you want to share?"

including the female teacher, were non-smokers; 3 of the teachers were former smokers, and 1 was a smoker at the time of the study.

Similar to the students, all 8 doctors were Malays. However, none of them were smokers or former smokers. The doctors were between 31 and 45 years old (Table 3); 6 were female, and 2 were male.

Participants' perception of the effect of the national tobacco control programme on the cessation of adolescent smoking

The majority of the participants agreed that the national tobacco control programme was ineffective in causing teenagers to quit smoking. This is clearly described by the following excerpts:

> "Putting up posters alone does not guarantee that the message really gets through." (Doctor, male, non-smoker)
>
> "Tobacco duty is not high enough to make teenagers quit smoking."
> (School counsellor, male, ex-smoker)
>
> "It does not matter. Even if the police arrest me, I will still continue smoking." (Teenager, male, smoker)

In fact, some of the teenagers admitted that nothing, except for themselves, could make them quit. One of them said:

> "Nothing [can make us stop smoking]."

However, a number of the participants felt that the anti-smoking campaign and tobacco duty might have positive effects on teenagers' smoking behaviour. They said:

> "They [disseminating knowledge about the impact of smoking] are effective [to teenagers]. If not for all, even if we can attract a percentage of students to stop smoking... those are still results"
> (School counsellor, male, ex-smoker)
>
> "The tax might have some effect in reducing the number of smokers."
> (Teacher, male, non-smoker)

Some participants believed that instead of leading active smokers to quit, the anti-smoking campaign could only prevent smoking initiation in those who had never previously smoked. For example:

> "The campaign is not effective [to cause teenagers to stop smoking], but if we want to prevent teenagers from starting to smoke... it is possible."
> (Teenager, male, ex-smoker)

Even though a number of adult participants felt that the tobacco duty was effective in curbing teenage smoking, the teenagers disagreed. One of them said:

> "Even if they [the Government] make it [the tobacco duty] high, people [teenagers] will still buy [cigarettes]."

Participants' opinions about problems with the anti-smoking campaign

The participants admitted that there were a number of problems with the anti-smoking campaign. These problems could be categorised into inadequacy of message content, lack of exposure to the programme, and poor presentation and execution.

According to the teenagers, repetitively displaying information about the health hazards of smoking through the campaign was not effective in making them quit. In fact, they believed that they were already well-informed about these

Table 3: Sociodemographic characteristics of the participants

Parameter	Doctors		Teachers		Students	
	GD	IDI	GD	IDI	GD	IDI
Age (years)	31–35	45	23–54	25	16	16
Gender						
Female	5	1	1	-	-	3
Male	2	-	6	1	9	-
Race						
Malay	7	1	6	1	9	3
Chinese	-	-	1	-	-	-
Smoking status						
Non-smoker	7	1	4	-	-	-
Smoker	-	-	1	-	7	2
Ex-smoker	-	-	2	1	2	1

Abbreviation: GD = group discussion, IDI = in-depth interview.

health hazards. More importantly, they felt that the campaign lacked information about how to quit.

> "[They do not show] how to quit smoking. They only… give talks… just talks… and put up posters [showing 'smoking is dangerous for your health']."

Consequently, the teenagers relied on methods suggested by their friends for quitting, and these were often ineffective. Several examples of these methods for quitting included drinking a lot of water, chewing gum, and eating sweets. One of the teenagers explained:

> "'You should do this… take sweets,' said my friend who taught me [how to quit smoking]… 'You should drink water… it will surely work.'"

Many of the participants thought the effort put into the campaign advertisements and activities was inconsistent. They felt that the strategies were not extensive and failed to reach all teenagers throughout the country. Examples of the excerpts are as follows:

> "We always concentrate on teenagers at school. We should not forget teenagers who do not go to school [drop-out and expelled teenagers]."
>
> (Doctor, male, non-smoker)
>
> "There are programmes specific for school students… but they need to be strengthened. A lot more need to be done. At this moment, the programmes are carried out only in selected states."
>
> (Doctor from the Tobacco Unit, female, non-smoker)

Additionally, the participants, particularly the teenagers, felt that the campaign advertisements and activities (mainly talks and exhibitions) were uninteresting. Therefore, the campaign did not attract the attention and participation of the participants. One of the teenagers said:

> "I felt sleepy when they were talking."

Similarly, some of the participants thought that the advertisement designs had flaws. They believed that the image of cigarettes in the advertisements could provide cues for smoking, thus further triggering their urge to smoke. One of the teachers who was an active smoker said:

> "Once, I actually stopped smoking for almost a week. But, when I saw an anti-smoking advertisement (with an image of cigarette), I felt the urge to start smoking again."

He highlighted that smokers would be drawn to images of cigarettes in advertisements but would ignore the images of smoking-related diseases.

> "[When I see an anti-smoking poster] I notice the disease that it's showing… but I notice the cigarette in the poster more. Other images become unnoticeable."

Participants' opinions about problems with the tobacco control regulations and enforcement

The majority of the participants could not see any benefit in restricting the accessibility of cigarettes to teenagers, as they believed that this strategy failed to cause teenagers to stop smoking. One teenager said:

> "Even if there is a police officer… we can ask someone older to buy cigarettes for us."

The teenagers claimed that they could easily purchase cigarettes from local stores, and one of them stated:

> "[When you wear a school uniform] you cannot buy [cigarettes]. When you wear casual attire… you can buy cigarettes."

A number of factors were suggested as possible reasons for this:

(a) Failure of retailers to comply with the law, as voiced by one of the teenagers:

> "People said that retailers could only sell cigarettes to those above 18 years old… but we always see… young kids [buying cigarettes from them]."

The participants felt that retailers' ignorance was related to their priority of making a profit from selling cigarettes to all customers, regardless of their age. As one of the teenagers said:

> "Surely retailers will not obey the law [that against the sale of cigarettes to minors]… they want profits."

(b) Poor enforcement of the law, as one teenager described:

> "Nothing (not afraid of buying cigarettes from retailers who put up signs against the sale of cigarettes to minors). No one… no one would enforce the law."

This poor law enforcement was thought to be due to the followings:

a) Poor resources

> "Our enforcement officers… they are not just enforcing tobacco policies… it is impossible to enforce the policies against selling cigarettes to minors every day. You cannot be everywhere at all times."
>
> (Doctor from the Tobacco Unit, female, non-smoker)

b) Lack of public co-operation in ensuring law compliance by retailers

> "When the retailer sold cigarettes to the young kids, other adults [who were there] just watched. No one said anything."
>
> (Teenager, female, smoker)

c) Current law deficiency in only allocating the enforcement of power to certain bodies (mainly police officers, health officers, and custom officers):

> "Outside the school compound... the enforcement power belongs to police officers. Teachers are not allowed [to enforce law against tobacco in the community]." (Teacher, male, non-smoker)

Some of the teenagers in this study conveyed the idea that because of addiction, "no matter how strong the law is enforced, they will always find ways to obtain cigarettes", as shown by the following excerpts:

> "[We] steal their [friends'] cigarettes."
>
> "[I] try to find [cigarettes] until I get them. Get from friends."

The availability of cigarettes from social sources (friends and siblings) was also a hindrance and made the high tobacco duty ineffective for restricting the accessibility of cigarettes to teenagers. The teenagers declared that they could always share the cost of cigarettes with their friends, as one of them said:

> "We shared our money to buy cigarettes."

Furthermore, the teenagers claimed that cheap, smuggled cigarettes were easily obtained, thus making cigarettes more affordable to them. This was supported by many adult participants who agreed that illegal smuggling of cigarettes was an important barrier to curbing smoking problems in Malaysia.

> "Malaysia is exposed to smuggling. So when we raise the price of tobacco, smuggling will take advantage."
>
> (Doctor from the Tobacco Unit, female, non-smoker)

Discussion

In general, the majority of the participants in this study believed that the national and local tobacco control programmes were ineffective in promoting smoking cessation among teenagers. This negative perception is comparable to the findings of other studies (29–31). Only a small number of the participants believed that some of the strategies could trigger their desire to quit, reduce their cigarette consumption, and make them quit. This is consistent with a number of studies (32–34) that showed certain strategies, which were part of the comprehensive anti-tobacco programmes, were effective in curbing teenage smoking. These comprehensive strategies included mass media campaigns, school and community programmes, the youth access law and its enforcement, and a high tobacco duty.

In many studies in western countries (35–38), anti-smoking campaigns have been shown to be effective in reducing the prevalence of teenage smoking, decreasing the cigarette consumption of teenagers, reducing the rate of progression to chronic smoking, preventing smoking initiation and relapse, and increasing the number of quit attempts. However, the majority of the participants in this study agreed that the campaign could not ensure successful quitting among teenagers, as was also found in other studies (29–31). The participants suggested a number of reasons for this, which included an inadequacy of the message content, a lack of exposure to the campaign, and poor presentation and delivery.

In Malaysia, the main message that is highlighted in the anti-smoking campaign is the adverse health risks related to smoking. This message is delivered through advertisements, particularly on posters and billboards. Previous studies showed that this strategy was effective in preventing smoking behaviour and causing smoking cessation (32,39). However, the participants in our study believed that they were already well-informed about the health risks, so repetitively showing them such information was futile. The participants thought that the campaign lacked vital information regarding how to quit. Because most teenagers are unfamiliar with effective methods for quitting (30), the teenagers relied on those methods suggested by their friends. These methods included drinking a lot of water, chewing gum, and eating sweets. Hence, the combination of emotional jolting, which is associated with the health risks of smoking, and supportive messages in anti-smoking campaigns might be effective in increasing smokers' intentions and attempts to quit (32,35,39).

The participants also suggested that the lack of exposure to the campaign programme, which was due to infrequent campaign advertisements and activities, was a cause of its ineffectiveness. The campaign failed to reach out to teenagers throughout the country, and the participants believed that the limited budget and resources were the underlying reasons (39). Because high exposure of a campaign is crucial for ensuring that it has a substantial impact on teenage smoking (37,39), strategies to increase the frequency, duration, and coverage areas of the campaign should be implemented. Exposure to the campaign could also be enhanced by increasing the collaboration between organisations within the local communities in conducting anti-smoking

activities, such as promotions, contests, and No Tobacco Days (39).

In this study, the participants believed that problems with the execution and presentation of the advertisements were responsible for the ineffective campaign. These problems included uninteresting activities and advertisements that failed to attract the teenagers' attention (11,40,41). Because the appropriate use of language and graphics in campaigns are important for ensuring the teenagers' ability to relate to the campaigns (38), teenagers should be included in the planning and execution. Through this participation, more appealing and effective programmes may be created.

A number of participants also considered the design of the campaign advertisements to be flawed because of the inclusion of cigarette images on the advertisements. The participants believed that the image could trigger teenagers to increase their smoking habits. This smoking cue reactivity is common among smokers and has been demonstrated by a number of experimental studies (42–44). Through functional magnetic resonance imaging, these studies have demonstrated increased neural responses in the addiction centres of the brain among deprived smokers when presented with images of smoking (42,43). Along with smoking cue reactivity, our study highlighted the presence of an attention bias for smoking-related images among smokers. This attention bias phenomenon was demonstrated by Bonitz and Gordon (45). Their study showed that smokers selectively attended to smoking-related objects when presented with various scenes (45). Therefore, to minimise the effects of smoking cue reactivity and attention bias, images of cigarettes should be excluded in any advertisements. This has just recently been realised in Malaysia.

The majority of the participants in this study did not believe that the youth access law and the tobacco duty were effective for making teenagers quit and preventing them from obtaining cigarettes. However, the impacts of these strategies on teenage smoking in other studies (4,34,46) conflict with our findings. A number of contributing factors were suggested by the participants, including a failure of retailers to comply with the law, poor law enforcement, the accessibility of teenagers to cigarettes via social sources, and easy availability of cheap, smuggled cigarettes.

The easy commercial access of teenagers to cigarettes that was highlighted by this study was also found in previous studies (7,14,47). The participants in our study felt that this could be attributed to retailers' ignorance and their desire to profit from selling cigarettes to all customers, regardless of their age. Furthermore, the non-compliance of these retailers to the law may be related to poor law enforcement (4).

Poor law enforcement was believed to be caused by poor resources, the lack of public co-operation in ensuring retailers' compliance with the law, and the current deficiency in the law regarding the allocation of the enforcement of power to only certain people. To decrease the accessibility of teenagers to cigarettes, multiple strategies have been suggested. These strategies include increasing merchant compliance checks at retail outlets and allocating the enforcement of power to other local bodies. However, statements made by the teenagers, such as "no matter how strong the law is enforced, they will always find ways to obtain cigarettes", should raise questions about the effectiveness of the youth access law even if this law is strongly enforced. The ineffectiveness of some of the enforcement strategies has been shown by recent studies (4,48). In these studies, a high level of tobacco retailers' compliance was not associated with a change in teenagers' perception of cigarette accessibility. This is because teenagers can obtain their cigarettes from friends, family members, and other social sources (49,50), as was also described by the teenagers in our study.

Participants in our study believed that the social sources of cigarettes decreased the effect of a tobacco duty on teenage smoking. The ineffectiveness of the tobacco duty may also be due to the teenagers' practice of sharing the cost of cigarettes with their friends. Because western studies (4,32) have demonstrated that a tobacco duty can reduce both teenagers' consumption of cigarettes and their smoking prevalence, the findings of this study may imply that the current tobacco duty might not be high enough to have a similar impact on these teenagers. However, the participants thought that the positive effects of a high tobacco duty would be difficult to achieve because of the rampant, illegal cigarette smuggling in Malaysia (18).

In summary, the majority of the participants believed that the national tobacco control programme in Malaysia was ineffective in advocating smoking cessation among teenagers. Various factors were found to impair the effectiveness of the programme and consisted not only of problems with the programmes but also teenagers' cunning behaviour (personal factor) and their poor efficacy to overcome nicotine addiction (behavioural factor). This complex interaction between environmental,

personal, and behavioural factors was supported by SCT, which could explain teenage smoking in Malaysia. Therefore, multiple strategies beyond educating teenagers about the dangers of smoking and restricting cigarettes to teenagers should be implemented to ensure smoking cessation (Figure 2). Because this study has shown the suitability of SCT in our local context, SCT could be used as the foundation in the development of comprehensive strategies.

Although this study could provide insight about possible problems with the national tobacco control programme in Malaysia, the limitations of our study should not be overlooked. Many of the limitations are related to the methodology of the study, and thus, careful consideration must be taken before implementing the findings into practice. The purposive-sampling method, which allowed us to recruit participants who had certain characteristics (e.g., mainly 16-year-old Malay teenagers from urban areas), limits the generalisation of our findings to other populations. For example, the opinions of the teenagers in our study who were from one urban, public day-school might not be comparable to the opinions of those from boarding schools, who have different exposure to anti-smoking strategies. Thus, before applying these findings to practical use, the similarity between the study's context and the existing situation should be confirmed. Future research is also required to confirm the significance of the highlighted problems of the national tobacco control programmes.

Conclusion

The comprehensive national tobacco control programme is required to ensure smoking cessation in teenagers. The programme should include multiple strategies that can overcome the identified problems, as highlighted by this study. Improving the content, presentation, and execution of the anti-tobacco campaign and increasing the campaign's exposure to

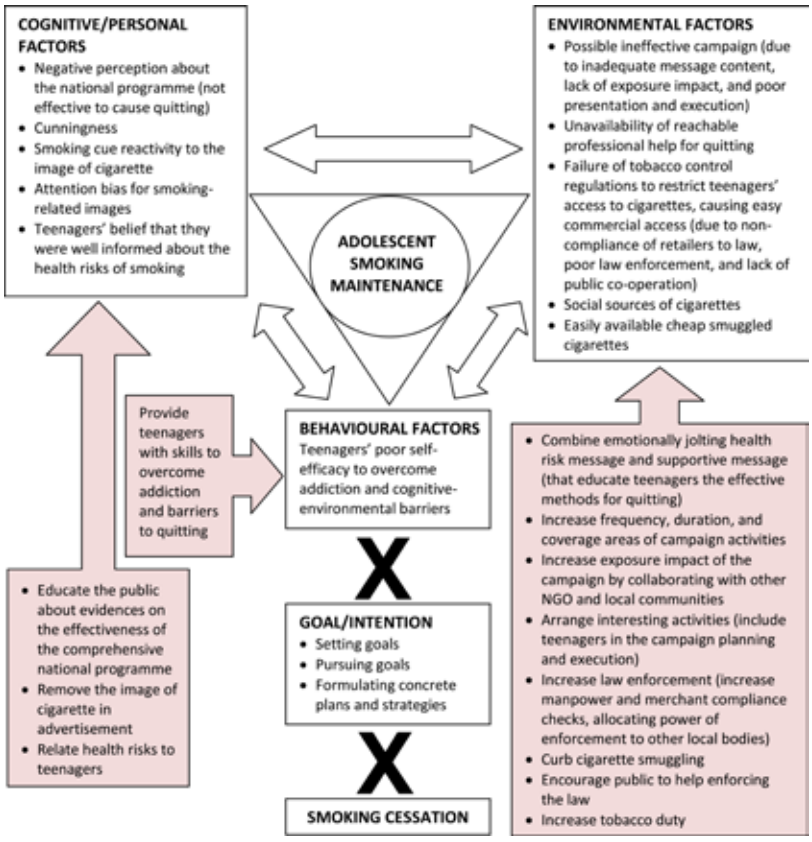

Figure 2: Application of the study's findings using SCT as the background framework. Shaded boxes contain practical recommendations. Abbreviation: NGO = non-governmental organisations.

teenagers could increase smoking cessation among teenagers. Moreover, enhancing law enforcement, increasing the tobacco duty, finding better strategies to curb cigarette smuggling, and providing self-efficacy skills could also improve the smoking cessation rate among teenagers. In addition, a good theoretical framework that is as comprehensive as SCT should be the foundation of the programme, as this allows for holistic management in ensuring smoking cessation among teenagers.

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Authors' Contribution

Conception and design, analysis and interpretation of the data: HT, NMI, NAM, KO
Obtaining of funding: HT, KO
Provision of study materials, collection and assembly of the data: HT, NMI
Drafting and critical revision of the article: HT
Final approval of the article: HT, FNMA, AEAA
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References

1. Trends in the prevalence of tobacco use: National YRBS: 1991–2009 [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2009 [cited 2010 Jun 16]. Available from: http://www.cdc.gov/healthyyouth/yrbs/pdf/us_tobacco_trend_yrbs.pdf.

2. Scollo MM, Winstanley M, editors. *Tobacco in Australia: Facts and Issues* [Internet]. 3rd ed. Melbourne (AU): Cancer Council Victoria; 2008 [cited 2011 Feb 16]. Available from: http://www.tobaccoinaustralia.org.au/.

3. Statistics on smoking in England 2010 [Internet]. Leeds (UK): The NHS Information Centre; 2010 [cited 2011 Feb 27]. Available from: http://www.ic.nhs.uk/pubs/smoking10.

4. Wakefield M, Chaloupka F. Effectiveness of comprehensive tobacco control programmes in reducing teenage smoking in the USA. *Tob Control*. 2000;**9(2)**:177–186.

5. Centers for Disease Control and Prevention. *Best practices for comprehensive Tobacco Control Programs*—2007. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2007.

6. Nelson DE, Mowery P, Asman K, Pederson LL, O'Malley PM, Malarcher A, et al. Long-term trends in adolescent and young adult smoking in the United States: Metapatterns and implications. *Am J Public Health*. 2008;**98(5)**:905–915.

7. Krishnan *M. Global Youth Tobacco Survey (GYTC) Malaysia* [Internet]. Kuala Lumpur (MY): Non Communicable Disease Control Section, Disease Control Division, Ministry of Health; 2003 [cited 2009 Nov 18]. Available from: http://www.wpro.who.int/NR/rdonlyres/147D9E32-CC77-4185-A2FD-AF5CC5C942BD/0/GYTSMalaysia.pdf.

8. Institute for Public Health. *The Third National Health and Morbidity Survey (NHMS III)*. Kuala Lumpur (MY): Institute for Public Health; 2006.

9. Teh KH, Ling KH. Smoking among students in a rural secondary school. *JUMMEC*. 2000;**5(2)**:85–88.

10. Naing NN, Ahmad Z, Musa R, Abdul Hamid FR, Ghazali H, Abu Bakar MH. Factors related to smoking habits of male adolescents. *Tob Induc Dis*. 2004;**2(3)**:133–140.

11. Zulkifli A, Rogayah J, Razlan M, Nyi Nyi N. Adolescent's attitudes towards health warning message on cigarette packs. *Malays J Med Sci*. 2001;**8(1)**:20–24.

12. Lee LK, Paul CY, Kam CW, Jagmohni K. Smoking among secondary school students in Negeri Sembilan, Malaysia. *Asia Pac J Public Health*. 2005;**17(2)**: 130–136.

13. Lim KH, Amal NM, Hanjeet K, Mashod MY, Wan Rozita WM, Sumarni MG, et al. Prevalence and factors related to smoking among secondary school students in Kota Tinggi District, Johor, Malaysia. *Trop Biomed*. 2006;**23(1)**:75–84.

14. Afiah MZ, Hejar AR, Kulanthayan KC, Fadhilah J, Law TH. Prevalence of smoking and drinking habits among Form Six students in Petaling District, Selangor. *Med J Malaysia*. 2006;**61(1)**:41–47.

15. Lim KH, Sumarni MG, Kee CC, Christopher VM, Noruiza Hana M, Lim KK, et al. Prevalence and factors associated with smoking among form four students in Petaling District, Selangor, Malaysia. *Trop Biomed*. 2010;**27(3)**:394–403.

16. Khairani O, Norazua R, Zaiton A. Prevalence and reasons for smoking among upper secondary schoolboys in Hulu Langat, Malaysia. *Med Health*. 2007;**2(1)**:80–85.

17. Morrow M, Barraclough S. Tobacco control and gender in Southeast Asia. Part I: Malaysia and the Philippines. *Health Promot Int*. 2003;**18(3)**: 255–264.

18. Efroymson D, Jones L, Velasco MG, editors. Regional research report on tobacco [Internet]. Bangkok (TH): Sountheast Asia Tobacco Control Alliance; 2007 [cited 2009 Nov 18]. Available from: http://resources.seatca.org/Regional%20research%20summaries/Regional%20Research%20Report%20on%20Tobacco%20Summary.pdf.

19. Food Act 1983: Control of tobacco product regulations. Kuala Lumpur (MY): Ministry of Health Malaysia; 2004.

20. Baranowski T, Perry CL, Parcel GS. How individuals, environments and health behavior interact. In: Glanz K, Rimer BK, Lewis FM, editors. *Health behavior and health education: Theory, Research, and Practice*. 3rd ed. San Francisco (CA): Jossey-Bass; 2002. p. 165–184.

21. Conner M, Norman P. *Predicting health behaviour: Research and practice with social cognition models*. 2nd ed. Buckingham (GB); Open University Press; 2005.

22. Bandura A. Health promotion by social cognitive means. *Health Educ Behav*. 2004;**31(2)**:143–164.

23. Grimshaw GM, Stanton A. Tobacco cessation interventions for young people. *Cochrane Database Syst Rev*. 2006;**(4)**:CR003289.

24. Yin RK. *Applications of case study research*. Newbury Park (CA): SAGE Publications; 1993.

25. Simon H. *Case study research in practice*. 1st ed. London (GB): SAGE Publications; 2009.

26. Patten CA, Offord KP, Ames SC, Decker PA, Croghan IT, Dornelas EA, et al. Differences in adolescent smoker and nonsmoker perceptions of strategies that would help an adolescent quit smoking. *Ann Beh Med*. 2003;**26(2)**:124–133.

27. Pope C, Mays N. *Qualitative research in health care*. 3rd ed. Oxford (GB): Blackwell Publishing; 2006.

28. Flick U. *An introduction to qualitative research*. 4th ed. London (UK): SAGE Publications; 2009.

29. Vuckovic N, Polen MR, Hollis JF. The problem is getting us to stop. What teens say about smoking cessation. *Prev Med*. 2003;**37(3)**:209–218.

30. Balch GI, Tworek C, Barker DC, Sasso B, Mermelstein R, Giovino GA. Opportunities for youth smoking cessation: Findings from a national focus group study. *Nicotine Tob Res*. 2004;**6(1)**:9–17.

31. Hutcheson TD, Greiner KA, Ellerbeck EF, Jeffries SK, Mussulman LM, Casey GN. Understanding smoking cessation in rural communities. *J Rural Health*. 2008;**24(2)**:116–124.

32. Cummings KM, Fong GT, Borland R. Environmental influences on tobacco use: Evidence from societal and community influences on tobacco use and dependence. *Annu Rev Clin Psychol*. 2009;**5**: 433–458.

33. Mermelstein R. Teen smoking cessation. *Tob Control*. 2003;**12 (Suppl 1)**:i25–i34.

34. Backinger CL, Fagan P, Matthews E, Grana R. Adolescent and young adult tobacco prevention and cessation: Current status and future directions. *Tob Control*. 2003;**12(Suppl 4)**:IV46–IV53.

35. Klein JD, Havens CG, Carlson EJ. Evaluation of an adolescent smoking-cessation media campaign: GottaQuit.com. *Pediatrics*. 2005;**116(4)**:950–956.

36. Farrelly MC, Davis KC, Haviland ML, Messeri P, Healton CG. Evidence of a dose-response relationship between "truth" antismoking ads and youth smoking prevalence. *Am J Public Health*. 2005;**95(3)**: 425–431.

37. Johnston LD, Terry-McEllrath YM, O'Malley PM, Wakefield M. Trends in recall and appraisal of anti-smoking advertising among American youth: National survey results, 1997–2001. *Prev Sci*. 2005;**6(1)**:1–19.

38. Smith KH, Stutts MA. The influence of individual factors on the effectiveness of message content in antismoking advertisements aimed at adolecents. *J Cons Aff*. 2006;**40(2)**:261–293.

39. Schar EH, Gutierrez KK. Smoking cessation media campaigns from around the world: Recommendations from lessons learned [Internet]. Copenhagen (DK): Centers for Disease Control and Prevention, World Health Organization; 2001 [cited 2011 Mar 6]. Available from: http://www.ash.org.uk/files/documents/ASH_324.pdf.

40. Crawford MA, Balch GI, Mermelstein R; Tobacco Control Network Writing Group. Responses to tobacco control policies among youth. *Tob Control*. 2002;**11(1)**:14–19.

41. Amos A, Wiltshire S, Haw S, McNeill A. Ambivalence and uncertainty: Experiences of and attitudes towards addiction and smoking cessation in the mid-to-late teens. *Health Educ Res*. 2006;**21(2)**:181–191.

42. David SP, Munafo MR, Johansen-Berg H, Smith SM, Rogers RD, Matthews PM, et al. Ventral striatum/nucleus accumbens activation to smoking-related pictorial cues in smokers and nonsmokers: A functional magnetic resonance imaging study. *Biol Psychiatry*. 2005;**58(6)**:488–494.

43. Due DL, Hall WG, Rubin DC. Smoking cues induce neural activation in deprived smokers. *Neuroimage*. 2000;**11(5)**:S37.

44. Upadhyaya HP, Drobes DJ, Thomas SE. Reactivity to smoking cues in adolescent cigarette smokers. *Addict Behav*. 2004;**29(5)**:849–856.

45. Bonitz VS, Gordon RD. Attention to smoking-related and incongruous objects during scene viewing. *Acta Psychol (Amst)*. 2008;**129(2)**:255–263.

46. Fichtenberg CM, Glantz SA. Youth access interventions do not affect youth smoking. *Pediatrics*. 2002;**109(6)**:1088–1092.

47. Hammond D, Kin F, Prohmmo A, Kungskulniti N, Lian TY, Sharma SK, et al. Patterns of smoking among adolescents in Malaysia and Thailand: Findings from the International Tobacco Control Southeast Asia survey. *Asia Pac J Public Health*. 2008;**20(3)**: 193–203.

48. Dent C, Biglan A. Relation between access to tobacco and adolescent smoking. *Tob Control*. 2004;**13(4)**:334–338.

49. Chapman S, Freeman B. Regulating the tobacco retail environment: Beyond reducing sales to minors. *Tob Control*. 2009;**18(6)**:496–501.

50. Doubeni CA, Li W, Fouayzi H, Difranza JR. Perceived accessibility as a predictor of youth smoking. *Ann Fam Med*. 2008;**6(4)**:323–330.

Original Article

Comparison of Refractive Error and Visual Impairment between Native Iban and Malay in a Formal Government School Vision Loss Prevention Programme

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Abstract

Background: **The epidemiological study of vision problems is important for developing national strategies for the prevention of visual impairment. There was a lack of information regarding vision problems among school children in East Malaysia. The purpose of this study was to compare the refractive errors and degrees of visual impairment between Native Iban and Malay school children who participated in a formal government vision loss prevention programme conducted in a rural area of Betong Division, Malaysia.**

Methods: **In total, 293 Native Iban and Malay school children (Standard 1, Standard 6, and Form 3) received refractive assessments by an optometrist after failing tests in the formal government school vision screening programme in 2008. A criterion for referral was a visual acuity of 6/9 or worse in either eye. Assessments of the refractive errors of the children were performed using dry retinoscopy and subjective refraction techniques at community clinics.**

Results: **The overall prevalences of refractive error and visual impairment among the sampled populations were 47.7% and 3.5%, respectively. Approximately 97.1% of reported cases were myopia. The Malay sample population was found to be more myopic than the Native Iban population (U = 8240.50, P < 0.05, r = 0.14), but no significant association was found between myopia and ethnicity (χ^2 = 2.66, P > 0.05). Both Native Iban and Malay children in education levels higher than Standard 1 were more likely to have myopia (P < 0.05). Myopia was found to be more likely to affect females than males at a statistically significant level among Native Iban children (χ^2 [1.N = 170] = 6.279, P < 0.05, odds ratio = 2.327, 95% CI = 1.184–4.575). There was no statistically significant association between visual impairment and ethnicity (χ^2 = 1.60, P > 0.05). Approximately 94.1% of children with refractive errors suffered from having either the wrong prescription (7.8%) or having uncorrected refractive errors (92.2%).**

Conclusion: **The Native Iban population was found to be less myopic than the Malay population despite having a similar frequency of myopia. The proportion of children with myopia increased with the level of education in both ethnicities. A high percentage of untreated refractive error problems among Native Iban and Malay children in the Betong Division indicates that there is a need for government intervention for the purpose of economic and healthcare improvements.**

Keywords: *child, myopia, optometry, refractive errors, visually impaired persons*

Introduction

The prevalence of refractive error varies (2.9% to 22.1%) depending on the population studied, the sample selection, and the definitions that are used for its classification (1–6). In Malaysia, refractive error became an important health issue because it was a major cause of preventable visual impairment (7), and it was the most commonly reported vision problem among Malaysian children; its prevalence ranged 5.8%–33.3% (8–11). Extensive studies of myopia were conducted due to its high prevalence and its progression that occurs along with ocular development. A higher prevalence of myopia was found among the Chinese population compared with both in Caucasian populations and in other Asian populations (1–6). Refractive error studies in Malaysia showed a similar distribution (8–14). Among children, myopia was reported to affect

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the Chinese population most frequently (with a prevalence between 42.0%–45.3%), followed by Indian (15.5%–16.0%), Malay (3.5%–13.9%), and indigenous populations (1.5%). In contrast, the highest prevalence of hyperopia was reported among the indigenous population (29.4%), followed by Malay (14.3%), Indian (1.7%), and Chinese populations (0.9%).

Ethnicity, geographical location, environmental factors, and age may have contributed to the prevalence and distribution pattern of refractive errors, particularly those of myopia (1–14). When comparing the prevalences of myopia in Malays in Kelantan, in a suburban area of the Gombak District, and in Singapore, it was determined that the prevalence of myopia was somewhat higher in better socio-economic or urban locations (9). A study (14) of vision problems among members of indigenous ethnic populations in a rural area of Selangor also demonstrated a low prevalence of myopia (1.5%). These results were similar to results from studies conducted in other countries (15–17). Myopia and urban location were independent of other conventional myopia risks such as ethnicity, parental myopia, degree of near work, and outdoor activity (9,17). The lower prevalence of myopia in Australia relative to its prevalence in Asia suggested that lifestyle and schooling might influence the development of myopia (18,19). In Malaysia, The National Eye Survey 1996 (7) reported that the prevalence of refractive error in a population of young people was higher among children between 10 and 19 years old (1.4%) than it was among children younger than 10 years old (0.3%). The prevalence of myopia was reported to be lower in pre-school children, 3.5% (11), than in school-aged children, 5.4% to 33.3% (8–10). The effect of gender on the prevalence of myopia was inconclusive (6–13).

Previous studies (8,9) have also reported visual impairment (with 0.7%–2.7% prevalences) among school-aged children in Malaysia. The causes of visual impairment were amblyopia, corneal diseases, congenital anomaly, and other unexplained factors. No significant differences in visual impairment due to uncorrected refractive error were found among the Malay, Chinese, Indian, and indigenous populations in Malaysia (7).

Previous studies in Malaysia were conducted in West Malaysia (the peninsular region) and predominantly focused on 3 main ethnic groups (Malay, Chinese, and Indian). Less information about vision problems among populations in the rural areas of East Malaysia, which had a different ethnic composition, was reported. This study aimed to compare refractive error and visual impairment between Native Iban and Malay school children who participated in a formal government vision loss prevention programme conducted in a rural area of the Betong Division, Malaysia. The associations between myopia and ethnicity, gender, and level of education were also investigated. Native Iban and Malay populations are among the largest ethnic populations in East Malaysia. Data from this study will provide a valuable addition to the information about vision problems among school children in Malaysia; this information is important for both the development and enhancement of a preventative vision programme at the national level.

Materials and Methods

In 2008, a formal government vision screening programme was conducted in 105 primary schools (Standard 1 and Standard 6) and 12 secondary schools (Form 3) in the Betong Division of Sarawak, Malaysia. Children who failed the vision screening were referred to an optometrist at a community clinic for further assessment. This cross-sectional study was based on the screening data collected from August 2008 to October 2008, and the analysis included only Native Iban and Malay children. This project adhered to the ethical considerations that were put forth in the Declaration of Helsinki, 1975. Approval to conduct the visual examinations was obtained from the Betong Department of Education and the Betong Department of Health.

Malaysia comprises 2 geographically distinct areas, West Malaysia and East Malaysia, which are separated by South China Sea. West Malaysia is attached to the main continent (the peninsular region), while East Malaysia is located on the island of Borneo. Betong is a division of Sarawak, which is a state in East Malaysia. The Betong Division administrative area consists of 2 districts and 7 subdistricts. The population of the Betong Division consists of approximately 100 000 people living within a 4000 km^2 area, and it can be divided into 4 main ethnicities: Malay (51%), Native Iban (42%), Chinese (5%), and others (2%) (20).

Vision screening was conducted by assistant medical officers or nurses using Snellen visual acuity (VA) charts, and the criterion for referral to a community clinic was having a VA of 6/9 or worse in either eye. At these clinics, optometrists performed further vision assessments. Due to our study objective, only findings from VA and

refractive assessments will be reported here. VA was tested monocularly using alphabetical or tumbling E Snellen acuity charts at a distance of 6 m. Each child's refractive status was assessed using dry retinoscopy and subjective refraction. Children who did not achieve a best-corrected VA (BCVA) of 6/6 using dry retinoscopy and subjective refraction techniques were referred to an eye clinic for further evaluation. In the eye clinic, cycloplegic refraction was performed by an optometrist using 1.0% cyclopentolate; 2 drops were administered 5 minutes apart, and a 3rd drop was administered 20 minutes later. After 15 minutes, the degrees of pupil dilatation and cycloplegia were evaluated, and cycloplegia was considered to be complete when the pupil was dilated to a width of 6 mm or more (8). Myopia was defined as having a refractive error with a spherical equivalent (SE) of at least −0.50 D, and hyperopia was defined as having a refractive error with an SE of +1.50 D or more (8). Children were classified as having visual impairment if their BCVA after cycloplegic refraction was 6/12 or worse in either eye (8). Visual impairment was categorised into 3 groups: 1) bilateral visual impairment (BCVA of 6/12 in the better eye), 2) unilateral visual impairment (BCVA of 6/12 or worse in either eye), and 3) low vision (BCVA of 6/18 or worse in the better eye). The exclusion criteria included incomplete data and unavailability of a child's medical record during the study period. Children who were referred to an optometrist for reasons other than failing a VA test and children with congenital unilateral blindness or blindness due to injury were also excluded. Each child's ethnicity was determined according to his or her birth certificate.

Data entry and analysis were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, US). A non-parametric Mann–Whitney U test was used in the analysis of the degree of refractive error because the data were not normally distributed. The associations between myopia and ethnicity, gender, and level of education were investigated using logistic regressions.

Results

Demographic information about the subjects was shown in Table 1. In total, 293 children (174 Native Iban, 59.4%, and 119 Malay, 40.6%) each received a refractive assessment by an optometrist. Eight children were excluded from this study because they had incomplete medical records or failed to attend a follow-up appointment (4 cases), they had unilateral blindness (2 cases), or they were referred for reasons other than failing the VA assessment (2 cases).

The overall prevalence of refractive error in the studied population was 47.7%. In total, 132 children were found to be myopic (72 Native Iban, 60 Malay), and 4 children were hyperopic (3 Native Iban, 1 Malay). The distribution of refractive errors was shown in Table 2. The SE ranged from −0.50D to −10.50D for the myopic group and from +2.00D to +4.50D for the hyperopic group. The mean (SD) spherical equivalent in the right eyes of Native Iban and Malay children were −0.77 D (SD 1.37) and −1.12 D (SD 1.52), respectively; and in the left eyes, −0.70 D (SD 1.45) and −0.96 D (SD 1.45), respectively. A Mann–Whitney U test of the right eye data indicated that the Malay sample population was more myopic than the Native Iban sample population (U = 8240.50, P < 0.05, r = 0.14); however, no significant difference in refractive error between the 2 populations was found for the left eye.

The distribution of visual impairment among Native Iban and Malay children according to

Table 1: Demographic data of the study subjects

Level of education	Gender	Native Iban (n = 170)		Malay (n = 115)	
Standard 1	Male	18	(10.6)	8	(7.0)
	Female	19	(11.2)	9	(7.8)
Standard 6	Male	19	(11.2)	17	(14.8)
	Female	34	(20.0)	39	(33.9)
Form 3	Male	21	(12.3)	10	(8.7)
	Female	59	(34.7)	32	(27.8)

Data are presented in number (percentage).

the children's level of education, associated refractive error conditions, and severity of visual impairment was shown in Table 3. Ten children (3.5%) were unable to achieve a BCVA of 6/12 or better following assessment with cycloplegic refraction. The proportion of children with visual impairment was not found to correlate with ethnicity ($\chi^2 = 1.60$, $P > 0.05$), and all of the children with visual impairment also had refractive error problems. Children with visual impairment were found to have either anisometropia or high astigmatism. The number of children with visual impairment was relatively higher in male children than in female children, and this number was also higher among children with lower levels of education than among children in Form 3 in both ethnicities. Both cases of visual impairment in Form 3 children belonged to the Native Iban ethnic group.

Fourteen children wore corrective visual aids on the day of the examination, but 10 of them had visual acuities poorer than 6/12 while wearing their current glasses. Approximately 94.1% of children with refractive errors suffered from either having the wrong prescription (7.8%) or from uncorrected refractive errors (92.2%). The distribution of improperly treated refractive problems according to the type of refractive error, ethnicity of the child, and level of education was shown in Table 4. Two children who had incorrect prescriptions were visually impaired, and the other 8 children with visual impairment did not have any type of visual correction.

Because myopia accounted for 97.1% of the refractive errors, further evaluation of the data from children with myopia was conducted. Information regarding the ethnicity, gender, and level of education of children with myopia was shown in Table 5. Among Native Iban children, female children were 2 times more likely to have myopia than male children (χ^2 [1.N = 170] = 6.279, $P < 0.05$, odds ratio = 2.327, 95% CI.= 1.184–4.575]. Myopia was also found to be more common in children with education levels higher than Standard 1 in both Native Iban (χ^2 [1.N = 170] = 17.406, $P < 0.05$, odds ratio = 3.819, 95% CI = 1.433–10.176) and Malay (χ^2 [1.N = 115] = 9.231, $P < 0.05$, odds ratio = 6.500, 95% CI = 1.787–2.644) children.

Table 2: Distribution of refractive error in Native Iban and Malay children according to severity

Variable	Level of education	Native Iban (n = 170)				Malay (n = 115)			
		Right eye		Left eye		Right eye		Left eye	
High myopia	Standard 1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
(>−5.00 D)	Standard 6	1	(0.6)	1	(0.59)	2	(1.7)	1	(0.8)
	Form 3	0	(0.0)	0	(0.0)	2	(1.7)	2	(1.7)
Moderate myopia	Standard 1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
(−2.00 D to −5.00 D)	Standard 6	15	(8.8)	13	(7.6)	11	(9.5)	7	(6.0)
	Form 3	16	(9.4)	14	(8.2)	12	(10.4)	11	(9.5)
Low myopia	Standard 1	3	(1.7)	6	(3.5)	2	(1.7)	4	(3.4)
(−0.50 D to −1.75 D)	Standard 6	14	(8.2)	17	(10.0)	17	(14.7)	19	(16.5)
	Form 3	13	(7.6)	19	(11.2)	14	(12.2)	12	(10.4)
Emmetropia	Standard 1	34	(20.0)	31	(18.2)	15	(13.0)	13	(11.3)
(+1.25 D to −0.25 D)	Standard 6	23	(13.5)	20	(11.8)	25	(21.7)	29	(25.2)
	Form 3	50	(29.4)	46	(27.1)	14	(12.2)	17	(14.7)
Low hyperopia	Standard 1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
(+1.50 D to +2.00 D)	Standard 6	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Form 3	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Moderate hyperopia	Standard 1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
(+2.25 D to +5.00 D)	Standard 6	0	(0.0)	2	(1.2)	1	(0.8)	0	(0.0)
	Form 3	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)

Data are presented in number (percentage). Refractive errors are given in spherical equivalent.

Table 3: Distribution of visual impairment in Native Iban and Malay children according to gender, level of education, associated refractive error conditions, and severity

Variable	Native Iban (n = 170)	Malay (n = 115)
Gender		
Male	4 (2.4)	2 (1.7)
Female	3 (1.8)	1 (0.9)
Level of education		
Standard 1	1 (0.6)	1 (0.9)
Standard 6	4 (2.4)	2 (1.7)
Form 3	2 (1.2)	0 (0.0)
Associated refractive error condition		
Astigmatism (≥ 2.00 D)	4 (2.4)	2 (1.7)
Anisometropia (≥ 2.00 D)	3 (1.8)	1 (0.9)
Severity of visual impairment		
Low vision (BCVA ≥ 6/18 in the better eye)	0 (0.0)	1 (0.9)
Bilateral visual impairment (BCVA ≥ 6/12 in the better eye)	3 (1.8)	0 (0.0)
Unilateral visual impairment (BCVA ≥ 6/12 in the worse eye)	4 (2.4)	2 (1.7)

Data are presented in number (percentage). Abbreviation: BCVA = best-corrected visual acuity.

Table 4: Distribution of improperly treated refractive problems according to the type of refractive error, ethnicity, and level of education

Variable	Wrong prescription (n = 10)	Uncorrected refractive error (n = 118)
Type of refractive error		
Myopia	10 (100.0)	114 (96.7)
Hyperopia	0 (0.0)	4 (3.3)
Ethnicity		
Malay	6 (60.0)	54 (45.7)
Native Iban	4 (40.0)	64 (54.2)
Level of education		
Standard 1	2 (20.0)	8 (6.8)
Standard 6	5 (50.0)	53 (44.9)
Form 3	3 (30.0)	57 (48.3)

Data are presented in number (percentage).

Discussion

Native Iban children were found to be less myopic than Malay children, which suggested that ethnicity might have contributed to the distribution pattern of myopia. Previous researchers have suggested that differences in lifestyle between different ethnic groups might contribute to differences in the progression of myopia (19), as there is no evidence to support an association between axial length and ethnicity despite the hereditary nature of myopia (21). It has also been reported that excessive axial length is a major cause of myopia in children regardless of their ethnicity (21).

Table 5: Frequency of myopia according to ethnicity, gender, and level of education

Variable		Total	Myopia		Odds ratio	*P* value
			n	(%)		
Ethnicity						
Native Iban		170	72	42.4	1.455	0.103
Malay		115	60	52.2		
Gender						
Native Iban	Male	60	17	10.0	2.327	0.014*
	Female	110	55	32.3		
Malay	Male	35	16	13.9	1.451	0.360
	Female	80	44	38.2		
Level of education						
Native Iban	Standard 1	37	6	3.5		
	Standard 6	53	32	18.8		
	Form 3	80	34	20.0	3.819	< 0.001*
Malay	Standard 1	17	4	3.5		
	Standard 6	56	28	24.3		
	Form 3	42	28	24.3	6.500	0.010*

* Significant difference with $P < 0.05$ by chi-square test.

Despite the fact that the Malay population was more myopic than the Native Iban population, both ethnic groups were found to have similar proportions of myopia. Previous studies in Malaysia reported a relatively lower prevalence of myopia among indigenous people in a rural area (14) compared with those of other ethnicities in urban area (8–10,12,13). An increased prevalence of myopia was also found to be associated with a better socio-economic or urban location (9,15–17). Geographical location and environmental factors might predispose these 2 ethnicities to have similar prevalences of myopia. Both Native Iban and Malay children in this study lived in similar locations and were possibly exposed to similar environments. This result also supported the notion that the association between myopia and geographical location was independent of other confounding factors such as ethnicity (17).

The proportion of children with myopia was found to increase with their level of education. Children in education levels higher than Standard 1 were more likely to have myopia. These findings suggested that vision screenings in rural areas should be performed more regularly, rather than being given only to children in Standard 1, Standard 6, and Form 3 as they are in the current school health programme. Although the present approach might be adequate for children in more urban areas due to its cost effectiveness and practicality, a different approach might be more appropriate for children in rural areas because these children have limited access to eye health services. Regular vision screening allows for the early detection of vision problems that can prevent further, and possibly irreversible, vision loss.

Myopia was found to be associated with female Native Iban children; however, there was no significant association between myopia and gender in Malay children. These findings supported the varied and inconsistent outcomes of other studies (6–13). It has been suggested that different preferences between genders regarding their daily activities might influence the result more than gender itself; specifically, female children might prefer more indoor activities and tasks that require near vision than male children.

This study also revealed that 3.5% of the children were both visually impaired and had uncorrected refractive errors. The frequency of visual impairment was similar between Native Iban and Malay children, and this finding

supported a previous study (7) that suggested that visual impairment might occur in children regardless of their ethnicities.

The high percentage of improperly treated refractive error problems among school-aged children in the Betong Division of Malaysia suggested that the visual health programme should be improved. A national strategy for the ocular health programme should be more concerned with both vision loss prevention programmes, such as ocular health education and vision screening, and the improvement of eye care facilities. Otherwise, children who fail vision screenings and are diagnosed with vision problems will not be able to obtain appropriate treatment or intervention.

This study of refractive error among Native Iban and Malay children in the rural area of Sarawak, Malaysia, supports the existing data and provides information for planning improvements in the national health programme. Screening for refractive error is important for preventing visual impairment among children, but the current vision loss prevention programme may not be adequately equipped to resolve these problems. It has been suggested that screening for these conditions should initially be conducted in preschool-aged children and then regularly throughout the schooling period to prevent undetected visual impairment in children and to offer them an opportunity to receive early treatment. There is also a need to improve eye health services in rural areas; the need for better facilities and preventative strategies is particularly profound.

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Authors' Contributions

Conception and design: NFAB, AHC
Obtaining of funding: NFAB, AHC, ARMN
Provision of study materials, collection and assembly of the data, statistical expertise, administrative, technical, or logistic support: NFAB
Analysis and interpretation of the data, drafting and critical revision of the article: NFAB, AHC, PPG
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References

1. Pokharel GP, Negrel AD, Munoz SR, Ellwein LB. Refractive error study in children: results from Mechi Zone, Nepal. *Am J Ophthalmol.* 2000;**129(4)**: 436–444.

2. Murthy GV, Gupta SK, Ellwein LB, Munoz SR, Pokharel GP, Sanga L, et al. Refractive error in children in an urban population in New Delhi. *Invest Ophthalmol Vis Sci.* 2002;**43(3)**:623–631.

3. Zhao J, Pan X, Sui R, Munoz SR, Sperduto RD, Ellwein LB. Refractive error study in children: Results from Shunyi District, China. *Am J Ophthalmol.* 2000;**129(4)**:427–435.

4. Maul E, Barosso S, Munoz SR, Sperduto RD, Ellwein LB. Refractive error study in children: Results from La Florida, Chile. *Am J Ophthalmol.* 2000;**129(4)**: 445–454.

5. El-Bayoumy BM, Saad A, Choudhury AH. Prevalence of refractive error and low vision among schoolchildren in Cairo. *East Mediterr Health J.* 2007;**13(3)**:575–579.

6. Giordano L, Friedman DS, Repka MX, Katz J, Ibironke J, Hawes P, et al. Prevalence of refractive error among preschol children in an urban population: The Baltimore Pediatric Eye Disease Study. *Ophthalmology*. 2009;**116(4)**:739–746.

7. Zainal M, Ismail SM, Ropilah AR, Elias H, Arumugam G, Alias D, et al. Prevalence of blindness and low vision in Malaysian population: Results from the National Eye Survey 1996. *Br J Ophthalmol.* 2002;**86(9)**: 951–956.

8. Goh PP, Abqariyah Y, Pokharel GP, Ellwein LB. Refractive error and visual impairment in school-age children in Gombak District, Malaysia. *Ophthalmology*. 2005;**112(4)**:678–685.

9. Hashim SE, Tan HK, Wan-Hazabbah WH, Ibrahim M. Prevalence of refractive error in Malay primary school children in suburban area of Kota Bharu, Kelantan, Malaysia. *Ann Acad Med Singapore.* 2008;**37(11)**:940–946.

10. Reddy SC, Hassan M. Refractive errors and other eye diseases in primary school children in Petaling Jaya, Malaysia. *Asian J Ophthalmol*. 2006;**8(5)**:195–198.

11. Hussin DA, Omar R, Knight VF. Causes of visual impairment among pre-school children in Sitiawan District, Perak, Malaysia. *Sains Malaysiana*. 2009;**38(6)**:959–964.

12. Chung KM, Mohidin N, Yeow PT, Tan LL, O'Leary D. Prevalence of visual disorders in Chinese school children. *Optom Vis Sci*. 1996;**73(11)**:695–700.

13. Mohidin N, Mohd Akhir S, Mohd Ali B, Mohammed Z, Sharanjeet K, Chung KM. The association between myopia and gender in Indian schoolchildren in Kuala Lumpur. *Jurnal Sains Kesihatan Malaysia*. 2005;**3(2)**:49–54.

14. Norlaila MD, Mohd Ali B, Mohammed Z, Bashirah I, Sharanjeet K, Mohidin N, et al. Prevalens kesalahan refraktif satu sampel populasi orang asli di Malaysia. *Jurnal Kesihatan Masyarakat*. 2002;**8 Spec**:43–45.

15. Goss DA. Development of ametropias. In: Benjamin WJ, editor. *Borish's Clinical Refraction*. 2nd ed. Philadelphia (PA): Butterworth-Heinnemann Elsevier; 2006. p. 56–92.

16. He M, Zheng Y, Xiang F. Prevalence of myopia in urban and rural children in main land China. *Optom Vis Sci*. 2009;**86(1)**:40–44.

17. Ip JM, Rose KA, Morgan IG, Burlutsky G, Mitchell P. Myopia and the urban environment: Findings in a sample of 12-year-old Australian school children. *Invest Ophthalmol Vis Sci*. 2008;**49(9)**:3858–3863.

18. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, life style, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol*. 2008;**126(4)**:527–530.

19. Junghans BM, Crewther SG. Little evidence for an epidemic of myopia in Australian primary school children over the last 30 years. *BMC Ophthalmol*. 2005;**5**:1.

20. Population distribution and basic demographic characteristics report 2010 [Internet]. Putrajaya (MY): Department of Statistics Malaysia; 2011 [cited 2012 Mar 21]. Available from: www.statistics.gov.my.

21. Zadnik K, Mutti DO. Incidence and distribution of refractive anomalies. In: Benjamin WJ, editor. *Borish's Clinical Refraction*. 2nd ed. Philadelphia (PA): Butterworth-Heinnemann Elsevier; 2006. p. 35–55.

Original Article

Relationship between Food Habits and Tooth Erosion Occurrence in Malaysian University Students

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Abstract

Background: **Tooth erosion is a growing dental problem; however, the role of diet in the aetiology of tooth erosion is unclear. A cross-sectional study was conducted to determine the association between tooth erosion occurrence and the consumption of acidic foods and drinks among undergraduate university students.**

Methods: **A total of 150 undergraduate students (33 males and 117 females) aged 19 to 24 years at Universiti Kebangsaan Malaysia participated in this study. The Basic Erosive Wear Examination was used to assess the occurrence of tooth erosion. Information regarding dental hygiene practices, usual dietary habits, and consumption of acidic foods and drinks was obtained through a structured questionnaire.**

Results: **In all, 68% of subjects had tooth erosion. Subjects who reported having received information about healthy eating were less likely to have tooth erosion (χ^2 [1, N = 150] = 7.328, *P* = 0.007). The frequencies of milk (OR = 0.29, 95% CI = 0.13–0.67) and tea/coffee (adjusted OR = 0.42, 95% CI = 0.19–0.95) consumption were negatively associated with tooth erosion. Dental hygiene practice, the frequency and amount of acidic food and drink intake, and body mass index classification were not significantly associated with the risk of tooth erosion (*P* > 0.05).**

Conclusion: **A high prevalence of tooth erosion was observed among this group of students. Preventive measures, such as dietary advice and increased consumption of milk at a younger age, may reduce the occurrence of tooth erosion among this age group.**

Keywords: *beverages, cross-sectional study, food habits, public health, tooth erosion, young adult*

Introduction

Tooth erosion is defined as a pathological disease characterised by the loss of dental hard tissue due to its chemical removal from the surface by an acid or chelation without bacterial involvement (1). The causative factors of this multi-factorial disease are divided into extrinsic and intrinsic types. Extrinsic causes include the environment, medication, lifestyle factors, and diet. Intrinsic tooth erosion may occur if gastric acid reaches the month due to regurgitation, vomiting, or gastro-oesophageal reflux disease (2). An individual may not be aware of having this problem until it reaches the dentine and pulp, which eventually leads to tooth sensitivity, altered occlusion, and poor aesthetics (3).

There is a considerable body of evidence from laboratory studies to indicate that the acidity of carbonated drinks, sports drinks, and fruit juices can cause tooth erosion. Research has demonstrated that drinks with a pH of 5.5 or less tend to erode and soften the enamel surface. Examples of common acidic food items that have an increased potential for causing tooth erosion include carbonated beverages (4,5), sports drinks (2,6), citrus fruits, and fruit juices (7,8). Carbonated soft drinks have a pH ranging 2.3–3.4, whereas acidic fruit juices and alcoholic drinks have a pH ranging 2.1–3.6 and 2.8–3.9, respectively (6,9). In vitro and in situ studies have also found that natural fruit juices (10,11) and fruit-flavoured drinks have an increased erosive potential (12–14). In addition, certain dietary habits, such as retaining an acidic drink in the mouth for a longer period of time, could

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also cause this dental problem (15). A laboratory study indicated that yogurt does not have erosive potential on enamel, even though it is acidic (16). In addition, it was found that milk and tea have little or no potential for causing erosion (5).

Most studies on children and adolescents support the finding that acidic foods and drinks cause tooth erosion (3,5,8,17,18), but comparatively few have assessed these risk factors in adults (19,20). In Malaysia, data regarding the prevalence of tooth erosion in all age groups is limited. Studies about tooth erosion and its relationship with dietary factors in any age group are also limited. In Kelantan, on the East Cost of Malaysia, Saerah et al. (21) reported that the proportion of raw tooth wear was 100%, and pathological tooth wear was 20.1% among 16-year-old teenagers. Tooth wear is a non-caries loss of dental tissue that results from an interaction between 3 processes: abrasion, attrition, and erosion, which may happen in isolation or in combination. Although this study included erosion as a component of tooth wear, they did not report tooth erosion as a separate dental problem that may be related to an individual's dietary pattern. Among 81 adults aged 18–80 years who attended a dental clinic in Kelantan, 29 (35.8%) had abrasion, 25 (30.9%) had attrition, 1 (1.2%) had erosion, and 26 (32.1%) presented a combined type of tooth wear (22). In this study, the prevalence of tooth erosion was low, and the dietary patterns of patients who attended dental clinics may not be representative of other adults. Thus, the aim of the present study was to investigate the association between dietary patterns and tooth erosion among young adults.

Materials and Methods

Study population and design

A cross-sectional study was conducted at Universiti Kebangsaan Malaysia, Kuala Lumpur campus. A convenience sample of 150 students from various departments was recruited. Based on the sample size calculation formula (23), 150 subjects were required to provide 80% power at a significance level of 5%. The prevalence of tooth erosion was obtained from a previous study among university students in China (24). Ethical approval for this study was obtained from the Ethics Research Committee of Universiti Kebangsaan Malaysia. An information sheet about the study was given to all subjects, and informed consent was obtained from each subject before participation in the study. Undergraduate students who were not pregnant and were not receiving orthodontic treatment were eligible for this study. Subjects were excluded if they were postgraduate students, had medical problems, such as gastro-oesophageal reflux disease, bulimia, or anorexia nervosa, or were professional swimmers.

Questionnaire

A self-administered questionnaire was designed to obtain information about demographics, dental health history, medical history, oral hygiene practices, and dietary patterns. Subjects were asked to recall the frequency and amount of acidic foods and drinks consumed per day, per week, and per month for the past 1 month using a self-administered questionnaire adapted from previous studies (18,19,25). The questionnaire was pilot tested for clarity among 30 undergraduate students, and minor amendments to the questionnaire were made as needed. The reliability of the questionnaire was assessed; Cronbach's alpha coefficient showed a satisfactory result of 0.78.

Subjects completed the questionnaire before dental examinations were performed. A food frequency questionnaire was used to calculate participants' mean daily consumption. Actual dietary habits of the subjects may not have been captured accurately if they were asked to recall their consumption of acidic foods and drinks for the past 24 hours or 1 week, or to record their diet intake in 3-day food diary. Therefore, dietary data were assessed for the past 1 month. Food frequency questionnaires are the recommended method for research on diet-disease relationships (25).

Acidic foods were classified into 2 groups: acidic drinks and acidic foods. Acidic drinks included fruit juice (natural fruit juice and diluted fruit juice), fruit-flavoured drinks (cordial diluted and cocktail drinks), sugared carbonated drinks (carbonated drinks and sparkling water), non-sugared carbonated drinks, sports drinks (also known as isotonic drinks), alcoholic drinks, and honey drinks. Non-erosive drinks included tea, coffee, and milk. Acidic foods included ketchup, pickles, citrus fruit–flavoured ice-cream, vinegar-containing foods, baked beans, fruit jam, sour sweets, dried fruits, and fruits (26). Non-erosive foods included cheese and yogurt; these 2 foods are also high in calcium.

Clinical examination

A tooth erosion assessment was performed using the Basic Erosive Wear Examination (BEWE) index (27). Dental examinations were performed

by a final-year dental student and were calibrated against a dental specialist. The kappa value was 0.75. Clinical examinations were conducted in the main hall of the students' accommodation. The BEWE is a partial scoring system recording the most severely affected surface in a sextant, and the cumulative score guides the management of the condition for the practitioner. The 4-level score (0–3) grades the appearance or severity of wear on the teeth as no surface loss (0), initial loss of enamel surface texture (1), distinct defect, hard tissue (dentine) loss of less than 50% of the surface area (2), or hard tissue loss of greater than 50% of the surface area (3). The reliability of the BEWE has been proven to be acceptable for scoring the severity of dental erosive wear and for recording such lesions in prevalence studies (28). The result of the BEWE is not only a measure of the severity of the condition for scientific purposes but, when transferred into risk levels, is also a possible guide towards management.

Buccal/facial, occlusal, and lingual/palatal surfaces were examined for the highest score recorded. The examination was repeated for all teeth in a sextant, but only the surface with the highest score was recorded for each sextant. Once all the sextants had been assessed, the sum of the scores was calculated.

Anthropometry measurement

Anthropometry measurements, including body weight and height, were conducted at the first meeting with subjects. Body weight was measured using a TANITA digital scale HD-306 (TANITA Corporation, JP) to the nearest 0.1 kg, and height was measured using a SECA 208 body meter (SECA, DE) to the nearest 0.1 cm. During body weight measurements, subjects were required to wear minimal clothing and to stand on the centre of the scale with their weight distributed evenly between both feet. Height measurements were performed using the stretch stature method. Subjects were asked to stand with their feet together and their heels, buttocks, and upper part of their back touching the scale, with their head positioned in the Frankfort plane. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of height (m) and was classified into 4 categories: underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2) (29).

Statistical analyses

Data were compiled and analysed using SPSS version 17.0 (SPSS Inc., Chicago, IL, US). Data normality was tested using the Kolmogorov–Smirnov test. Descriptive analyses were performed to determine the percentages, means, and standard deviations for qualitative data. A chi-square analysis was used to test the associations between tooth erosion occurrence and dietary and socio-demographic variables. Normally distributed data were presented using the mean and standard deviation. Fisher's exact test was used to test the association between the frequencies of acidic food and drink consumptions and the occurrence of tooth erosion. Binary logistic regression was used to calculate the adjusted odds ratio for the amount of non-erosive drinks consumed and tooth erosion occurrence with the inclusion of confounding factors, such as ethnicity, gender, whether the participant had ever received dietary advice, saliva volume, and the frequency of milk consumption. The significance level was set to 0.05.

Results

A total of 150 subjects completed the questionnaire and underwent dental examination for tooth erosion (a response rate of 100%). The majority of subjects were females (78.0%), Chinese (60.0%), aged between 19 and 21 years (80.7%), and had father (54.0%) and mother (52.7%) with an educational level of secondary school (Table 1).

Sixty-eight percent (n = 102) of the subjects had tooth erosion (Table 1). A total of 78.4% (n = 80) of females and 21.6% (n = 22) of males had tooth erosion (χ^2 [1, N = 150] = 0.035, P = 0.853). A greater percentage of Chinese students (65.7%) had tooth erosion compared with Malays (27.4%) and Indians (6.9%) (χ^2 [1, N = 150] = 4.448, P = 0.108); however, the difference was not statistically significant. There was no significant difference in the percentage of students with tooth erosion by age groups (P = 0.705) as well as by father's (P = 0.730) and mother's (P = 0.084) educational levels (Table 1).

A greater percentage of subjects without tooth erosion (50.0%) reported that they had received information about healthy eating compared with subjects with tooth erosion (27.5%) (Table 2). The risk of tooth erosion among subjects who had ever received information on healthy eating was lower than for those who had not (OR = 2.64, 95% CI = 1.30–5.94). Subjects reported that parents, friends/relatives, and television/magazines were the primary sources of their dietary information. More than two-thirds of the subjects in both groups reported that

Table 1: Occurrence of dental erosion according to the socio-demographic characteristics

Characteristic	Dental erosion				*P* value [a]
	Yes		No		
	n	(%)	*n*	(%)	
Gender					
Male	22	(21.6)	11	(22.9)	0.853
Female	80	(78.4)	37	(77.1)	
Ethnicity					
Malay	28	(27.4)	19	(39.6)	0.108
Chinese	67	(65.7)	23	(47.9)	
Indian	7	(6.9)	6	(12.5)	
Age (years)					
19–21	83	(81.3)	38	(79.2)	0.705
22–24	19	(18.7)	10	(20.8)	
Father's educational level [b]					
Primary school	22	(23.2)	9	(19.1)	0.730
Secondary school	52	(54.7)	29	(61.8)	
Tertiary education	21	(22.1)	9	(19.1)	
Mother's educational level [c]					
Primary school	34	(34.0)	7	(15.9)	0.084
Secondary school	51	(51.0)	28	(63.6)	
Tertiary education	15	(15.0)	9	(20.5)	

[a] Data were analysed using chi-square test. There were [b] 8 missing data for fathers' educational level and [c] 6 missing data for mother's educational level.

their most recent dental check-up was more than 6 months ago. There was no significant difference in the dental hygiene practices between subjects with and without tooth erosion (Table 2). Based on anthropometry measurements, the majority of subjects with (61.8%) and without (66.7%) tooth erosion had a normal BMI (Table 3). There was no significant difference in the occurrence of tooth erosion between subjects with different BMI classifications ($P = 0.468$).

Food and drink intake frequencies were dichotomised into 2 categories: high consumption and low consumption (Table 4). The majority of subjects frequently consumed non-erosive drinks, which included tea or coffee and milk, compared with acidic drinks. Less than 5% of subjects consumed any acidic drinks or milk more than 4 to 5 times daily. However, 22.7% of subjects consumed tea or coffee 4 to 5 times daily. No significant association was found between the frequency of acidic drink consumption and the occurrence of tooth erosion. However, there was a significant negative association between the frequency of milk consumption and the occurrence of tooth erosion ($P = 0.004$). For subjects who reported a greater frequency of milk consumption, only 12.7% had tooth erosion compared with 87.3% in the low consumption group (OR = 0.29, 95% CI = 0.13–0.67, $P = 0.004$). Subjects with and without tooth erosion reported low frequencies of acidic food consumption, except for fruits (Table 5). Less than half of the subjects (49.0%) reported a high frequency of fruit intake. Although a greater percentage of subjects with tooth erosion (49.0%) consumed fruits at a higher frequency than subjects without tooth erosion (41.7%), there was no association found between the frequency of fruit consumption and the risk of tooth erosion (OR = 1.35, 95% CI = 0.67–2.69).

Dietary analysis indicates that the amounts of acidic and erosive foods consumed by the subjects were low and were not associated with the risk of tooth erosion (Table 6). However, based on the amount of non-erosive drinks consumed, tea or

Table 2: Occurrence of dental erosion according to the status of receiving information on healthy eating and dental hygiene practices

Variable	Dental erosion				*P* value [a]	OR (95% CI)
	Yes		No			
	n	(%)	*n*	(%)		
Ever received information on healthy eating?						
Yes	28	(27.5)	24	(50.0)	0.007 [b]	2.64 (1.30–5.94)
No	74	(72.5)	24	(50.0)		
Source of dietary information on healthy eating [c]						
Medical doctors	9	(8.8)	10	(20.8)	–	–
Parents	22	(21.6)	13	(27.1)		
Friends/relatives	17	(16.7)	11	(22.9)		
Dentists	5	(4.9)	4	(8.3)		
Television/magazines	17	(16.7)	12	(25.0)		
Dieticians	2	(2.0)	5	(10.4)		
Nurses	2	(2.0)	0	(0.0)		
School teachers	11	(10.8)	7	(14.6)		
Last dental check-up						
> 6 months ago	71	(69.6)	35	(72.9)	0.678	1.18 (0.55–2.52)
Recently/within last 6 months	31	(30.4)	13	(27.1)		
Type of toothbrush						
Hard/medium bristled toothbrush	62	(60.8)	34	(70.8)	0.232	1.57 (0.75–3.28)
Soft-bristled toothbrush/unsure	40	(39.2)	14	(29.2)		
Frequency of daily teeth brushing						
1–2 times per day	77	(75.5)	37	(77.1)	0.831	1.09 (0.49–2.46)
≥ 3 times per day	25	(24.5)	11	(22.9)		

[a] *P* values were based on chi-square test, with [b] $P < 0.05$ considered significant. [c] Only respondents who had received information on healthy eating answered this question, and they were allowed to choose more than 1 answer.

Table 3: Occurrence of dental erosion according to the body mass index classification

Body mass index	Dental erosion						*P* value [a]
	Yes		No		Total		
	n	(%)	*n*	(%)	*n*	(%)	
Underweight (< 18.5)	28	(27.5)	9	(18.7)	37	(24.7)	0.468
Normal weight (18.5–24.9)	63	(61.8)	32	(66.7)	95	(63.3)	
Overweight or obese (25.0–34.9)	11	(10.7)	7	(14.6)	18	(12.0)	

[a] *P* values were based on chi-square test.

Table 4: Occurrence of dental erosion according to the frequency of acidic and non-acidic drink consumption

Consumption level	Dental erosion				*P* value [a]	OR (95% CI)
	Yes		No			
	n	(%)	*n*	(%)		
Acidic drink						
Fruit juice						
High [c]	4	(3.9)	4	(8.3)	0.268	0.45 (0.11–1.88)
Low [d]	98	(96.1)	44	(91.7)		
Fruit-flavoured drink						
High [c]	6	(5.9)	4	(8.3)	0.727	0.69 (0.19–2.56)
Low [d]	96	(94.1)	44	(91.7)		
Sugared carbonated drink						
High [c]	3	(2.9)	1	(2.1)	> 0.95	1.42 (0.14–14.06)
Low [d]	99	(97.1)	47	(97.9)		
Non-sugared carbonated drink						
High [c]	2	(2.0)	1	(2.1)	> 0.95	0.94 (0.08–10.63)
Low [d]	100	(98.0)	47	(97.9)		
Sports drink						
High [c]	1	(1.0)	1	(2.1)	0.539	0.47 (0.03–7.60)
Low [d]	101	(99.0)	47	(97.9)		
Non-acidic drink						
Tea or coffee						
High [c]	34	(33.3)	21	(43.8)	0.276	0.64 (0.32–1.30)
Low [d]	68	(66.7)	27	(56.2)		
Milk						
High [c]	13	(12.7)	16	(33.0)	0.004 [b]	0.29 (0.13–0.67)
Low [d]	89	(87.3)	32	(67.0)		

[a] *P* values were based on Fisher's exact test, with [b] $P < 0.05$ considered significant. [b] High consumption was defined as drink consumption of 4–5 times per week or more than once per day. [c] Low consumption was defined as drink consumption of 1–3 times per week or never.

coffee intake of more than 150 mL/day (the 75th percentile) indicated a reduced risk (to 43%) of experiencing tooth erosion (OR = 0.43, 95% CI = 0.21–0.90) (Table 6). In addition, a significantly reduced risk of tooth erosion was found at 107 mL/day (the 75th percentile) of milk intake (OR = 0.46, 95% CI = 0.22–0.94). However, after adjustment for confounding factors, binary logistic regression analysis revealed that the risk of tooth erosion remained statistically significant only for tea or coffee intake 150 mL/day or more, with a reduction in the risk of tooth erosion to 42% (Table 7).

Discussion

More than half of the university students aged 19–24 years who participated in this study had dental erosion. Unfortunately, limited data are available on the prevalence of tooth erosion among young adults in Malaysia. Although it is difficult to accurately compare the results of this study with other prevalence studies due to the differences in the indices used, the study criteria, the diagnostic criteria, and the tooth surfaces examined, it appears that the prevalence of tooth erosion in this study is greater than that reported

Table 5: Occurrence of dental erosion according to the frequency of acidic food consumption

Consumption level	Dental erosion				*P* value [a]	OR (95% CI)
	Yes		No			
	n	(%)	*n*	(%)		
Yogurt						
High [b]	1	(1.0)	1	(2.1)	0.539	0.47 (0.03–7.60)
Low [c]	101	(99.0)	47	(97.9)		
Ketchup						
High [b]	4	(3.9)	1	(2.1)	> 0.95	1.92 (0.21–17.64)
Low [c]	98	(69.1)	47	(97.9)		
Fruit jam						
High [b]	3	(2.9)	2	(4.2)	0.655	0.70 (0.11–4.32)
Low [c]	99	(97.1)	46	(95.8)		
Sour candy						
High [b]	4	(3.9)	1	(2.1)	> 0.95	1.92 (0.21–17.64)
Low [c]	98	(69.1)	47	(97.9)		
Dried fruit						
High [b]	12	(11.8)	6	(12.5)	> 0.95	0.93 (0.33–2.66)
Low [c]	90	(88.2)	42	(87.5)		
Fruit						
High [b]	50	(49.0)	20	(41.7)	0.483	1.35 (0.67–2.69)
Low [c]	52	(51.0)	28	(58.3)		

[a] *P* values were based on Fisher's exact test. [b] High consumption was defined as food consumption of 4–5 times per week or more than once per day. [c] Low consumption was defined as food consumption of 1–3 times per week or never.

by an aforementioned local study among adults in Kelantan (21), among university students in the United States of America (36.5%) (19) and among adults aged 26–30 years in Switzerland (29.9%) (20). Tooth erosion was reportedly higher (77%) among Saudi military men similar in age to the participants in our study (19–25 years old) (30). In the present study, there was no significant difference in the proportion of tooth erosion between genders, ethnic groups, or parental education levels. A study among adolescents aged 13–14 years in Brazil (18) also reported that gender and socio-economic class were not significantly associated with the risk of tooth erosion.

Our study found that there were no relationships between tooth erosion and the frequency and amount of acidic foods and drinks consumed. Tooth erosion is more frequently reported to be associated with acidic drinks among children (31), adolescents (5,31–33) and adults (15) when the consumption was high, and the association is not reported in children (3) when the consumption was low. In our study, the proportion of subjects who reported frequently consuming acidic drinks was too small to show a significant association with tooth erosion occurrence.

Another potential explaination for why dietery habits were not found to have any significant association with tooth erosion is that the study was cross-sectional, and therefore only assessed dietary patterns 1–2 months prior to the study. Dietary patterns during data collection may not have been the same as the dietary patterns when tooth erosion occurred. Moreover, tooth erosion is a progressive disease resulting from frequent and prolonged exposure to acidic food items. Finally, the risk of tooth erosion is multi-factorial in nature and is influenced by the tooth composition and structure and the saliva composition (31), which we did not examine in this study due to financial and time constraints.

The present study found that the amount of

Table 6: Consumption of acidic foods and non-erosive drinks, in percentiles and crude ORs

Parameter	Percentile					
	25th	OR (95% CI)	50th	OR (95% CI)	75th	OR (95% CI)
Acidic and erosive food						
Acidic drink (mL/day) [a]	36	0.67 (0.31–1.46)	97	1.00 (0.50–1.98)	197	0.83 (0.38–1.81)
Acidic non-fruit food (g/day) [b]	0	–	3	0.96 (0.48–1.91)	14	0.725 (0.33–1.57)
Acidic fruit (g/day) [c]	14	0.97 (0.44–2.16)	50	0.86 (0.45–1.76)	148	1.03 (0.47–2.26)
Non-erosive drink						
Tea or coffee (mL/day)	0	–	43	1.15 (0.58–2.30)	150	0.43 [d] (0.21–0.90)
Milk (mL/day)	0	–	17	1.95 (0.97–3.94)	107	0.46 [d] (0.22–0.94)

[a] Acidic drinks included natural fruit juice, diluted fruit juice, cordial drinks, carbonated drinks (low-calorie and non-low-calorie), soda drinks, sports drinks, sparkling drinks, alcoholic drinks, fruit cocktail drinks, and honey drinks. [b] Acidic foods included ketchup, pickles (sour, fruits, vegetables), citrus fruit-flavoured ice-cream, vinegar-containing foods, baked beans, fruit jam, sour candies, dried fruits (prunes, apricots), and raisins. [c] Acidic fruits included apple, grape, kiwi, mango, orange, lemon, mandarin orange, pineapple, star fruit, mangosteen, pear, plum, prune, strawberry, guava, and tomato. [d] Results were significant with $P < 0.05$.

Table 7: Binary logistic regression model for the amount of non-erosive drinks consumed

Parameter	Crude OR	95% CI	Adjusted OR [a]	95% CI
Tea or coffee (≥ 150/< 150 mL per day)	0.43	0.21–0.90	0.42 [b]	0.19–0.95
Milk (≥ 107/< 107 mL per day)	0.46	0.22–0.94	0.47	0.22–1.01

[a] OR adjusted for ethnicity, gender, receipt of dietary advice, and frequency of milk consumption. [b] Result was significant with $P < 0.05$.

acidic fruits consumed was not associated with the occurrence of tooth erosion. This finding is consistent with previous studies (34–36). Associations between fruit consumption and tooth erosion were reported only in studies when consumption was excessive. In case-control studies, a considerable risk of erosion has been reported when citrus foods were eaten more than twice per day (10,34). Less than half of the subjects in the present study consumed fruits 4 to 5 times per day, with a median intake of 56 g among subjects with erosion and 46 g among subjects without tooth erosion. Fruit juices are more likely to initiate tooth erosion compared with fruits themselves (37). However, we did not find a significant association between fruit juices and tooth erosion in this study ($P = 0.268$), which may be because the majority of subjects reported low fruit juice and acidic food intake.

In the present study, we found that the occurrence of tooth erosion was lower among subjects who reported greater milk consumption. One study (31) indicated that children and adults with erosion drank milk significantly less than children with no erosion. Laboratory studies have demonstrated that milk is protective against tooth erosion due to its high concentration of calcium. The calcium and phosphate in foods may have a protective effect against erosion on tooth enamel. Calcium is crucial for dental health because it helps to maintain the teeth's mineral composition in the process of demineralisation and remineralisation, which depends on dietary factors, pH, and the oral environment (2,38). Cow's milk has been demonstrated to strengthen tooth enamel by re-hardening it after exposure to acidic drinks

(4). Milk consumption among all subjects in this study was low, with a median daily consumption of 4 mL/day among subjects with tooth erosion and 46 mL/day among subjects without tooth erosion. Low consumption of milk by the subjects in this study is in agreement with data from the national survey among adults in Malaysia in 2006; the survey reports that the average milk consumption among adults was 0.14 servings per day, compared with the recommendation of 1 to 2 servings per day (39). Only 17.1% of adults in this population consumed milk 1.4 times daily (39). According to the Recommended Nutrient Intake Malaysia, adults aged 19 to 65 years should consume 800 mg of calcium per day, and the Malaysian Dietary Guidelines recommend 1–3 glasses of milk as part of a balanced diet (40). The association between the risk of having tooth erosion and milk consumption was not significant when other confounding factors were taken into account. This may be because milk consumption was low among our participants.

The present study found that tea and coffee consumption greater than 150 mL/day was associated with a reduction in the risk of tooth erosion to 42% after other confounding factors were taken into consideration. We asked the subjects in this study to recall the frequency and amount of tea and coffee consumption, but we did not specifically ask them to recall these beverages separately. We also did not ask the participants to specify whether they added milk, sugar, or both to their coffee/tea. It is possible that some subjects in this study added milk to their coffee or tea, which may have provided a protective effect. In addition, it has been reported that tea has a complex composition, and its consumption has been recognised as having some beneficial dental effects because of its appreciable fluoride content (41–43). Although tea is acidic, with a pH of 4.9, it only reduces 1 pH unit on the tooth surface, and resting pH levels are restored within approximately 2 minutes after drinking (44). Despite the possible advantages of tea, excessive consumption may lead to problems of staining of the dentition. In addition, among groups at risk of iron deficiency, such as young infants and the elderly, excessive consumption of tea should be avoided to prevent possible effects on intestinal mineral absorption. We could not find any evidence to indicate any potential protective effects of drinking coffee on tooth erosion. Further studies are highly recommended to test and clarify this finding.

The present study found that the frequency of yogurt consumption was not associated with tooth erosion. Yogurt reportedly contains high amounts of calcium and phosphate, but it is also an acidic food (16). A laboratory study (45) indicated that yogurt has no erosive potential on enamel, although it can induce the deposition of hydroxyapatite and fluorapatite, components of tooth enamel.

Subjects who reported that they had not received dietary information about healthy eating were significantly more likely to have tooth erosion compared with their counterparts. More than two-thirds of subjects reported that their most recent dental check-up was more than 6 months before the study was conducted, which indicates that dental healthcare awareness should be promoted. In this study, subjects reported that parents, relatives/friends, and television/magazines were the primary sources of dietary advice related to dental health. This indicates that dental health promotion should be channelled through parents and media to reach out to this age group. Dentists, nutritionists, and dieticians should play an important role in promoting healthy eating to maintain dental health.

Our study did not specify whether acidic foods and drinks were consumed as a meal or as a snack. Acidic foods and drinks are recommended to be consumed with meals to reduce the risk of tooth erosion, as saliva flow is high during meal time (38). In addition, the consumption of acidic drinks with swishing, holding, sipping, or using a straw was not specifically addressed in the questionnaire, which may have been very useful to study (46). This study was conducted at one of the universities in Malaysia; thus, the results of this study may not be representative of the tooth erosion occurrence and dietary patterns of the general population, due to educational status, individual preferences, and lifestyle differences. This study should be replicated using a larger sample size including subjects from a wider age range and across multiple ethnic groups. Despite these limitations, outcomes from this study have highlighted several points. First, a high occurrence of tooth erosion among young adults at the university should be addressed through oral health promotion. Second, the study supports the importance of the dietary aspect in managing tooth erosion; thus, feasible means of integrating dietary education into the dental setting and mainstream media warrants further investigation. Finally, our study demonstrates the complexity of the interaction between diet and tooth erosion in humans, as well as the need for further epidemiological studies with large, random populations.

Conclusion

This study demonstrates that subjects who consumed milk more frequently and those who had received dietary information were less likely to have tooth erosion than those who had not. The amount of tea/coffee consumed was independently associated with a reduction in the risk of tooth erosion, and this finding warrants further investigation in the future. A high occurrence of tooth erosion among university students in this study indicates that a proper health promotion programme should be implemented in schools, at the university level and in the media to increase awareness of tooth erosion and the importance of dental check-ups and healthy eating, which may help to combat tooth erosion.

Authors' Contributions

Conception and design: ZAM, NAY
Provision of study materials: BYHY, YWS
Collection and assembly of the data: LMT, NHMA, SS, JYP, BYHY, YWS
Analysis and interpretation of the data: ZAM, LMT, NHMA, SS, JYP, NHI, NAY
Statistical expertise: NHI
Drafting of the article: ZAM, LMT, NHMA, SS, JYP
Critical revision and final approval of the article: ZAM, NAY
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References

1. Ten Cate JM, Imfeld T. Dental erosion, summary. *Eur J Oral Sci*. 1996;**104(2 Pt 2)**:241–244.
2. Lussi A, Jaeggi T, Zero D. The role of diet in the aetiology of dental erosion. *Caries Res*. 2004;**38(Suppl 1)**:34–44.
3. Luo Y, Zeng XJ, Du MQ, Bedi R. The prevalence of dental erosion in preschool children in China. *J Dent*. 2005;**33(2)**:115–121.
4. Gedalia I, Dakuar A, Shapira L, Lewinstein I, Goultschin J, Rahamim E. Enamel softening with Coca-Cola and rehardening with milk or saliva. *Am J Dent*. 1991;**4(3)**:120–122.
5. Milosevic A, Bardsley PF, Taylor S. Epidemiological studies of tooth wear and dental erosion in 14-year old children in North West England. Part 2: The association of diet and habits. *Br Dent J*. 2004;**197(8)**:479–483; discussion 3; quiz 505.
6. Ehlen LA, Marshall TA, Qian F, Wefel JS, Warren JJ. Acidic beverages increase the risk of in vitro tooth erosion. *Nutr Res*. 2008;**28(5)**:299–303.
7. Lussi A, Jaeggi T, Schaffner M. Diet and dental erosion. *Nutrition*. 2002;**18(9)**:780–781.
8. Al-Majed I, Maguire A, Murray JJ. Risk factors for dental erosion in 5–6 year old and 12–14 year old boys in Saudi Arabia. *Community Dent Oral Epidemiol*. 2002;**30(1)**:38–46.
9. Seow WK, Thong KM. Erosive effects of common beverages on extracted premolar teeth. *Aust Dent J*. 2005;**50(3)**:173–178; quiz 211.
10. Kunzel W, Cruz MS, Fischer T. Dental erosion in Cuban children associated with excessive consumption of oranges. *Eur J Oral Sci*. 2000;**108(2)**:104–109.
11. Ren YF, Amin A, Malmstrom H. Effects of tooth whitening and orange juice on surface properties of dental enamel. *J Dent*. 2009;**37(6)**:424–431.
12. Parry J, Shaw L, Arnaud MJ, Smith AJ. Investigation of mineral waters and soft drinks in relation to dental erosion. *J Oral Rehabil*. 2001;**28(8)**:766–772.
13. Larsen MJ. Prevention by means of fluoride of enamel erosion as caused by soft drinks and orange juice. *Caries Res*. 2001;**35(3)**:229–234.
14. Jensdottir T, Arnadottir IB, Thorsdottir I, Bardow A, Gudmundsson K, Theodors A, et al. Relationship between dental erosion, soft drink consumption, and gastroesophageal reflux among Icelanders. *Clin Oral Investig*. 2004;**8(2)**:91–96.
15. Johansson AK, Lingstrom P, Birkhed D. Comparison of factors potentially related to the occurrence of dental erosion in high- and low-erosion groups. *Eur J Oral Sci*. 2002;**110(3)**:204–211.
16. Kargul B, Caglar E, Lussi A. Erosive and buffering capacities of yogurt. *Quintessence Int*. 2007;**38(5)**:381–385.
17. Peres KG, Armenio MF, Peres MA, Traebert J, De Lacerda JT. Dental erosion in 12-year-old schoolchildren: A cross-sectional study in Southern Brazil. *Int J Paediatr Dent*. 2005;**15(4)**:249–255.
18. Auad SM, Waterhouse PJ, Nunn JH, Steen N, Moynihan PJ. Dental erosion amongst 13- and 14-year-old Brazilian schoolchildren. *Int Dent J*. 2007;**57(3)**:161–167.

19. Mathew T, Casamassimo PS, Hayes JR. Relationship between sports drinks and dental erosion in 304 university athletes in Columbus, Ohio, USA. *Caries Res*. 2002;**36(4)**:281–287.

20. Lussi A, Schaffner M, Hotz P, Suter P. Dental erosion in a population of Swiss adults. *Community Dent Oral Epidemiol*. 1991;**19(5)**:286–290.

21. Saerah NB, Ismail NM, Naing L, Ismail AR. Prevalence of tooth wear among 16-year-old secondary school children in Kota Bharu Kelantan. *Arch Orofac Sci*. 2006;**1**:21–28.

22. Daly RWR, Wan Bakar WZ, Husein A, Ismail NM, Amaechi BT. The study of tooth wear patterns and their associated aetiologies in adults in Kelantan, Malaysia. *Arch Orofac Sci*. 2010;**5(2)**:47–52.

23. Lwanga SK, Lemeshow S. *Sample size determination in health studies: A practical manual*. Geneva (CH): World Health Organization; 1991.

24. Hou XM, Zhang Q, Gao XJ, Wang JS. Pilot study of dental erosion and associated factors in university student volunteers. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2005;**40(6)**:478–480.

25. Lee RD, Nieman DC. *Nutritional Assessment*. 4th ed. New York (NY): McGraw-Hill; 2007.

26. Gregory JR, Lowe S, Bates CJ, Prantice A, Jackson LV, Smithers G, et al. *National Diet and Nutrition Survey: Young people aged 4 to 18 years. Volume 1: Report of the diet and nutrition survey*. London (GB): The Stationery Office; 2000.

27. Bartlett D, Ganss C, Lussi A. Basic Erosive Wear Examination (BEWE): A new scoring system for scientific and clinical needs. *Clin Oral Investig*. 2008;**12 (Suppl 1)**:65–68.

28. Mulic A, Tveit AB, Wang NJ, Hove LH, Espelid I, Skaare AB. Reliability of two clinical scoring systems for dental erosive wear. *Caries Res*. 2010;**44(3)**: 294–299.

29. World Health Organization. *Obesity: Preventing and managing the global epidemic: Report of a WHO Consultation on Obesity, Geneva*, 3–5 June 1997. Geneva (CH): World Health Organization; 1998.

30. Johansson AK, Johansson A, Birkhed D, Omar R, Baghdadi S, Carlsson GE. Dental erosion, soft-drink intake, and oral health in young Saudi men, and the development of a system for assessing erosive anterior tooth wear. *Acta Odontol Scand*. 1996;**54(6)**: 369–378.

31. O'Sullivan EA, Curzon ME. A comparison of acidic dietary factors in children with and without dental erosion. *ASDC J Dent Child*. 2000;**67(3)**:186–192, 160.

32. Al-Dlaigan YH, Shaw L, Smith A. Dental erosion in a group of British 14-year-old, school children. Part I: Prevalence and influence of differing socioeconomic backgrounds. *Br Dent J*. 2001;**190(3)**:145–149.

33. Harding MA, Whelton H, O'Mullane DM, Cronin M. Dental erosion in 5-year-old Irish school children and associated factors: A pilot study. *Community Dent Health*. 2003;**20(3)**:165–170.

34. Jarvinen VK, Rytomaa, II, Heinonen OP. Risk factors in dental erosion. *J Dent Res*. 1991;**70(6)**:942–947.

35. Moynihan P, Petersen PE. Diet, nutrition and the prevention of dental diseases. *Public Health Nutr*. 2004;**7(1A)**:201–226.

36. Caglar E, Kargul B, Tanboga I, Lussi A. Dental erosion among children in an Istanbul public school. *J Dent Child (Chic)*. 2005;**72(1)**:5–9.

37. Grobler SR, Senekal PJ, Kotze TJ. The degree of enamel erosion by five different kinds of fruit. *Clin Prev Dent*. 1989;**11(5)**:23–28.

38. Moynihan PJ. The role of diet and nutrition in the etiology and prevention of oral diseases. *Bull World Health Organ*. 2005;**83(9)**:694–699.

39. *Malaysian Adult Nutrition Survey 2003: Habitual food intake of adults aged 18–59 years*. Volume 7. Putrajaya (MY): Nutrition Section, Family Health Development Division, Ministry of Health Malaysia; 2008.

40. *RNI: Recommended nutrient intakes for Malaysian: A report of the technical working group on nutritional guidelines*. Putrajaya (MY): National Coodinating Committee on Food and Nutrition, Ministry of Health Malaysia; 2005.

41. Duckworth SC, Duckworth R. The ingestion of fluoride in tea. *Br Dent J*. 1978;**145(12)**:368–370.

42. Walters CB, Sherlock JC, Evans WH, Read JI. Dietary intake of fluoride in the United Kingdom and fluoride content of some foodstuffs. *J Sci Food Agric*. 1983;**34(5)**:523–528.

43. Zohouri FV, Rugg-Gunn AJ. Sources of dietary fluoride intake in 4-year-old children residing in low, medium and high fluoride areas in Iran. *Int J Food Sci Nutr*. 2000;**51(5)**:317–326.

44. Simpson A, Shaw L, Smith AJ. Tooth surface pH during drinking of black tea. *Br Dent J*. 2001;**190(7)**: 374–376.

45. Wongkhantee S, Patanapiradej V, Maneenut C, Tantbirojn D. Effect of acidic food and drinks on surface hardness of enamel, dentine, and tooth-coloured filling materials. *J Dent*. 2006;**34(3)**: 214–220.

46. Grobler SR, Jenkins GN, Kotze D. The effects of the composition and method of drinking of soft drinks on plaque pH. *Br Dent J*. 1985;**158(8)**:293–296.

Original Article

Acute Meningoencephalitis in Hospitalised Children in Southern Bangladesh

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Abstract

Background: **Acute meningoencephalitis is an important cause of morbidity and mortality around the globe. The objective of this study was to examine the distribution of acute meningoencephalitis and its aetiological agents among children admitted to a tertiary hospital in southern Bangladesh.**

Methods: **This prospective study was carried out in Khulna Medical College Hospital from 2007 to 2009. All of the admitted children between 1 month and 12 years of age were enrolled over a 2-year period if they met the inclusion criteria of having an acute onset of fever (≤ 14 days) and any of the following 3 signs: neck stiffness, convulsion, or altered mental status. Cerebrospinal fluid (CSF) was collected within hours and sent to the laboratory for cytological and biochemical analyses. CSF was examined by Gram staining and a latex agglutination test to detect common bacteria. Serum and CSF were also tested for Japanese encephalitis virus antibodies.**

Results: **A total of 140 children were included in the study, which accounted for 2.5% of admissions between 2007 and 2009. The number of acute meningoencephalitis cases was relatively higher (37.9%) during the monsoon season. The CSF report revealed a pyogenic form in 24 (18.5%) and a viral form in 13 (10.0%) cases. Altered mental status was significantly less frequent ($P < 0.001$) in cases of pyogenic meningoencephalitis (62.5%) than in cases of non-pyogenic meningoencephalitis (93.4%). Bacterial causes were identified in 11 (8.5%) children; the causative agents included *Streptococcus pneumoniae* ($n = 8$), *Neisseria meningitides* ($n = 2$), and *Haemophilus influenzae* ($n = 1$). Three (2.3%) patients were positive for Japanese encephalitis virus.**

Conclusion: ***S. pneumoniae*** **was the most common bacteria causing acute meningoencephalitis among the study subjects, and Japanese encephalitis virus was present in few patients.**

Keywords: *aetiology, Bangladesh, children, infectious diseases, meningoencephalitis, symptoms*

Introduction

Acute meningitis and acute encephalitis constitute significant public health problems worldwide (1,2). Although bacteria are predominantly responsible for meningitis, viruses can cause both meningitis and encephalitis with equal frequency (3). It is often difficult to reliably differentiate meningitis and encephalitis clinically (4). Therefore, the term acute meningoencephalitis (AME) is used to denote both conditions. Despite advancements in diagnostic techniques and antimicrobial therapies, AME remains an emergency infectious disease with a high fatality (5,6).

It has been estimated that 1–2 million cases of acute bacterial meningitis (ABM) occur annually worldwide (7). The problem is more acute in resource-poor countries in Latin America, sub-Saharan Africa, and South–East Asia (8). *Neisseria meningitides, Streptococcus pneumoniae*, and *Haemophilus influenzae* type b are pathogens most commonly associated with bacterial meningitis globally, accounting for almost 90% of reported cases in patients between 2 months and 5 years of age (9). The overall

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incidence of ABM in developed countries is 2–3 per 100 000, with peaks of incidence in infants and adolescents (10). The incidence of bacterial meningitis among children in developing countries is 10–20 per 100 000, a figure more than 10 times higher than that in Western Europe and the United States (11).

Viral meningoencephalitis is caused by a wide range of viruses, although most cases are caused by enterovirus, herpes simplex virus, and mumps virus (12). Japanese encephalitis (JE) virus is the main cause of meningoencephalitis in Asia, with 30 000–50 000 cases reported annually (13). Children between 5 and 15 years old are primarily affected, with a fatality rate of 20%–30%; in addition, one-third of survivors experience neuropsychiatric sequelae (13,14). The emerging Nipah virus causes severe febrile encephalitis, resulting in the death of 40%–75% of affected people, and in the recent past, several outbreaks of Nipah encephalitis have occurred in northwestern Bangladesh (15,16).

AME can be rapidly progressive, resulting in permanent sequelae in a relatively short period of time (6). The ability to treat the meningitis patients immediately depends upon the findings of the CSF examination. The emphasis is first not to miss bacterial meningitis and second not to treat viral meningitis with inappropriate antibiotics or steroids (17). Epidemiological and microbiological studies of AME are necessary to develop appropriate clinical management strategies and to implement effective preventive measures. However, national data on AME are extremely limited in Bangladesh. Therefore, this study was performed to determine the distribution of acute meningoencephalitis and the aetiological agents in children admitted to a tertiary care hospital in southern Bangladesh.

Subjects and Methods

This prospective study was carried out in the paediatrics ward of Khulna Medical College Hospital for a period of 2 years, from October 2007 to September 2009. Khulna Medical College Hospital is the only teaching hospital in southern Bangladesh and admits patients from all districts of the Khulna Division and from the neighbouring districts of other divisions. All of the admitted children between 1 month and 12 years of age who met the case definition of AME were included in this study. AME was defined as the acute onset of fever (1–14 days), followed by any of the followings: (a) signs of meningeal irritation, (b) convulsions, or (c) a change in mental status (18). Children diagnosed later with febrile convulsions, cerebral palsy, stroke, or epilepsy were excluded from the study. Written permission was obtained from each parent after he or she was informed about the purpose of the study. Ethical permission was obtained from the ethical review committee of the International Centre for Diarrhoeal Disease Research, Bangladesh, and of the Khulna Medical College Hospital.

After a provisional diagnosis of AME, a trained doctor recorded each patient's history, examined the patient, collected specimens, and monitored the progress of the disease. All of the information was noted in a pre-designed form. In addition to taking a blood sample, cerebrospinal fluid (CSF) was collected within 2 hours from all patient unless contraindicated and was sent for biochemical and cytological analyses. In the microbiology laboratory, CSF was tested by Gram staining and latex agglutination test to detect the antigens of *S. pneumoniae, N. meningitides,* and *H. influenzae*. The serum and CSF samples were aliquoted in the laboratory and stored in –20 °C freezer. The samples were transported in a cool box to the virology laboratory (Institute of Public Health) twice per month. The detection of JE virus IgM antibodies was carried out by enzyme-linked immunosorbent assays. Blood and CSF cultures could not be performed, and the serum was tested only for JE virus.

The CSF findings were categorised as viral or pyogenic based on the following criteria (17,19): (a) normal to high pressure, clear CSF, cell count of < 1000 cells/mm^3, predominance of lymphocytes, CSF-to-plasma glucose ratio of > 0.3, and protein level of 0.5–1 g/L indicate viral AME, and (b) high pressure, cloudy CSF, cell count of > 1000 cells/mm^3, predominance of neutrophils, CSF-to-plasma glucose ratio of < 0.3, and protein level of > 1 g/L indicate pyogenic AME. Based on physical characteristics of the CSF, treatment was started immediately. The treatment included parenteral antibiotics (ceftriaxone/cefotaxime), steroids, and supportive therapy for bacterial meningoencephalitis and was reassessed after receiving the bacteriology report (20). Cases of non-bacterial meningoencephalitis were managed symptomatically and by supportive therapy. Patients were observed twice daily, in the morning and evening, to monitor the recovery process or the development of complications.

The data were entered and analysed using SPSS version 12 (SPSS Inc., Chicago, IL, US). For continuous variables, the mean was calculated for symmetrical data, and the median was calculated for asymmetrical data. The categorical

variables were described using the frequency and percentages.

Results

During the 2-year study period, 5605 children were admitted to the paediatric ward; 140 (2.5%) of the children met the inclusion criteria for AME. The mean (SD) age of AME cases was 60 (46) months. Sixty-four cases (45.7%) were identified in children younger than 48 months, and 41 patients (29.2%) were infants (≤ 12 months). The male-to-female ratio of the children was 1.4:1. One hundred and thirty-two (94.3%) children were Muslims (Table 1). Most of the admitted children (80, 57.1%) were from Khulna, followed by Jessore (45, 32.1%). AME cases were present throughout the year, with few increases and decreases in the incidence, but a consistent high number of cases (53, 37.9%) was observed between July and October, which is the monsoon period in Bangladesh (Figure 1). Of the 3 JE-positive cases, 2 occurred in October, and the other occurred in November.

The prodromal phase, calculated from the onset of fever to the onset of neurological features, ranged 1–14 days, and mean period was 4.3 days (SD 3.5). According to the laboratory report, the CSF was classified into 3 categories. Lumber puncture could not be performed in 10 cases because of contraindications or refusal of the attendants. The reports were normal in 93 (71.5%) cases, pyogenic in 24 (18.5%) cases, and viral in 13 (10.0%) cases. The clinical presentation of the cases was analysed in relation to the CSF results (Table 2). The majority of cases (59, 45.4%) presented with 2 features, both altered mental status and seizure. Altered mental status was significantly more frequent ($P < 0.001$) in non-pyogenic AME (99 out of 106, 93.4%) than in pyogenic AME (15 out of 24, 62.5%).

Table 1: Demography of the study subjects

Parameter	*n*	%
Age		
1–48 months	64	45.7
49–96 months	43	30.7
97–144 months	33	23.6
Sex		
Male	82	58.6
Female	58	41.4
Religion		
Muslim	132	94.3
Hindu	8	5.7
Home district		
Khulna	80	57.1
Jessore	45	32.1
Kushtia	7	5.1
Others	8	5.7

The total number of subjects was 140.

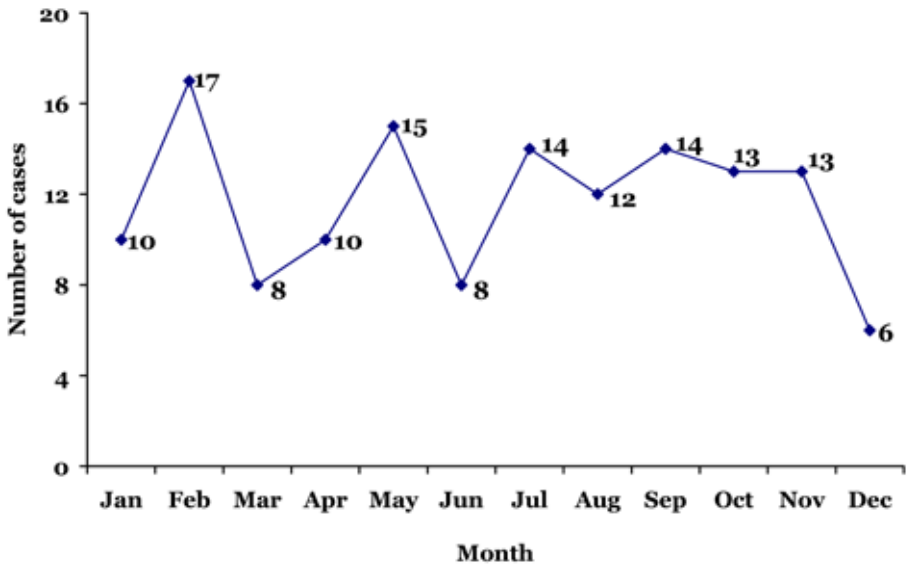

Figure 1: Monthly distribution of acute meningoencephalitis cases

In contrast, the proportion of patients with neck stiffness was higher for pyogenic AME (13 out of 24, 54.2%) than non-pyogenic AME (41 out of 106, 38.7%), but this difference was not statistically significant ($P = 0.246$).

The aetiological causes of AME were analysed with respect to the CSF results (Table 3). Bacterial causes were identified only in 11 (8.5%) children, all of whom had pyogenic AME. *S. pneumoniae* was detected more frequently (8 cases) than *N. meningitides* (2 cases) and *H. influenzae* (1 case). JE virus-specific IgM was found in 3 (2.3%) patients: 2 had antibodies in the CSF, and 1 had antibodies in the serum. All JE-positive cases except 1 had CSF results indicative of a viral infection.

Discussion

The AME cases constituted 2.5% of all hospital admissions during the study period. Young children, particularly infants (29.2%), were the most affected. No difference among affected children was found with respect to sex, religion, and location. In an Indian study (21), among all paediatric admissions, 1.5% were due to ABM. In Finland, the annual incidence of viral meningoencephalitis is 219, 27.8, and 7.6 per 100 000 for infants, children, and adult, respectively (12). Kabilan et al. (18) observed that the mean age of patients with JE was 5.5 years (SD 5.8), with a range from 6 months to 12 years. Nearly 70% of those patients were between 3 and 8 years old, and both the sexes were equally affected. The results of present study are, for the most part, in agreement with those of other reports.

The number of AME cases in this study was slightly higher during the monsoon period (37.9%), but the difference was not statistically significant. In contrast to this, two-third of the cases in Tamilnadu district of India were admitted during the monsoon period, coinciding with a high JE vector density during the period of cultivation (18). There were 8 human Nipah virus outbreaks in Bangladesh from 2001 to 2008, all occurring between December and May (22,23). Most cases of viral encephalitis in temperate climates occur

Table 2: Clinical features according to cerebrospinal fluid (CSF) categorical finding

Symptom/sign	CSF finding						Total	
	Normal		pyogenic		Viral			
Seizure	3	(2.3)	3	(2.3)	1	(0.8)	7	(5.3)
Neck stiffness	2	(1.5)	3	(2.3)	0	(0.0)	5	(3.8)
Altered mental status	7	(5.3)	1	(0.8)	2	(1.5)	10	(7.7)
Seizure + neck stiffness	1	(0.8)	3	(2.3)	0	(0.0)	4	(3.1)
Seizure + Altered mental status	48	(36.9)	7	(5.3)	4	(3.1)	59	(45.4)
Neck stiffness + Altered mental status	5	(3.8)	1	(0.8)	1	(0.8)	7	(5.4)
Seizure + neck stiffness + altered mental status	27	(20.8)	6	(4.6)	5	(3.8)	38	(29.2)
Total	93	(71.5)	24	(18.5)	13	(10.0)	130	(100.0)

The total number of samples was 130. Data are expressed in number of cases (percentage).

Table 3: Detection of pathogens according to the cerebrospinal fluid (CSF) biochemistry results

CSF results	Pathogen										Total	
	None		SP		NM		HI		JE			
Normal	92	(70.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	93	(71.5)
pyogenic	13	(10.0)	8	(6.2)	2	(1.5)	1	(0.8)	0	(0.0)	24	(18.5)
Viral	11	(8.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.5)	13	(10.0)
Total	116	(89.2)	8	(6.1)	2	(1.5)	1	(0.8)	3	(2.3)	130	(100.0)

The total number of samples was 130. Data are expressed in number of cases (percentage). Abbreviation: SP = *Streptococcus pneumoniae*, NM = *Neisseria meningitides*, HI = *Haemophilus influenzae*, JE = *Japanese encephalitis virus*.

during the summer and fall (3). The only viral aetiological agent tested for in this study was JE virus, and the seasonality could not be ascertained due to small number of JE cases.

The mean length of the prodromal phase of the AME cases was 4.3 days (SD 3.4). Regarding clinical features, altered mental status (88%) was the most frequent presentation and was significantly more frequent in patients with non-pyogenic AME ($P < 0.001$). The majority of patients (45.4%) presented with both altered mental status and seizure. Neck stiffness was more frequent in patients with pyogenic AME (54.1%) than in those with non-pyogenic AME (38.6%), but the difference was not significant ($P = 0.246$). In Mexico, 21% of ABM patients presented on admission with the classic clinical triad of fever, altered mental status, and nuchal rigidity (1). Seizure disorder was present in 54% of patients and was most commonly observed in children aged 6 to 12 months of age. A study from Mozambique (20) suggested that the most evident clinical difference in ABM between children and adults was neck stiffness. Diagana et al. (14) noted that the first sign of JE appeared after 6–14 days and that convulsions were experienced by 85% of subjects. The higher frequency of altered mental status in the present study suggested that the majority of AME cases were of viral origin. However, the prodromal phase and clinical presentation of the 3 JE-positive cases were not notably different from that of other types of meningoencephalitis.

The overall bacterial detection rate in this series was very low (8.5%), but it was 45.8% among patients with pyogenic meningoencephalitis. The majority of bacterial cases were due to *S. pneumoniae* (6.1%), followed by *N. meningitides* (1.5%) and *H. influenzae* (0.8%). The pre-hospital use of antibiotics was a major factor hindering the isolation of bacteria. Although this practice can reduce the mortality of patients, it can increase the rate of emergence of resistant bacteria (24). Majed et al. (25) studied 160 CSF samples from patients with bacterial meningitis and found that 31 (19.4%) were culture positive, revealing the growth of *H. influenzae* (45%), *S. pneumoniae* (29%), and *N. meningitides* (19%); among children under 5 years old, *S. pneumoniae* was found in 80% of culture-positive cases. Another hospital-based study from Bangladesh (26) revealed that among 24% bacteria-positive cases of ABM, 18% were due to *N. meningitides*, 3% were due to *S. pneumoniae*, and 3% were due to *H. influenzae*. In contrast to this observation, *H. influenzae* (70%) was recorded as the main agent, followed by *N. meningitides* (13%) and *S. pneumoniae* (10%), in the United States (27). Among the types of meningitis caused by the 3 important organisms, *H. influenzae* meningitis has decreased over time due to vaccination, but *S. pneumoniae* continues as persistent pathogen (28,29). Nearly 500 million people in the world harbour *N. meningitides* in their nasopharynx, but only a few develop meningococcaemia, and most of these cases occur in sub-Saharan Africa (29,30). Because the frequency of detection of bacteria in the CSF was low in this study and only 3 cases were positive for JE virus, other viruses such as herpes and Nipah could not be ruled out as causative agents.

The primary limitation of this epidemiological study was its hospital-based nature. The inability to isolate other viruses was also an obstacle in identifying the actual causative agent. Blood and CSF culturing, procedures not used in this study, could be very helpful, not only for detecting bacteria but also for choosing the proper antibiotic in the management of AME cases. An estimate of the cost of the care could better explain the burden of the problem.

Conclusion

AME remains as an important cause of emergency hospitalisation of children, particularly infants. It is difficult to differentiate bacterial and viral causes of AME by clinical features alone, but altered mental status is frequently associated with the non-pyogenic form of AME. Limited investigation of the aetiological agent revealed that *S. pneumoniae* tops the list of bacteria and that JE virus was present in a small number of patients. Further large-scale studies are required to explore the national picture of AME in Bangladesh.

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Authors' Contributions

Conception and design: MR
Analysis and interpretation of the data, CHR, FM, MJH, KUA
Drafting of the article: CHR, MJH
Critical revision and final approval of the article: CHR, FM, MJH, KUA, MR

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References

1. Franco-Paredes C, Lammoglia L, Hernandez I, Santos-Preciado JI. Epidemiology and outcome of bacterial meningitis in Mexican children: 10-year experience (1993–2003). I*nt J Inf Dis*. 2008;**12(4)**:380–386.
2. Mwangi I, Berkley J, Lowe B, Peshu N, Marsh K, Newton CR. Acute bacterial meningitis in children admitted to a rural Kenyan Hospital: Increasing antibiotic resistance and outcome. *Pediatr Infec Dis J*. 2002;**21(11)**:1042–1048.
3. Prober CG. Acute bacterial meningitis and viral meningoencephalitis. In: Behrman RE, Kliegman R, Jenson HB, editors. *Nelson textbook of pediatrics*. 17th ed. Philadelphia (PA): Saunders; 2004. p. 2038–2047.
4. Logan SA, Macmohan E. Viral meningitis. *BMJ*. 2008;**336(7634)**:36–40.
5. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med*. 2001;**336(10)**:708–716.
6. Robbins JB, Schneerson R, Gotschlich EC. Surveillence for bacterial meningitis by means of polymerase chain reaction. *Clin Inf Dis*. 2005;**40(1)**:26–27.
7. Bennet JV, Platonov AE, Slack MPE, Mala P, Burton H, Robertson SE. *Haemophilus influenzae type b (Hib) meningitis in the pre-vaccine era: A global review of incidence, age distribution, and case fatality rate*. Geneva (CH): World Health Organization; 2002.
8. Van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adult. *N Engl J Med*. 2006;**354(1)**:44–53.
9. Tzanakaki G, Mastrantonio P. Aetiology of bacterial meningitis and resistance to antibiotic of causative pathogens in Europe and in Mediterranean region. *Int J Antimicrob Agents*. 2007;**29(6)**:621–629.
10. Ramakrishnan KA, Levin M, Faust SN. Bacterial meningitis and brain abscess. *Medicine*. 2009;**37(4)**:567–573.
11. Kabani A, Jadavji T. Sequelae of bacterial meningitis in children. *Pediatr Infect Dis*. 1992;**45(6)**:209–217.
12. Rice P. Viral meningitis and encephalitis. *Medicine*. 2009;**37(11)**:574–578.
13. World Health Organization. Japanese encephalitis vaccines. *Wkly Epidemiol Rec*. 2006;**81**:331–340.
14. Diagana M, Preuex PM, Dumas M. Japanese encephalitis revisited. *J Neurol Sc*. 2007;**262(1–2)**: 165–170.
15. Epstein JH, Field HE, Luby S, Pullium JR, Daszak P. Nipah virus: Impact, origins, and causes of emergence. *Curr Inf Dis Rep*. 2006;**8(1)**:59–65.
16. Luby SP, Rahman M, Hossain MJ, Blum LS, Hussain MM, Gurley E et al. Food borne transmission of Nipah virus, Bangladesh. *Emer Infec Dis*. 2006;**12(12)**:1988–1994.
17. Chavanet P, Schaller C, Levy C, Flores-Cordero J, Arens M, Piroth L, et al. Performance of a predictive rule to distinguish bacterial and viral meningitis. *J Inf*. 2007;**54(4)**:328–336.
18. Kabilan L, Vrati S, Ramesh S, Srinivasan S, Appaiahgari MB, Arunachalam N, et al. Japanese encephalitis virus (JEV) is an important cause of encephalitis in children of Cuddalore district, Tamil Nadu, India. *J Clin Virol*. 2004;**31(2)**:153–159.
19. Kneen R, Solomon T. Management and outcome of viral encephalitis in children. *Paediatr Child Health*. 2007;**18(1)**:7–16.
20. Sigaque B, Roca A, Sanz S, Oliveiras I, Martinez M, Mandomando I, et al. Acute bacterial meningitis among children, in Manhica, a rural area in southern Mozambique. *Acta Trop*. 2008;**105(1)**:21–27.
21. Anjela S, Aggarwal A. Acute bacterial meningitis. *Indian Pediat*r. 1997;**34**:1097–1099.
22. International Centre for Diarrhoeal Disease Research, Bangladesh. Person-to-person transmission of Nipah infection in Bangladesh, 2007. *Health Sci Bull*. 2007;**5(4)**:1–6.
23. Luby SP, Gurley ES, Hossain MJ. Transmission of human infection with Nipah virus. *Clin Inf Dis*. 2009;**49(11)**:1743–1748.
24. Youssef FG, El-Sakk H, Azab A, Eloun S, Chapman GD, Ismail T, et al. Etiology, antimicrobial susceptibility profiles, and mortality associated with bacterial meningitis among children in Egypt. *Ann Epidemiol*. 2004;**14(1)**:44–48.
25. Mazed MA, Tarafdar S, Miah RAM. Antibacterial sensitivity pattern of bacteria causing meningitis in paediatric patients. *Bang J Child Health*. 2003;**27(1)**:1–5.

26. Gurley ES, Hossain MJ, Montgomery SP, Petersen LR, Sejvar JJ, Mayer LW, et al. Etiologies of bacterial meningitis in Bangladesh: Results from a hospital-based study. *Am J Trop Med Hyg*. 2009;**81(3)**: 475–483.

27. Gray LD, Fedorku DP. Laboratory diagnosis of bacterial meningitis. *Clin Microbiol Rev*. 1992;**5(2)**:130–195.

28. Singhi P, Bansal A, Geeta P, Singhi S. Predictor of long term neurological outcome in bacterial meningitis. *Ind J Pediatr*. 2007;**74(4)**:369–374.

29. Tzeng YL, Stephens DS. Epidemiology and pathogenesis of Neisseria meningitidis. *Microbes Infec*. 2000;**2(6)**:687–700.

30. Berkley JA, Mwangi I, Ngetsa CJ, Mwarumba S, Lowe BS, Marsh K, et al. Diagnosis of acute bacterial meningitis in children at a district hospital in sub-Saharan Africa. *Lancet*. 2001;**357(9270)**: 1753–1757.

Brief Communication

Financial Loss and Suicide

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Abstract

The current Western psychiatric wisdom states that suicide is always or almost always associated with mental disorder. Careful Asian studies are casting doubt on this conclusion. Using information from the public record (newspapers, coroner's reports, and various web-based sources), we sought evidence that, in the absence of mental disorder, suicide may be associated with major financial loss. Reports of 15 individuals who completed suicide following major financial loss were identified, thus an association between these events is supported.

Keywords: *life change events, medicalisation, stress, suicide, public health*

Introduction

The current Western psychiatric wisdom states that suicide is the result of mental disorder in 98% (1) or even 100% (2) of cases. However, a number of recent studies (3–5) have reported that, in Asian countries, mental disorder has been found in less than 50% of those who completed suicide.

In the late 19th century, Emil Durkheim, a sociologist, published (6) important observations. Durkheim found that suicide was primarily a function of social circumstances; he stated that people suicide when they are not supported by or well integrated into the society, and that mental disorder was relatively less important. The majority of his observations have been supported: for example, he found that marital breakdown frequently led to suicide, particularly among males, and this has been repeatedly demonstrated (7).

Our group has argued the importance of the predicament in which suicide is completed (8). In particular, we have demonstrated that suicide may occur in the absence of mental disorder when there is a loss of reputation (9) and in response to the threat of terminal illness (10).

Poverty is a risk factor for suicide, but only when there is great disparity in wealth: when some people are in poverty, but others nearby are wealthy. Personal debt is a risk factor (11), and suicide rates increase when the economy is in bad shape (12). A recent monograph (13) explores the motives for suicide as depicted in the movies, and finds that relationship and economic breakdown are commonly represented in this medium. We were interested to examine whether, in the real world, in the absence of mental disorder, loss of wealth might be associated with suicide.

Materials and Methods

As in previous studies (8–10), we examined the public record (newspapers, coroner's reports, and various web-based sources) for accounts of suicide associated with financial loss, and arranged these into groups. This approach has a predominantly qualitative research basis (directing attention away from epidemiological numbers and towards fellow human beings); however, it has the advantage of being able to refer to specific individuals and situations without confidentiality complications, as the materials are already publicly available.

Results

We located details of 15 people who had completed suicide in the setting of acute financial loss. Three separate groups can be determined:

1. A group who lost their life savings

This group includes Rene-Thierry Magon de la Villehuchet (65 years old, died in 2008, USA), Edna Coulic (43 years old, died in 2008, Canada), and Major William Foxon (65 years old, died in 2009, UK), who were defrauded. It also includes Ahmed Abdelaal (55 years old, died in 2008, Egypt) and Adolf Merckle (74 years old, died in 2009, Germany) who were not defrauded but had lost fortunes through the global financial crisis.

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2. A group who were being investigated for fraud

Fraud was only detected when those individuals who completed suicide had lost their own funds, such that they were no longer able to hide their activities. This group includes David Seaton (56 years old, died in 2006, UK), Jay Korn (70 years old, died in 2010, USA), Michael Greenberg (50 years old, died in 2010, USA), Kenneth McLeod (48 years old, died in 2010, USA), Ashvin Zaveri (71 years old, died in 2010, USA), Mark Madoff (46 years old, died in 2010, USA), and Dieter Frerichs (72 years old, died in 2010, Spain).

3. A group in financial difficulties, who killed other family members before killing themselves

This group includes William Parente (50 years old, died in 2009, USA) who was under investigation for fraud and killed 3 family members before himself, and Christopher Foster (50 years old, died in 2008, UK) whose business practices had been criticised in court, who later killed 2 family members before himself. This group also includes Karthik Rajaram (45 years old, died in 2008, USA) who was not under investigation for wrong doing but lost his fortune on the stock market and killed 5 family members before himself.

Discussion

Newspaper reports are written by experienced journalists who take care to discover all relevant facts; their reputations and livelihoods depend on accuracy. They pay particular attention to any evidence of mental disorder. Coroners also take great care (and have even greater access to information) as they make legal determinations, and their findings have been recommended as valuable sources for suicide research (14).

The public record (newspapers, substantiated in many cases by coroner's determinations) make no suggestion of mental disorder in either the first group of 5 individuals who had lost their life savings, or the second group of 7 individuals who had lost their assets and were also being investigated for fraud.

It is agreed that those who were being investigated for fraud suffered the stress of not only financial loss but also, potentially, loss reputation loss. Reputation loss can trigger suicide (9). However, for these people, the initial event was the financial loss, and their inclusion in this study is justified.

The killing of family members before completing suicide suggests mental disorder. However, the public record does not strongly support this notion. Christopher Forster, for example, attended a party with his family hours before the deaths, and no guests observed any evidence of mental disorder. It is possible (but doubtful) that such evidence was overlooked.

If necessary, this last group can be put aside. The remaining records of the 12 individuals from the first 2 categories still strenuously indicate that financial loss (with or without suspicion of fraud) can lead to suicide, in the absence of mental disorder. This finding supports the need to take a broad view of suicide and emphasises the potential benefit of considering the personal predicaments (8) of individuals, when attempting to prevent such actions.

Authors' Contributions

Conception and design, analysis and interpretation of the data, drafting, critical revision, and final approval of the article: SP, AR.

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References

1. Bertolote J, Fleischmann A, De Leo D, Wasserman D. Psychiatric diagnoses and suicide: Revisiting the evidence. *Crisis*. 2004;**25(4)**;147–155.

2. Dorpat TL, Ripley HS. A study of suicide in the Seattle area. *Compr Psychiatry*. 1960;**1**:349–359.

3. Manoranjitham SD, Rajkumar AP, Thangadurai P, Prasad J, Jayakaran R, Jacob KS. Risk factors for suicide in rural south India. *Br J Psychiatry*. 2010;**196(1)**:26–30.

4. Zhang J, Zhou L. A case control study of suicides in China with and without mental disorder. *Crisis*. 2009;**30(2)**:68–72.

5. Zhang J, Xiao S, Zhou L. Mental disorders and suicide among young rural Chinese: A case-control psychological autopsy study. *Am J Psychiatry*. 2010;**167(7)**:773–781.

6. Durkheim E. *Suicide: A study in sociology*. Spaulding JA, Simpson G, translators. New York (NY): Free Press; 1951.

7. Roskar S, Podlesek A, Kuzmanic M, Demsar LO, Zaletel M, Marusic A. Suicide risk and its relationship to change in marital status. *Crisis*. 2011;**32(1)**:24–30.

8. Pridmore S. Predicament suicide: Concept and evidence. *Australas Psychiatry*. 2009;**17(2)**:112–116.

9. Pridmore S, McArthur M. Suicide and reputation damage. *Australas Psychiatry*. 2008;**16(5)**:312–316.

10. Pridmore S, Reddy A. Suicide by couples from the public record. *Australas Psychiatry*. 2010;**18(5)**: 431–436.

11. Meltzer H, Bebbington P, Brugha T, Jenkins R, McManus S, Dennis MS. Personal debt and suicidal ideation. *Psychol Med*. 2011;**41(4)**:771–778.

12. Luo F, Florence CS, Quispe-Agnoli M, Ouyang L, Crosby AE. Impact of business cycles on US suicide rates, 1928-2007. *Am J Public Health*. 2011;**101(6)**:1139–1146.

13. Stack S, Bowman B. *Suicide movies: Social patterns: 1900–2009*. Cambridge (MA): Hogrefe; 2011.

14. Shiner M, Scourfield J, Rincham B, Langer S. When things fall apart: Gender and suicide across the life-course. *Soc Sci Med*. 2009;**69(5)**:738–746.

Case Report

Isolated Blunt Lingual Artery Injury Secondary to a Road Traffic Accident: Diagnostic and Therapeutic Approach

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Abstract

Neurologic and airway compromise as a result of traumatic vascular injuries to the neck region often lead to more severe complications and thus require special consideration. Furthermore, these cases pose diagnostic and therapeutic challenges to healthcare providers. Here, we report a case of a 28-year-old motorcyclist presenting with progressively enlarged Zone 2 neck swelling on the left side following a high impact collision. There were no symptoms or signs suggesting neurologic or laryngeal injury. Computed tomography angiogram of the neck revealed signs of an active arterial bleed. The apparent vascular injury was managed by close observation for signs of airway compromise, urgent angiogram, and selective catheter embolisation of the left lingual artery. The patient subsequently recovered without further operative exploration of the neck. At 6 months post-trauma, the neck swelling fully subsided with no complications from angioembolisation. This case illustrates the individualised treatment and multidisciplinary approach in managing such cases. We review our rationale for this diagnostic and therapeutic approach.

Keywords: *diagnostic imaging, embolisation, neck, trauma, vascular system injury*

Introduction

Traffic accidents are the leading cause of mortality among Malaysians aged 20–30 years. Neck injuries account for 5%–10% of all serious traumatic injuries. Even in this era of modern medicine, management of a patient with a neck injury still poses significant challenges. The neck is a compact conduit of various organ systems (airway, vascular, neurological, and gastrointestinal) anteriorly protected by skin and subcutaneous tissue only. Therefore, a single insult is capable of considerable harm. Life-threatening complications include airway occlusion and exsanguinating haemorrhage. A concerted multidisciplinary approach to the management of potential complications remains the cornerstone of diagnosis and treatment. Lingual artery avulsion rarely occurs in isolation without any associated cervical spine or facial trauma. The latter can be attributed to the beneficial effects of protective helmets. New advances in selective arterial embolisation allow better treatment outcomes in vascular injuries, preventing the need for exploratory neck surgery.

Case Report

A 28-year-old male was referred to the otolaryngology team 2 hours following a hit-and-run traffic accident with a rapidly expanding neck swelling on the left side. The patient had been involved in a high impact front collision with a car while wearing a protective strapped helmet, causing him to be thrown from his motorcycle. Primary and secondary examinations revealed no evidence of injury or haemorrhage to the head, neck, or face. He later underwent observation in the emergency department due to a history of post-traumatic amnesia in anticipation of other potential injuries. He developed a rapidly expanding swelling on the left side of his neck that started at Zone 2 but later expanded to Zone 1 of the neck over a period of 2 hours. It

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was associated with pain and reduced the range of movement in the neck area. There was no hoarseness, difficulty in breathing, swallowing problems, numbness, or weakness of the upper limbs. Local examination revealed a diffuse anterior mass on the left side of the neck, extending from the lower border of the mandible to the supraclavicular region and measuring 14 × 10 cm. The mass was neither expansile nor pulsatile, and there was no loss of carotid pulsation distal to the swelling. No palpable thrill or audible bruit was present. He had no signs of airway compromise nor did he show any cranial nerve deficit or peripheral nerve damage.

Contrasted computed tomography of the neck (Somatom Sensation 64; Siemens AG, Berlin, Germany) showed an intramuscular haematoma with its epicentre within the left sternocleidomastoid muscle. A mild tracheal shift to the right was noted, with no luminal narrowing. The haematoma presented with a thick, irregular, enhancing capsular wall with a hypodense centre. Within the hypodense centre, a focal hyperdense region of active contrast extravasation (indicating active haemorrhage) was noted during the arterial phase scanning, arising from a branch of the left external carotid artery (Figure 1). Due to the hairpin turn of this artery, the injured artery was initially thought to be the left lingual artery. The region of active haemorrhage was enlarged in the venous phase. Catheter angiography of the left external carotid artery revealed the injured artery to be a proximal branch of the left lingual artery (Figure 2). Gelfoam (Lyostypt, B Braun, Aesculap AG & Co, Tuttlingen, Germany) embolisation of the injured artery under selective cannulation of the lingual artery was performed. Reflux of embolic material into the lingual artery could not be avoided, as the calibre of the injured artery was not compatible with microcatheter superselective embolisation. Post-embolisation angiography showed successful embolisation of the transected artery (Figure 3).

The patient underwent the procedures 5 hours post-trauma without any deterioration of the airway. Post-embolisation, he was observed for 2 days, during which the neck swelling decreased in size by more than 50%. He did not experience ipsilateral tongue numbness or sustain any neurological deficits as a complication of the procedure. At 6 months post-trauma, his neck was healed with total resolution of swelling and normal mobility.

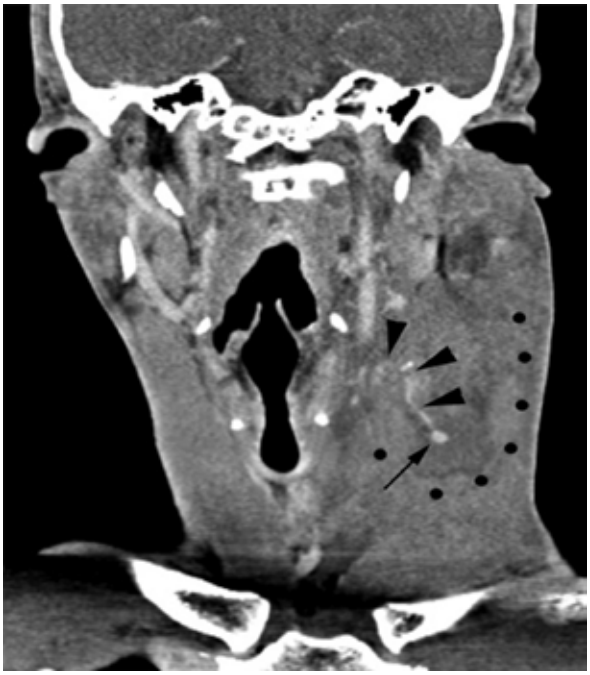

Figure 1: Coronal reformatted contrasted computed tomography of the neck showing an opacified artery (arrowheads) demonstrating a hairpin turn that leads to a focal ovoid region of active contrast extravasation (arrow) within the neck haematoma (its inferolateral margin is marked by dotted lines).

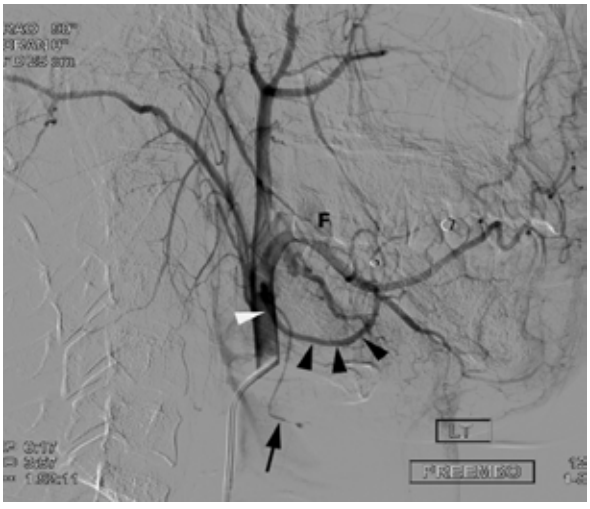

Figure 2: Digitally subtracted arteriogram of the pre-embolisation, left, external carotid artery. The artery showing contrast extravasation (arrow) is a proximal branch of the left lingual artery (arrowheads). F = left facial artery.

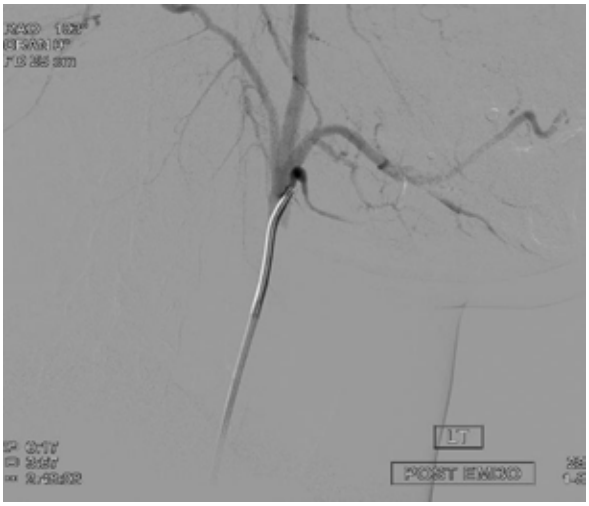

Figure3: Post-embolisation, digitally subtracted, selective angiography of the lingual artery shows non-opacification of the embolised artery.

Discussion

Ambroise Pare described the first case of successful management of a patient with a neck injury in 1552 (8). Over 400 years later, there is still continuing debate about the best approach to managing neck trauma. The role of a well-conceived multidisciplinary plan cannot be underestimated and is critical for improved patient outcome.

For clinical and uniformity purposes, in a trauma setting, the neck is divided into 3 zones. This anatomical division provides the means for a systematic approach to evaluating potential injuries (1). Clinical criteria used to diagnose vascular injury are divided into hard and soft signs. Hard signs include massive bleeding, pulsating haematoma, severe ischaemia, shock, and thrill or bruit. Soft signs include moderate haematoma, a reduced ankle-brachial index in a vessel close to the injury and nerve damage (1). However, these signs can be deceptive with low sensitivity, at 61% (2). Carotid pulsation distal to the haematoma is present in 36% of carotid injury cases, and bruits are detected in only 2% of the cases (2). In contrast, several articles have demonstrated the safety and reliability of physical examination alone in detecting Zone 2 vascular injuries that require treatment (3). A retrospective study of 2674 patients showed that physical examination yielding hard signs of vascular injury had a positive predictive value of nearly 100% in vascular trauma requiring surgery. In this series, only 2 vascular injuries were missed using physical examination alone (4).

The sensitivity of helical computed tomography angiography (CTA) in the detection of vascular neck injuries ranges from 80% to 100% (5) The morphology of an injured artery can be readily detected and serves as a triaging tool for further management strategies. Traumatic stenosis or occlusion can be managed conservatively; in contrast, pseudoaneurysm, active extravasation, and arteriovenous fistula require active management by either endovascular or open surgery (9).

Conventional or digital subtracted angiography (DSA) has traditionally been regarded as the standard of reference imaging modality for traumatic vascular lesions of the head and neck (6). In addition, haemorrhage control can be achieved through embolisation, stent placement, or temporary balloon occlusion (6). In some instances, CTA may be superior to DSA in regards to the relative speed of lesion detection. Cox et al. (7) noted that certain lesions readily detected on CTA were not detected by DSA until selection of the injured artery was performed. CTA, especially on multislice scanners with their multiplanar capabilities, also provides a useful "angiographic roadmap" to the interventional radiologist, enabling specific targeting of a vessel during DSA (7). By reviewing the available evidence and diagnostic options, the challenge in the current medical environment is to choose the imaging examination that is the least time consuming, least invasive, most readily available, and most cost effective.

In this particular case, the ideal embolisation procedure would have been the advancement of a suitable microcatheter into the distal active bleeding site using microcoils or permanent embolic material such as Histoacryl glue (10). However, the acute angle and the calibre of the arterial branch precluded the use of a microcatheter. Thus, Gelfoam was used as a temporary embolic agent, with the expectation of embolic reflux into the lingual artery. In our experience, inadvertent embolisation of arteries within richly vascularised anatomic regions (such as the head and the neck) very rarely leads to permanent vascular deficit of the affected end organs.

Existing reports of traumatic lingual artery injury are mainly of patients with trauma involving multiple organs, multiple fractures, and iatrogenic injury secondary to tonsillectomy. The incidence of blunt craniocervical arterial injury in a trauma setting is as low as 0.4% (11).

The lingual artery is the most vulnerable at its oblique, superficial portion as it branches from the external carotid artery and as it loops forward to its horizontal portion. These segments of the lingual artery can be injured by shear forces due to deceleration from high impact collision or helmet-strap–related injury, precluding other organ injuries.

In the past, mandatory surgical exploration for Zone 2 injuries that crossed the platysma muscle was the rule (8). However, several series of mandatory explorations yielded a negative rate of 40%–60% (9).

Selective non-operative management of neck injuries has steadily gained favour over the past few decades and even more so with recent advances in interventional radiology. It is generally thought that unstable patients should undergo emergency exploration while stable patients are reserved for interventional angiography. Although technically demanding, interventional angiography has diagnostic value and has been shown to significantly reduce morbidity rates (10). However, it is important that personnel trained to perform an emergency tracheostomy monitor the patient for signs of respiratory distress during this therapeutic procedure because loss of airway patency in neck trauma occurs precipitously, resulting in mortality rates as high as 33% (9).

The advantage of endovascular therapy in the avoidance of acute complications related to conventional open surgical repair (e.g., excessive haemorrhage and fluid shifts, possible anatomic distortion, and contaminated fields) is obvious (10). However, the challenge of endovascular repair remains the management of long-term complications, particularly in the case of endografts, due to their potential for migration and endoleaks (10).

In conclusion, isolated lingual arterial injury is uncommon in trauma settings. This report illustrates an example of safe and effective endovascular therapy of an actively haemorrhaging branch of the lingual artery.

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Authors' Contributions

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References

1. Larsen DW. Traumatic vascular injuries and their management. *Neuroimaging Clin N Am*. 2002;**12(2)**:249–269.

2. Sclafani SJ, Cavaliere G, Atweh N, Duncan AO, Scalea T. The role of angiography in penetrating neck trauma. *J Trauma*. 1991;**31(4)**:557–563.

3. Sekharan J, Dennis JW, Veldenz HC, Miranda F, Frykberg ER. Continued experience with physical examination alone for evaluation and management of penetrating zone II neck injuries: Results of 143 cases. *J Vasc Surg*. 2000;**32(3)**:483–489.

4. Atteberry LR, Dennis JW, Menawat SS, Frykberg ER. Physical examination alone is safe and accurate for evaluation of vascular injuries in penetrating Zone II neck trauma. *J Am Coll Surg*. 1994;**179(6)**:657–662.

5. LeBlang SD, Nunez DB Jr. Noninvasive imaging of cervical vascular injuries. *AJR Am J Roentgenol*. 2000;**174(5)**:1269–1278.

6. Demetriades D, Skalkides J, Sofianos C, Melissas J, Franklin J. Carotid artery injuries: Experience with 124 cases. *J Trauma*. 1989;**29(1)**:91–94.

7. Cox MW, Whittaker DR, Martinez C, Fox CJ, Feuerstein IM, Gillespie DL. Traumatic pseudoaneurysms of the head and neck: Early endovascular intervention. *J Vasc Surg*. 2007;**46(6)**:1227–1233.

8. Monson DO, Saletta JD, Freeark RJ. Carotid-vertebral trauma. *J Trauma*. 1969;**9(12)**:987-999.

9. Jarvik JG, Philips GR 3rd, Schwab CW, Schwartz JS, Grossman RI. Penetrating neck trauma: Sensitivity of clinical examination and cost-effectiveness of angiography. *AJNR Am J Neuroradiol*. 1995;**16(4)**:647–654.

10. Reuben BC, Whitten MG, Sarfati M, Kraiss LW. Increasing use of endovascular therapy in acute arterial injuries: Analysis of the National Trauma Data Bank. *J Vasc Surg*. 2007;**46(6)**:1222–1226.

11. Fleck SK, Langner S, Baldauf J, Kirsch M, Kohlmann T, Schroeder HWS. Incidence of blunt craniocervical artery injuries: Use of whole body CT trauma imaging with adapted CT angiography. *Neurosurgery*. 2011;**69(3)**:615-624.

Case Report

Breast Carcinoma Occurring from Chronic Granulomatous Mastitis

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Abstract

Chronic granulomatous mastitis is known as a benign and relatively rare disorder that is often difficult to differentiate from breast carcinoma. We highlight the case of a 34-year-old woman who had recurrent episodes of right breast swelling and abscess for 8 years. These were proven to be chronic granulomatous mastitis by tissue biopsies on 3 different occasions. Her condition improved on similar courses of antibiotics and high-dose prednisolone. However, she subsequently developed progressive loss of vision due to an orbital tumour. She then underwent a craniotomy and left orbital decompression with excision of the tumour, which proved to be a metastatic carcinoma. A trucut biopsy of the right breast was then done and showed features consistent with an infiltrating ductal carcinoma. This case illustrates the possibility that chronic granulomatous mastitis could be a precursor for malignancy and the difficulty in differentiating one from the other. The possible mechanisms of development and the implications for future management are also discussed.

Keywords: *breast, carcinoma, disease progression, granulomatous mastitis, surgery*

Introduction

Chronic granulomatous mastitis (CGM) is a relatively rare and benign chronic condition of unknown aetiology, with several cases reported in the literature. It occurs in women of child bearing age and is not associated with the classical risk factors of malignancy such as smoking, hormonal therapy, or family history. Clinically, the condition can present as an abscess or can mimic breast cancer and therefore is often difficult to differentiate from breast carcinoma. The diagnosis is by exclusion and is best made by tissue histology. Radiological modalities commonly used to diagnose other pathologies of the breasts, such as ultrasonography and mammography, have not been successful in diagnosing CGM (1). The management of the disease consists of high-dose, short-term steroid treatment, either with or without surgery. However, recurrence rates are as high as 50% (2). This is a report of a case in which recurrent chronic granulomatous mastitis subsequently presented with an infiltrating breast carcinoma. This complex progression illustrates the difficulty in diagnosing and managing the disease.

Case Report

A 34-year-old pre-menopausal woman presented 8 years previously with a right breast abscess that was treated with an incisional drainage and a course of antibiotics. The first biopsy done had shown fragments of breast tissue heavily infiltrated by chronic and acute inflammatory cells with several collections of epithelioid cells indicative of CGM. The patient was subsequently treated with a 3-week tapering course of high-dose prednisolone and recovered well. However, she developed another 3 recurrences over the next 8 years, which were also treated with incision and drainage along with similar courses of antibiotics and prednisolone. Two repeat biopsies taken during these recurrences were similar to the initial results of CGM (Figure 1). The patient did not report any history of fungal infections or tuberculosis exposure and had no previous history of breast disease or any other medical illnesses. She also has no history of breast cancer in her family, is a non-smoker, and was never on any hormonal contraception.

In between these recurrences of CGM, she was regularly followed up in our clinics

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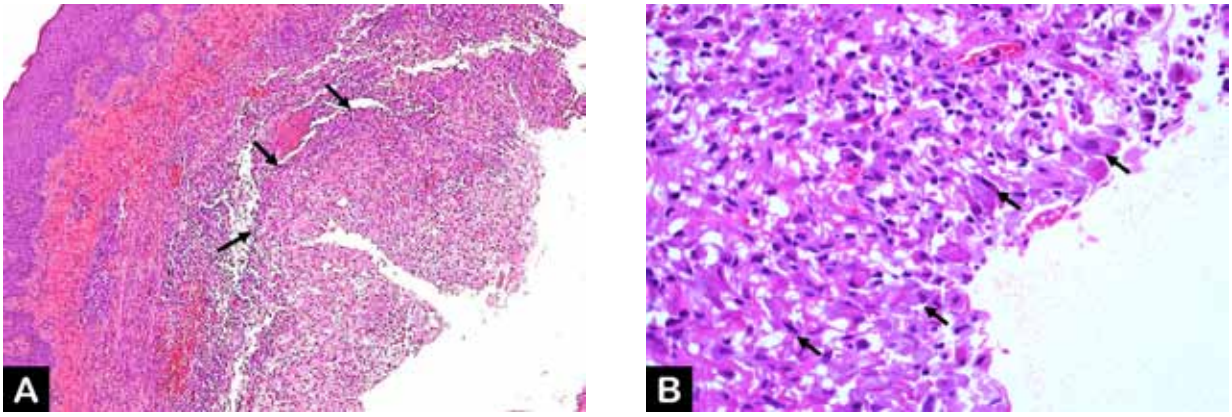

Figure 1: Breast tissue showing chronic granulomatous mastitis. (A) Vague granuloma formation (arrow) composed of epithelioid cells at the centre and lymphocytes at the periphery. No central necrosis or multinucleated giant cell is apparent (haematoxylin and eosin staining, 40× magnification). (B) The epithelioid cells (arrow) have abundant eosinophilic cytoplasm (haematoxylin and eosin staining, 400× magnification).

with routine physical and ultrasonographic examinations. These were unremarkable except for the presence of extensive fibrous scarring due to the repeated surgeries and inflammation. She was last seen and examined 2 months prior to her latest presentation. At the time, she was on another tapering course of prednisolone and was clinically asymptomatic.

Subsequently, the patient presented with a progressive loss of vision of the left eye. This was associated with intermittent headaches, anorexia, and a significant loss of weight. Magnetic resonance imaging (MRI) showed the presence of a left orbital apex tumour compressing the optic nerve (Figure 2). The patient then underwent a craniotomy and left orbital decompression with excision of the tumour. Biopsy results revealed metastatic carcinoma. In the search for a primary tumour, an MRI of the breasts showed extensive scarring of the right breast that looked suspicious of malignancy. A trucut biopsy of the right breast was then performed and revealed infiltration of malignant cells arranged in a vague tubular pattern and cords displaying large hyperchromatic nuclei with prominent nucleoli. These were indicative of the presence of an infiltrative ductal carcinoma of the right breast (Figure 3). The tumour was estrogen and progesterone receptor positive and c-erb negative (++). Staging radiological investigations then showed multiple bony metastases to the vertebrae with no evidence of hepatic or pulmonary spread.

The patient was then referred for palliative chemotherapy, but she declined treatment or any follow up and subsequently expired after 6 months.

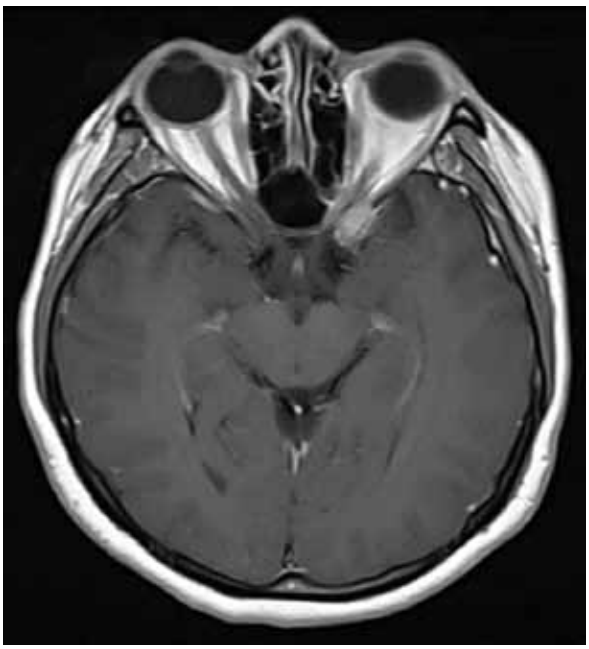

Figure 2: Gadolinium-enhanced T2-weighted magnetic resonance image showing a soft tissue lesion at the left orbital apex involving the intracallicular portion of the left optic nerve.

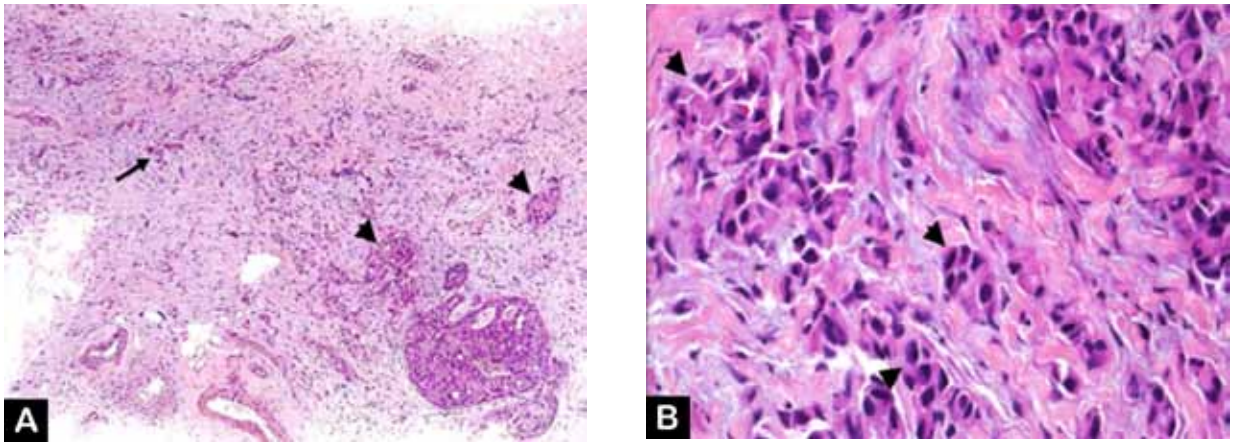

Figure 3: Infiltrating ductal carcinoma in breast biopsies. (A) Infiltration of malignant cells arranged in cords (arrow) and groups (arrow head) (haematoxylin and eosin staining, 40× magnification). (B) The groups of malignant cells (arrow head) display hyperchromatic nuclei with moderate amount of cytoplasm (haematoxylin and eosin staining, 400× magnification).

Discussion

CGM was first described by Kessler and Wolloch in 1972 (2) as a benign and rare disorder. To date, less than 150 cases have been reported. A significant number of these reports have addressed the issue of the diagnostic difficulties faced in confirming CGM. Researchers have suggested that the diagnosis of CGM is a diagnosis of exclusion and that CGM can mimic breast carcinoma (3,4). With the exception of a case by Handley in 1938 (5), no reported cases have suggested the possibility of an association between CGM and malignancy.

It is well accepted that the risk factors of developing breast cancer can be broadly divided into hormonal and non-hormonal factors. The former involve estrogen, and the latter include radiation exposure as well as the inheritance of the germline mutations BRCA-1 and BRCA-2. A literature search of infections associated with breast cancer has revealed only cross-species infection by the mouse mammary tumour virus initiating pathogenesis of breast cancer, although research establishing this connection remains preliminary (6). As mentioned earlier, chronic granulomatous inflammation by any cause has not been shown to lead to malignancy of the breast.

The theory that chronic inflammation leads to cancer is well documented (7). It is postulated that in response to infection from an offending microorganism, the host's defence mechanisms produce free radicals, which lead to DNA damage through oxidative processes and nitration of DNA bases. This could eventually lead to cell dysplasia and, subsequently, the development of cancer. It has been reported that nearly 15% of worldwide cancer is associated with microbial infection (8); however, breast cancer is not associated with such infections.

There are several indications that our patient initially had CGM, and this could have led to breast carcinoma rather than a missed diagnosis. First, 2 different histopathology biopsies taken approximately 3 years apart after the initial histopathological diagnosis of CGM indicated the presence of foamy macrophages and multinucleated giant cells forming granulomas and microabscesses, confirming the initial diagnosis. Second, the patient responded to steroid therapy after every recurrence and had periods in which she was completely asymptomatic. Finally, the long nature of the disease beginning from the first presentation to the diagnosis of malignancy, a total of 8 years, makes it unlikely she had breast cancer from the beginning.

The difficulty in differentiating breast carcinoma and CGM as well as the possibility that CGM could have led to cancer in our patient prompts us to raise the question of whether current management with regard to monitoring and surgical therapy is adequate and appropriate. Current practice indicates that following careful confirmation of the diagnosis of CGM, the initial treatment should be non-operative and that in patients with more severe symptoms, a course of prednisolone may be started. In more persistent cases, either further immunosuppressivetherapies like methotrexate or azathioprine may be used or the patient may be offered surgical management,

such as a wide surgical excision or a mastectomy. In a previous report (9), only 3 recurrences were noted in 18 cases diagnosed with CGM, suggesting that surgical excision has a higher success rate. Whether a more radical surgery is needed will remain a matter of debate, unless it can be proven that CGM can lead to cancer.

The patient in this case was regularly followed up in 4 to 6 month intervals by ultrasound and clinical examination, as is standard for a patient in her mid-30s. The affected breast was extensively scarred, rendering clinical examination and ultrasound findings less sensitive. In retrospect, annually imaging the patient with MRI would have helped in identifying malignancy at an earlier stage because extensive fibrous scarring would reduce the sensitivity of a mammogram. In such circumstances, MRI may be useful; although studies have shown mixed results. Kocaoglu et al. (10) showed that MRI produced varied appearances in patients diagnosed with CGM and thus might limit its utility as a diagnostic tool. However, in general, MRI is known to be more sensitive than mammograms in detecting lesions in fatty and dense breasts.

In summary, 3 different scenarios are possible in our patient. First, the patient had breast carcinoma throughout the years that was misdiagnosed as CGM. However, this is highly unlikely for the reasons mentioned earlier. Second, she was unfortunate enough to have developed breast carcinoma as a second, separate pathology in the same breast. Third, she developed breast carcinoma as a result of chronic inflammation leading to dysplasia and subsequent malignant change.

This case illustrates the difficulty in identifying and diagnosing breast cancer in a patient with a background history of CGM. Whether the patient could have developed cancer from CGM will be a matter of debate unless more cases are encountered and subsequent research can link breast cancer and CGM. The results of future research could affect the diagnosis and treatment of CGM and would certainly alter the course of its management.

Authors' Contributions

Conception and design, critical revision of the article: LM, SNAS, SJJ, NHML, SA, RM
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References

1. Engin G, Acunas G, Acunas B. Granulomatous mastitis: Gray-scale and color Doppler sonographic findings. *J Clin Ultrasound*. 1999;**27(3)**:101–106.

2. Kessler E, Wolloch Y. Granulomatous mastitis: A lesion clinically simulating carcinoma. *Am J Clin Pathol*. 1972;**58(6)**:642–646.

3. Azlina AF, Ariza Z, Arni T, Hisham AN. Chronic granulomatous mastitis: Diagnostic and therapeutic considerations. *World J Surg*. 2003;**27(5)**:515–518.

4. Tuli R, O'Hara BJ, Hines J, Rosenberg AL. Idiopathic granulomatous mastitis masquerading as carcinoma of the breast: A case report and review of the literature. *Int Sem Surg Oncol*. 2007;**4**:21.

5. Handley WS. Chronic mastitis and breast cancer: A family history of five sisters. *Br Med J*. 1938;**7**: 113–116.

6. Indik S, Gunzburg WH, Kulich P, Salmons B, Rouault F. Rapid spread of mouse mammary tumour virus in cultured human breast cells. *Retrovirology*. 2007;**4**:73.

7. Rakoff-Nahoum S. Cancer issue: Why cancer and inflammation? *Yale J Biol Med*. 2006;**79(3–4)**: 123–130.

8. Zlotnik A. Chemokines and cancer. *Int J Cancer*. 2006;**119(9)**:2026–2029.

9. Erhan Y, Veral A, Kara E, Ozdemir N, Kapkac M, Ozdedeli E, et al. A clinico-pathologic study of a rare clinical entity mimicking breast carcinoma: Idiopathic granulomatous mastitis. *Breast*. 2000;**9(1)**:52–56.

10. Kocaoglu M, Somuncu I, Ors F, Bulakbasi N, Tayfun C, Ilkbahar S. Imaging findings in idiopathic granulomatous mastitis. A review with emphasis on magnetic resonance imaging. *J Comput Assist Tomogram*. 2004;**28(5)**:635–641.

Case Report

Pheochromocytoma: An Uncommon Presentation of an Asymptomatic and Biochemically Silent Adrenal Incidentaloma

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Abstract

Pheochromocytomas are rare tumours originating from the chromaffin tissue. The clinical manifestations are variable and are not specific; as a result, pheochromocytomas often imitate other diseases. The diagnosis is usually established by biochemical studies, i.e., the measurement of catecholamines or their metabolites in urine or plasma, followed by radiographic and scintigraphic studies for localisation. Surgical removal of the tumour is the preferred treatment. We report a 30-year-old woman presenting with an adrenal incidentaloma that was 7.6 × 5.3 × 4.8 cm in size on an abdominal computed tomography scan. Investigations for adrenal hormones, including a low-dose dexamethasone suppression test, plasma aldosterone level, 24-hour urinary metanephrine and vanillylmandelic acid levels, and plasma metanephrine level were all within the normal ranges. During the surgical resection, the patient had a hypertensive spell. Surgery was postponed, and the blood pressure was adequately controlled with α blockers, followed by β blockers. After 2 weeks, the surgery was followed by a pathological biopsy that confirmed the pheochromocytoma diagnosis.

Keywords: *adrenal incidentaloma, catecholamines, hypertension, pheochromocytoma, scintigraphy*

Introduction

Pheochromocytomas are catecholamine-producing tumours arising from chromaffin cells in the sympathoadrenal system. Their prevalence is estimated at 0.1% to 0.6%, and 80% to 85% of them arise from the adrenal medulla; however, tumours of the adrenal medulla predominantly secrete norepinephrine over epinephrine, whereas the adrenal medulla normally secretes 80% epinephrine (1). The various catecholamines give rise to sustained or paroxysmal hypertension, along with symptoms of headaches, palpitations, profuse sweating, breathlessness, anxiety, a sense of dread, chest pain, nausea, vomiting, tremors, and paraesthesia. Hyperglycaemia due to the anti-insulinaemic actions of catecholamines can produce polyuria and polydipsia. In severe cases, a patient can present with myocardial infarction, heart failure, pulmonary oedema, arrhythmias, or intracranial haemorrhage (2). A diagnosis is established by measuring the levels of metanephrines in the urine or blood (2). Localisation of the tumour is performed by computed tomography (CT) or magnetic resonance imaging (MRI). Occasionally, the tumour can present as an asymptomatic adrenal incidentaloma after radiography. Here, we report one such interesting case.

Case Report

A 30-year-old woman was referred to the department of endocrinology for an evaluation of an adrenal incidentaloma that was detected on a CT scan. She did not have any complaints of episodic headaches, palpitations, sweating, chest pain, or hypertension. There was no history of weight gain, excess hair growth on the body, acne, proximal muscle weakness, or menstrual irregularity. No previous history of hypertension, weakness, anorexia, vomiting, abdominal pain,

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fever, diarrhoea, polyuria, or polydipsia could be elucidated.

On examination, patient's pulse rate was 76 beats/min, blood pressure (BP) was 110/70 mmHg, without any postural drop, and respiratory rate was 20 breaths/min. Her height was 152 cm, and her weight was 47.2 kg. She was pale and without oedema. There was no evidence of moon facies, hirsutism, acne, purple abdominal striae, acanthosis nigricans, or knuckle or mucosal pigmentation. Her systematic examination, which included a fundoscopy, was normal.

Routine haemogram, urine examination, liver and kidney function tests, and other laboratory parameters including serum electrolytes, arterial blood gas analysis, and plasma calcium and phosphorous levels were normal. No abnormalities were noted in the electrocardiography or chest X-ray. Biochemical tests to determine the functional hormone secretion were found to be normal and are depicted in Table 1.

CT of the abdomen revealed a well-defined, heterogeneous enhancing mass lesion that was 7.6 × 5.3 × 4.8 cm in size, with an attenuation score of 35 HU, and without any calcifications at the upper pole of the right kidney. The left adrenal gland appeared to be normal (Figure 1). Considering the possibility of a non-functional adrenal incidentaloma that was more than 6 cm in size and with a CT attenuation score of 35 HU, neither of which suggest a benign lesion, the patient was subjected to a surgical resection. Intra-operatively, the patient had a spell of hypertensive emergency with a BP of 230/120 mmHg. The surgery was postponed, and the patient was prescribed 5 mg of prazosin twice daily, followed by 50 mg of metoprolol twice daily after testing for the adequacy of the α blockade. Two weeks later, with a BP of 140/80 mmHg, the patient underwent a laparoscopic tumour resection. The pathological study revealed an encapsulated tumour that had a nested arrangement of large polygonal cells with moderate granular cytoplasms and round to oval nuclei, which confirmed the pheochromocytoma diagnosis (Figure 2). Post-operatively, the patient required 5 mg of prazosin twice daily. One month later, the patient was treated with 5 mg of prazosin once daily without any recurrence of hypertension.

Discussion

Here, we discuss the case of a biochemically negative pheochromocytoma that presented with an intra-operative hypertensive crisis. Approximately 5.0%–6.5% of adrenal incidentalomas are pheochromocytomas, and 8% of the patients with a pheochromocytoma are completely asymptomatic and usually have a familial form. In approximately 8%–9% of

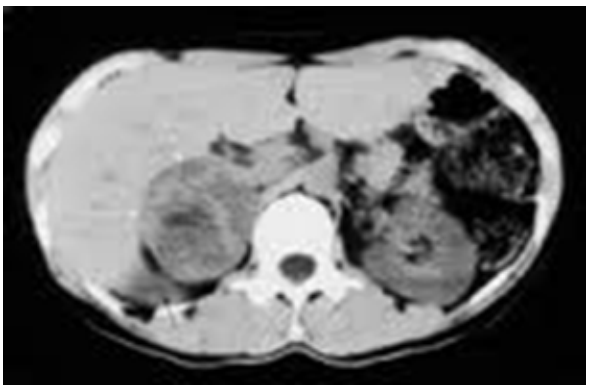

Figure 1: A computed tomography of the abdomen showing a well-defined, heterogeneous enhancing mass lesion that was 7.6 × 5.3 × 4.8 cm in size without any calcifications at the upper pole of right kidney. The left adrenal gland appears to be normal.

Table 1: The baseline biochemical parameters of the patient

Parameter	Value	Normal range
Plasma cortisol at 8:00 AM (μg/dL)	17.2	5–25
Plasma cortisol after ONDST (μg/dL)	2.4	< 5
Plasma aldosterone (ng/dL)	5.4	2–20
24-hour urine fractionated metanephrines (mg/24 h)	0.7	< 1.3
24-hour urine VMA (mg/24 h)	5.3	1–8
Plasma metanephrines (μg/dL)	34	< 60

Abbreviation: ONDST = overnight 1-mg dexamethasone suppression test, VMA = vanillylmandelic acid

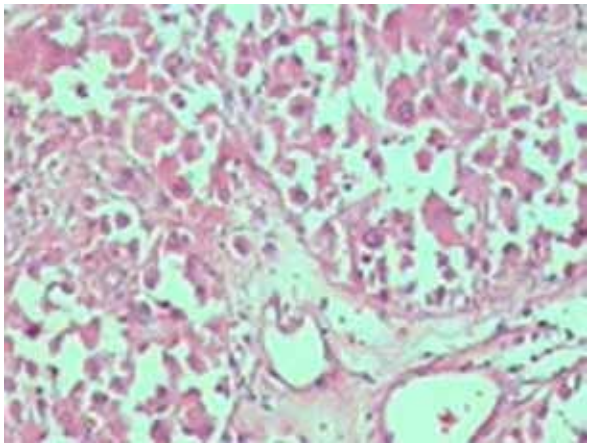

Figure 2: The histopathology of the biopsy specimen, showing a nested arrangement of large polygonal cells with moderate granular cytoplasms and round to oval nuclei.

patients with sporadic paragangliomas and 21%–31% with hereditary paragangliomas, plasma and urinary concentrations of the catecholamines are normal (2). Timmers et al. (3) have reported on biochemically silent abdominal paragangliomas in 4 patients with a mutation in the succinate dehydrogenase subunit B (*SDHB*) gene. The reason provided was a defective catecholamine synthesis that resulted from the absence of tyrosine hydroxylase. In a recent case series of 20 patients by Vanderveen et al. (4), 2 patients with false negative biochemical tests were found.

The widespread use of radiological investigations has increased the detection of adrenal incidentalomas in individuals over 30 years of age. The clinical parameters that need to be considered include functionality and aggressiveness (5). An identification of the functionality of cortisol, aldosterone, and catecholamine and androgen secretion is essential, and in our patient, all of these parameters were within normal limits. Some imaging features favour a malignancy: these include a large size (more than 6 cm), irregular margins, heterogeneity, high unenhanced CT attenuation values (more than 10 HU), calcification, a delayed wash out of contrast on an enhanced CT, and a high to intermediate signal intensity on a T_2-weighted MRI. A biopsy would confirm the nature of the lesion, which in our case was a benign pheochromocytoma.

A CT scan with contrast-enhanced images and an MRI scan are used to localise adrenal pheochromocytomas (6). Metaiodobenzylguanidine (MIBG) and positron emission tomography (PET) scanning are largely reserved for an extra-adrenal paraganglioma or particularly large tumours to rule out metastasis. In PET scanning, the Gallium-DOTA-TOC/NOC and DOPA-PET were found to perform better than FDG-PET in detecting the paragangliomas. Heterogeneity, a high Hounsfield density on a CT (more than 10 HU), a marked enhancement with intravenous contrast and delayed contrast washout (less than 60% at 10 minutes), a high signal intensity on a T_2-weighted MRI, and cystic or haemorrhagic changes indicate a pheochromocytoma, adrenocortical carcinoma, or metastasis. However, a pheochromocytoma with lipid degeneration can result in low attenuation scores (less than 10 HU) and more than 60% washout in delayed CT scanning (7). Motta-Ramirez et al. (8) have elucidated that, although there was an increasing trend towards calcification in the CT scan findings of symptomatic patients, no significant differences were found in asymptomatic patients with respect to the age at presentation, the volume/diameter of the mass, the necrosis score, or the attenuation (all had scores of more than 10 HU). Benign adrenal incidentalomas are characterised by having a size less than 5 cm, sharp margins, smooth contours, a lack of demonstrable growth on serial examinations, attenuation scores less than 10 HU, and more than 60% washout by delayed CT scanning (6,9). In our patient, the CT scan revealed a nonhomogeneous mass of 35 HU without any calcification.

It has been reported that an incidental pheochromocytoma of less than 1 cm in size has no symptoms (7). Our patient, who had a much larger mass, had no symptoms or signs of the disease. Possible reasons for this finding include the following: (i) the presence of a smaller piece of functional tissue, (ii) the release of a small amount of unmetabolised catecholamines due to a rapid intratumoural turnover rate, (iii) episodically secreting tumours, (iv) silent stress-activated tumours, and (v) false negative results due to the high-temperature handling of the laboratory specimen and an ingestion of caffeine 24 hours prior to the testing.

The biochemical diagnosis of a pheochromocytoma is made by measuring the 24-hour urinary fractionated metanephrines (98% sensitivity and 98% specificity) and fractionated catecholamines (10). There is a high specificity for the 24-hour urinary vanillylmandelic acid (95%) and the 24-hour

urinary total metanephrines (99%). The plasma metanephrines are the preferred screening test for patients who are considered to have a high risk for a pheochromocytoma and for those suspected of having a familial form. Because the free metanephrines are formed extraneuronally, and to a large extent within the chromaffin tissues (e.g., the adrenal medulla and pheochromocytomas), these metabolites are also the more sensitive markers for a pheochromocytoma than the other catecholamine metabolites that are derived mainly from neuronal sources. Other tests, including plasma catecholamines and 24-hour urinary catecholamines, have a poor diagnostic accuracy. Though biochemically silent, the characteristic findings and biopsy diagnosis of a pheochromocytoma in our patient justified the use of an α blocker.

Histologically, paragangliomas are capsulated and are composed of round or polygonal epithelioid/chief cells arranged in the characteristically compact cell nests (zellballen) or trabecular patterns. The chief cells have centrally located nuclei with finely clumped chromatin and a moderate amount of eosinophilic, granular cytoplasm. Spindle-shaped sustentacular or supporting cells are located peripherally. Tumours of a higher grade are characterised by a progressive loss in the relationship between the chief cells and the sustentacular cells and a decrease in the number of sustentacular cells. In our patient, although the typical zellballen pattern was not found, the presence of an encapsulated tumour with a nested arrangement of large polygonal cells with moderate granular cytoplasms and round to oval nuclei confirmed the pheochromocytoma diagnosis. The presence of markers such as chromogranin A (CGA), neuron-specific enolase, and synaptophysin would confirm the neuroendocrine nature of the chief cells (11). Algeciras-Schimnich et al. (12) have determined that the likelihood ratio for having a pheochromocytoma/paraganglioma was 7.9 with CGA levels greater than 270 ng/mL; however, for CGA levels less than 270 ng/mL, this ratio was 0.15. Therefore, a patient in whom both the fractionated plasma metanephrines and CGA are positive is more than 50 times more likely to have a chromaffin tumour than a patient with only positive plasma fractionated metanephrines. For a combination of plasma and urine fractionated metanephrines, the corresponding likelihood ratios were 4.6 and 0.11 (12). Our patient did not undergo any of the marker-based investigations.

Malignant pheochromocytomas are histologically and biochemically similar to benign ones. The only reliable clue to the presence of a malignant pheochromocytoma is a local invasion or distant metastases, which may occur as long as 20 years after a resection (13). Thus, even when pheochromocytomas or paragangliomas are considered benign on a pathological examination, a long-term follow-up is indicated for all patients to confirm that diagnosis. Other markers for a malignancy are an absent or weak expression of the inhibin/activin βB subunit (14) and the presence of the *SDHB* subunit. In the absence of any invasion, we considered the mass in our patient to be benign.

Approximately 15%–20% of patients with catecholamine secreting tumours have a germ-line mutation in genes such as *SDHB, SDHC, SDHB* (familial paraganglioma), *RET* (MEN 2 A & B), *MENIN* (MEN-1), *NF-1* (neurofibromatosis), and *VHL* (von Hippel–Lindau syndrome). Suspicious circumstances, including bilaterality, a family history of pheochromocytoma, younger age (20 years or below), or the presence of co-phenotypes, call for genetic testing (15,16). In our patient, the factors of age of presentation at 30 years, a unilateral pheochromocytoma, and the absence of a family history and other co-phenotypes supported the decision against a familial origin. Karasek et al. (17) describes the appropriate genetic testing pattern for nonsyndromic, non-familial cases that is based on a histological evaluation, the localisation of the tumour, and a biochemical phenotype of pheochromocytomas/paragangliomas, e.g., "the rule of three".

Pre-operative optimisation of blood pressure requires an adequate α blockade with increasing doses followed by a β blockade. The Roizen's criteria (18) for a significant α blockade are used (Table 2). A surgical resection is the appropriate treatment and cures 90% of patients. A laparoscopic removal is commonly performed. A laparotomy is reserved for tumours that are more than 8 cm in size and that show local invasion (19). Both of these approaches are equally successful in terms of overall survival. The greatest intra-operative concern is a release of catecholamines leading to life-threatening hypertension. Hypertensive crises can cause myocardial infarction, heart failure, dysrhythmia, and cerebral haemorrhage. Severe hypertension can occur at any time during the surgery, but the induction, intubation, and tumour palpation tend to lead to the greatest catecholamine release. In our patient, the presence of a mass that was 7.6 × 5.3 × 4.8 cm in size called for a laparoscopic resection.

Table 2: The Roizen's criteria (18) for an appropriate pre-operative α blockade and surgical optimisation

- No in-hospital pre-surgical blood pressures measuring higher than 165/90 mmHg 24 hours prior to surgery
- No orthostatic hypotension with a blood pressure measuring lower than 80/45 mmHg
- No electrocardiogram showing ST-T changes 1 week prior to surgery
- No more than 1 premature ventricular contraction every 5 minutes

Induction agents should be titrated slowly to maintain normotension. A short-acting narcotic, such as fentanyl, with its minimal myocardial depression, in combination with a sedative/hypnotic is preferable. An adequate depth of anaesthesia is required to prevent the patient's response to the stimulus of intubation (20). Vecuronium or rocuronium, which have few cardiovascular effects, may be used for muscle relaxation; however, pancuronium should be avoided because of its sympathomimetic effects. Inhalational agents (isoflurane, sevoflurane, or desflurane) may be used with or without intravenous agents. Other medications known to trigger the release of catecholamines, including metoclopramide, pentazocine, droperidol, atracurium, succinylcholine, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, imipramine, opioids, and curare, should be avoided (21).

Intra-operatively, the α blockade is continued with phentolamine. Its most common side effect is a reflex tachycardia due to the baroreceptor reflex following an α2 blockade. Labetalol should be used to control the tachycardia. Calcium channel blockers and nitroprusside can be used a second line of therapy (21). In our case, intravenous phentolamine was used.

Following early ligation of the vein that drains the pheochromocytoma, intravenous fluid administration is essential for volume expansion. The sudden drop in catecholamines can lead to significant hypotension, which requires aggressive fluid replacement with a combination of crystalloids and colloids. Pressors may be necessary to maintain blood pressure in severe hypotension, but they are best avoided and are contraindicated if the patient is hypovolaemic. Often, the hypotension of a pheochromocytoma is refractory to agents such as norepinephrine, epinephrine, and dopamine because of the desensitisation of the sympathetic receptors to the previous persistently high levels of catecholamines (20).

The 24-hour urinary fractionated metanephrines should be measured 1 to 2 weeks after surgery; normal values indicate a complete resection. A periodic follow-up for blood pressure is needed. Furthermore, annual biochemical testing to assess metastatic disease, tumour recurrence, or a delayed appearance of a primary tumour is recommended, and this was advised for our patient (16).

Conclusion

Pheochromocytoma is a clinically important disorder because it leads to high morbidity and mortality rates if untreated. Fractionated metanephrines and catecholamines in a 24-hour urine analysis is the preferred biochemical test. In a biochemically silent pheochromocytoma, characteristic CT findings should identify its possible presence. A combination of anatomical imaging studies (CT or MRI) with functional imaging studies (MIBG and PET) is used to locate adrenal, extra-adrenal, recurrent, and metastatic tumours. An adequate α and β blockade should be ensured before proceeding to tumour removal. For individuals with adrenal tumours larger than 4–6 cm, a surgical resection is appropriate. However, for a pheochromocytoma, surgery is recommended irrespective of the size and is even recommended in the context of normal biochemical study results to prevent future complications.

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Authors' Contributions

Conception and design, critical revision of the article: SUKK, SIKK, SP, KDM
Analysis and interpretation of the data: SUKK, SIKK
Drafting of the article: SUKK, SIKK, SP
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References

1. Anderson GH Jr, Blakeman N, Streeten DH. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens*. 1994;**12(5)**:609–615.

2. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma: Which test is best? *JAMA*. 2002;**287(11)**:1427–1434.

3. Timmers HJLM, Pacak K, Huynh TT, Abu-Asab M, Tsokos M, Merino MJ, et al. Biochemically silent abdominal paragangliomas in patients with mutations in the succinate dehydrogenase subunit B gene. *J Clin Endocrinol Metab*. 2008;**93(12)**:4826–4832.

4. Vanderveen KA, Thompson SM, Callstrom MR, Young WF Jr, Grant CS, Farley Dr, et al. Biopsy of pheochromocytomas and paragangliomas: Potential for disaster. *Surgery*. 2009:**146(6)**:1158–1166.

5. Chen YY. Pheochromocytoma presenting with normal urinary catecholamines and metabolites: A case report. Formos *J Endocrin Metab*. 2009;**1(1)**:33–37.

6. Szolar DH, Korobkin M, Reittner P, Berghold A, Bauernhofer T, Trummer H, et al. Adrenocortical carcinomas and adrenal pheochromocytomas: Mass and enhancement loss evaluation at delayed contrast enhanced CT. *Radiology*. 2005;**234(2)**:479–485.

7. Blake MA, Krishnamoorthy SK, Boland GW, Sweeney AT, Pitman MB, Harisinghani M, et al. Low-density pheochromocytoma on CT: A mimicker of adrenal adenoma. *AJR Am J Roentgenol*. 2003;**181(6)**: 1663–1668.

8. Motta-Ramirez GA, Remer EM, Herts BR, Gill IS, Hamrahian AH. Comparison of CT findings in symptomatic and incidentally discovered pheochromocytomas. *AJR Am J Roentgenol*. 2005;**185(3)**:684–688.

9. Boraschi P, Braccini G, Grassi L, Campatelli A, Di Vito A, Mosca F, et al. Incidentally discovered adrenal masses: Evaluation with gadolinium enhancement and fat-suppressed MR imaging at 0.5 T. *Eur J Radiol*. 1997;**24(3)**:245–252.

10. Kudva YC, Sawka AM, Young WF Jr. Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: The Mayo Clinic experience. *J Clin Endocrinol Metab*. 2003;**88(10)**:4533–4539.

11. Kliewer KE, Wen DR, Cancilla PA, Cochran AJ. Paragangliomas: Assessment of prognosis by histologic, immunohistochemical, and ultrastructural techniques. *Hum Pathol*. 1989;**20(1)**:29–39.

12. Algeciras-Schimnich A, Preissner CM, Young WF Jr, Singh RJ, Grebe SKG. Plasma chromoganin A or urinary fractionated metanephrines follow-up testing improves the diagnostic accuracy of plasma fractionated metanephrines for pheochromocytoma. *J Clin Endocrinol Metab*. 2008;**93(1)**:91–95.

13. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, Morgan WM 3rd, Neblett WW 3rd, Oates JA, et al. Clinical experience over 48 years with pheochromocytoma. *Ann Surg*. 1999;**229(6)**:755–766.

14. Salmenkivi K, Arola J, Voutilainen R, Ilvesmaki V, Haglund C, Kahri AI, et al. Inhibin/activin betaB-subunit expression in pheochromocytomas favors benign diagnosis. *J Clin Endocrinol Metab*. 2001;**86(5)**:2231–2235.

15. Gimm O, Koch CA, Januszewicz A, Opocher G, Neumann HP. The genetic basis of pheochromocytoma. *Front Horm Res*. 2004;**31**:45–60.

16. Young WF Jr. Endocrine hypertension. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. *Williams textbook of endocrinology*. 11th ed. Philadelphia (PA): Saunders Elsevier; 2008. p. 505–537.

17. Karasek D, Frysak Z, Pacak K. Genetic testing for pheochromocytoma. *Curr Hypertens Rep*. 2010;**12(6)**:456–464.

18. Roizen MF, Horrigan RW, Koike M, Eger IE 2nd, Mulroy MF, Frazer B, et al. A prospective randomized trial of four anesthetic techniques for resection of pheochromocytoma. *Anesthesiology*. 1982;**57**:A43.

19. Assalia A, Gagner M. Laparoscopic adrenalectomy. *Br J Surg*. 2004;**91(10)**:1259– 1274.

20. Grant F. Anesthetic considerations in the multiple endocrine neoplasia syndromes. *Curr Opin Anaesthesiol*. 2005;**18(3)**:345–352.

21. Dortzbach K, Gainsburg DM, Frost EA. Variants of pheochromocytoma and their anaesthetic implications—A case report and literature review. *Middle East J Anesth*. 2010;**20(6)**:897–905.

Case Report

Acute Lower Gastrointestinal Haemorrhage Secondary to Small Bowel Ascariasis

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Abstract

Acute lower gastrointestinal haemorrhage secondary to small bowel ascariasis is extremely rare. A high level of suspicion should be maintained when dealing with acute gastrointestinal haemorrhage in migrants and travellers. Small bowel examination is warranted when carefully repeated upper and lower endoscopies have failed to elicit the source of bleeding. Appropriate test selection is determined by the availability of local expertise. We present a case of acute lower gastrointestinal haemorrhage secondary to jejunal ascariasis and a literature search on lower gastrointestinal haemorrhage associated with jejunal infestation with *Ascaris*.

Keywords: *ascariasis, aetiology, complications, diagnosis, gastrointestinal haemorrhage, jejunal diseases, melaena, parasitology*

Introduction

Lower gastrointestinal haemorrhage is defined as intraluminal blood loss from a source distal to the ligament of Treitz. Typical causes include large bowel diverticular disease, anorectal pathologies, benign or malignant neoplasias, inflammatory bowel disease, vascular malformations, and angiodysplasias. Small bowel haemorrhages account for 5% of lower gastrointestinal haemorrhages and often are the source of obscure gastrointestinal haemorrhage when the diagnosis cannot be established by conventional upper and lower endoscopy. We present a case of acute lower gastrointestinal haemorrhage secondary to jejunal ascariasis and a literature search on lower gastrointestinal haemorrhage associated with jejunal infestation with *Ascaris*.

Case Report

A 65-year-old Indonesian woman was referred from a district hospital with a 1-day history of passing a black, tarry stool. She had no abdominal discomfort, no constitutional symptoms and no alteration in appetite or bowel habits. Upon examination, although she was alert and not in distress, her conjunctiva was pale. Her vital signs were stable with no evidence of hypovolaemic shock. An abdominal examination was unremarkable, and a digital rectal examination revealed fresh melaena. Otherwise, her examination was normal.

Laboratory investigations revealed that her haemoglobin level was 4.8 g/dL and that her platelet count was 496 000 U/L. She had no coagulopathy. An emergency upper gastrointestinal endoscopy performed upon admission was normal. She was then admitted, underwent blood transfusion, and was scheduled for colonoscopy the next day. Colonoscopy result showed stale melaena along the entire length of her large bowel, with no identifiable source of bleeding.

During admission, she continued to pass fresh melaena and was transfused a total of 9 units of packed cells because she was persistently anaemic. An emergency computed tomography (CT) angiogram identified active bleeding into the jejunum that originated from one of the branches of the superior mesenteric artery. Interventional embolisation was initiated, but the bleeding stopped during the procedure. The procedure was abandoned as there was no further demonstrable angiographic evidence of active bleeding from either the celiac or the superior mesentery arteries. The following day, she began to bleed again while in the ward, and a decision to perform surgery was made.

A laparotomy did not show any gross pathology of the stomach, small bowels, or colon. An enterotomy was performed at the jejunum (130 cm from the duodenojejunal [DJ] flexure) and was followed by an on-table enteroscopy. With a soft bowel clamp applied distally to the enterotomy, the endoscope was advanced proximally, which revealed fresh blood

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oozing from mucosal erosions of the jejunum approximately 120 cm from the DJ flexure. Further examination proximal to the mucosal erosions revealed a viable adult *Ascaris* over the proximal jejunum (Figure 1). Enteroscopic examination distal to the enterotomy towards the ileocaecal valve showed haematin stains along the entire length of the distal jejunum and ileum. The parasite was removed via a second enterotomy 60 cm from the DJ flexure. A small bowel resection with end-to-end anastomosis was performed for the length of the jejunum that had the bleeding erosions. Histopathological examination of the resected jejunum showed a normal small bowel with lymphoid hyperplasia.

The patient recovered uneventfully with no further episodes of gastrointestinal haemorrhage and was well at discharge with oral albendazole (400 mg). Examination of the parasite confirmed an adult *Ascaris lumbricoides*.

Discussion

The World Health Organization (1) estimated that more than 1 billion of the world's population is infected with one or more of the soil transmitted helminths, particularly *Ascaris lumbricoides, Trichuris trichiura,* and *Necator americanus* or *Ancylostoma duodenale*. These infections, together with schistosomiasis, represent more than 40% of the disease burden caused by all tropical diseases, excluding malaria (2).

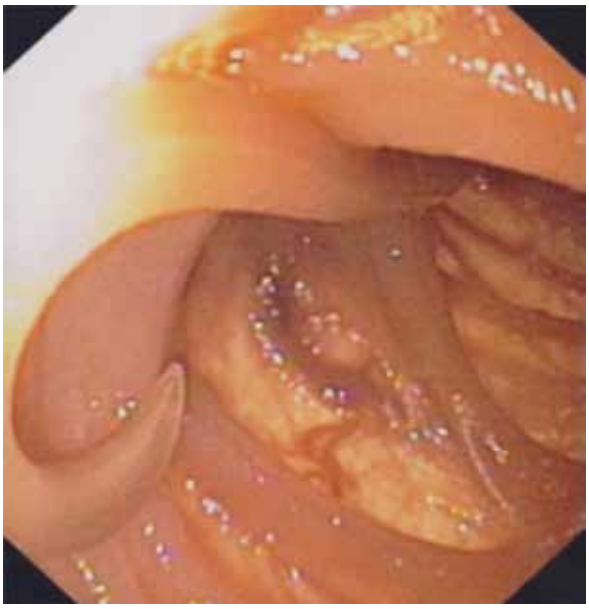

Figure 1: On-table enteroscopic finding of an *Ascaris*.

Ascariasis is a common infection in children of tropical countries due to poor sanitation. It is, however, rare in adults. Infection is acquired via faecal-oral transmission through ingestion of food, water, or soil contaminated with embryonated eggs (3). Upon ingestion, the eggs hatch in the stomach and duodenum and release the larvae into the duodenum. The larvae then penetrate the intestinal wall to enter the portal circulation. From there, the larvae follow the venous and the lymphatic systems to enter the right side of the heart, the pulmonary circulation and, finally, the pulmonary capillaries. In the lung, the larvae penetrate through the capillaries into the alveoli and travel up the trachea into the pharynx, where they return to the small intestine through the swallowing of bronchial secretions. The larvae mature into adult roundworms within the lumen of the small intestine, especially the jejunum, and reach a size of 15–35 cm in approximately 2 months. Adult worms can survive in the intestine for 6–18 months. After mating, the females begin egg production 2–3 months after the initial infection. The adult female ascarids are somewhat larger than the males, measuring 22–35 cm in length and 3–6 mm in width, whereas the males are 15–31 cm in length and 2–4 mm in width. The adult worms are fusiform and cylindrical in shape and white or creamy-pink in colour. The anterior end of the ascarid is blunt, whereas the posterior end is pointed and, in the male, coiled (4).

Ascaris lumbricoides can cause a myriad of surgical complications in the abdomen. The most common complication of ascariasis is intestinal obstruction caused by a worm bolus, which may present as an acute or subacute intestinal obstruction or alternatively as intussusceptions, perforation and gangrene of the small bowel (5). Other areas where adult worms could lodge are in the appendix, causing acute appendicitis and appendicular perforation, or in the biliary and pancreatic ducts, causing hepato¬pancreatic ascariasis. In addition, acute upper airway obstruction due to roundworms has been documented.

Gastrointestinal bleeding appears to be uncommon with ascariasis. Typically, ascariasis may present with chronic occult bleeding and anaemia, but rarely with acute gastrointestinal bleeding. The clinical disease is largely restricted to individuals with a high worm load. Intestinal mucosal ulceration is thought to be due to the mechanical trauma from the worm's attachment to the intestinal lining and to mucosal chemical irritation caused by the worm's secretions (6).

The first report published in English medical literature on acute massive jejunal bleeding caused by ascariasis was by Sharma et al. (6) in 2000. The authors described the use of push enteroscopy to diagnose the presence of *Ascaris* and reported the presence of multiple rounded or oval erosions, 2–4 mm in size, associated with fresh blood oozing from erosions. Since then, few reports have emerged to describe the presence of *Ascaris lumbricoides* during capsule endoscopic examinations for obscure gastrointestinal haemorrhage (7,8).

As a general rule, melaena occurs when the source of bleeding is proximal to the ligament of Treitz. The time required for blood to be broken down in the intestinal lumen is approximately 14 hours. Therefore, the explanation for why this patient had melaena rather than haematochesia is that the bleeding was slow and the transit time was greater than 14 hours.

In patients with overt obscure gastrointestinal bleeding with negative upper endoscopy and colonoscopy, further investigations of the small bowel should be performed early. Various approaches have been used in the diagnosis and treatment of small bowel bleeding. These include radiographic approaches, such as small-bowel follow-through and enteroclysis; various forms of enteroscopy, such as push, double or single balloon, and spiral; radionuclide red blood cell scans; angiography; capsule endoscopy; and intra-operative enteroscopy. No single technique has emerged as the most efficient way to evaluate small bowel bleeding, and the procedure chosen should be tailored to the clinical scenario, availability, and local expertise (9).

Angiography may be helpful in patients with active bleeding greater than 0.5 mL/minutes in whom highly vascular non-bleeding lesions such as angiodysplasia and neoplasms can be identified (9). In our case, CT angiography was able to localise the site of the haemorrhage and prompted us to plan for embolisation. However, the repeat angiography did not demonstrate any active extravasation into the lumen of the bowel due to the fact that the bleeding may have stopped.

Intra-operative enteroscopy during laparotomy was used as a last resort in our patient as she continued to bleed, requiring blood transfusions. However, this technique has a moderate therapeutic efficacy because it only identifies the site of occult bleeding in up to 40% of undiagnosed cases and allows examination of just 50% to 80% of the small bowel (10). In our case, its diagnostic accuracy was aided by pre-operative CT angiographic localisation.

In summary, acute lower gastrointestinal haemorrhage secondary to ascariasis is extremely rare. A high level of clinical suspicion is required when dealing with acute gastrointestinal haemorrhage in migrants and travellers.. In the near future, less invasive forms of investigation, such as capsule and balloon enteroscopy, may be available to identify obscure gastrointestinal bleeding. Otherwise, laparotomy and intra-operative enteroscopy are often used as a last resort to identify the source of bleeding.

Acknowledgement

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Authors' Contributions

Conception and design, provision of patient, critical revision and final approval of the article: SLS Collection and assembly of data, drafting of the article: DDS

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References

1. World Health Organization. *Deworming for health & development. Report of the third global meeting of the partners for parasite control*. Geneva (CH): *World Health Organization*. 2005.

2. Al-Mekhlafi MS, Atiya AS, Lim YA, Mahdy AK, Ariffin WA, Abdullah HC, et al. An unceasing problem: Soil-transmitted helminthases in rural Malaysian communities. *Southeast Asian J Trop Med Pub Health*. 2007;**38(6)**:998–1007.

3. Gaash B. *Ascaris lumbricoides*. *Indian J Practising Doctor*. 2004;**1(3)**:11–12.

4. Palmer PES, Reeder MM. *The imaging of tropical diseases: With epidemiological, pathological and clinical correlation: Volume 1*. 2nd ed. Maryland: Springer; 2001.

5. Refeidi A. Live *Ascaris lumbricoides* in the peritoneal cavity. *Ann Saudi Med*. 2007;**27(2)**:118–121.

6. Sharma BC, Bhasin DK, Bhatti HS, Das G, Singh K. Gastrointestinal bleeding due to worm infestation, with negative upper gastrointestinal endoscopy findings: Impact of enteroscopy. *Endoscopy*. 2000;**32(4)**:314–316.

7. Floro L, Pak G, Sreter L, Tulassay Z. Wireless capsule endoscopy in the diagnosis of helminthiasis. *Gastrointest Endosc*. 2007;**65(7)**:1078–1079.

8. Balachandran P, Prasad VG. Intestinal parasites seen on capsule endoscopy. *Gastrointest Endosc*. 2006;**64(4)**:651.

9. Leighton JA, Goldstein J, Hirota W, Jacobson BC, Johanson JF, Mallery JS, et al. Obscure gastrointestinal bleeding. *Gastrointest Endosc*. 2003;**58(5)**:650–655.

10. Mitchell SH, Schaefer DC, Dubagunta S. A new view of occult and obscure gastrointestinal bleeding. *Am Fam Physician*. 2004;**69(4)**:875–878.

Letter to The Editor:

A new start with fMRI

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Dear Editor,

Neurotechnology, which involves information obtained from magnetic and electrical based images, is at its growing phase in Malaysia. The article titled "Coping with Brain Disorders using Neurotechnology", published in the *Malaysian Journal of Medical Sciences*, Volume 19, Issue 1, 2012 (1), has caught our interest. Although functional magnetic resonance (fMRI) is not a new tool in neuroimaging, it is relatively new in our Hospital Universiti Sains Malaysia, which has begun to use the technology for patients' care and research. This particular technology is used solely in nervous system diseases for either medical or surgical-related purposes. Two of the major applications in neurosurgery are pre- and post-operative assessments of diseases (2–4). The pre-operative assessment is essential to obtain best operative results, especially when the eloquent areas of the brain are involved.

The fMRI has been in place for more than a decade; until now, it is used more in the research field. However, there are many useful clinical applications of fMRI, although they are not done routinely. The minimal machine strength for an fMRI study is 1.5 Tesla. In Malaysia, even though there are many centres with fMRI system of either 1.5 or 3.0 Tesla, the application of fMRI is still minimal and at an early stage.

The fMRI examination requires proper training for both radiographers and radiologists: the usage technique is important, and so is the result interpretation. Interpretation of fMRI images requires knowledge of radiology, neurology, as well as some technical MRI physics and its limitations.

Pre-operative localisation of eloquent cortices adjacent to the brain tumours is the most common clinical application of fMRI along with diffusion tensor imaging. In most assessment, there are paradigms to assess for motor, sensory, visual, and auditory functions.

The Philips Achieva 3 Tesla MRI was recently installed in the Department of Radiology. With the incorporation of the fMRI software and paradigms, at least 10 functional assessments can be performed. It is also incorporated with high intensity focused ultrasound system. We are pleased, as at this moment our machine is equipped with full fMRI facility.

Initial clinical assessments determine which functional assessments are required. The patient should be able to stand the long examination period.The patient should also understand how the examination is carried out and should be able to complete the fMRI paradigm appropriately. There is an MR simulator machine where the patient can do practical sessions with the planned paradigms. Paradigms can be modified according to the patient's clinical assessment and ability.

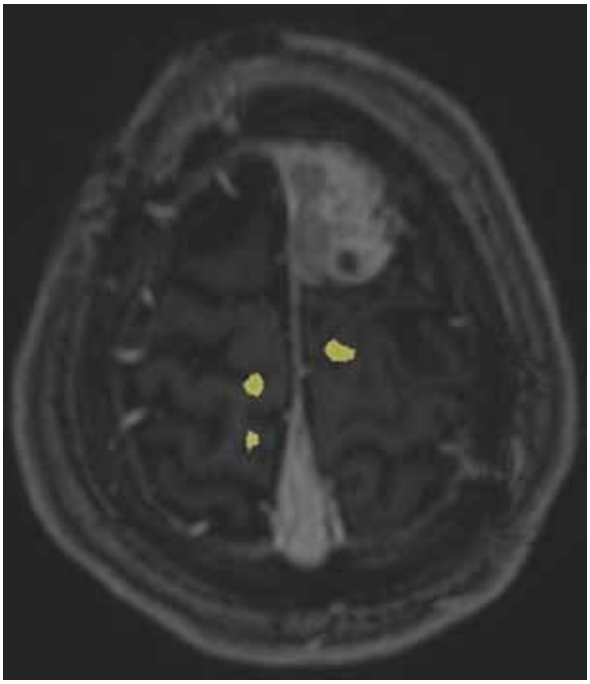

Figure 1: Functional magnetic resonance image of the foot motor task showed cortical activation in the medial part of left precentral gyrus (yellow colour). Residual enhancing tumour is seen in the left frontal region.

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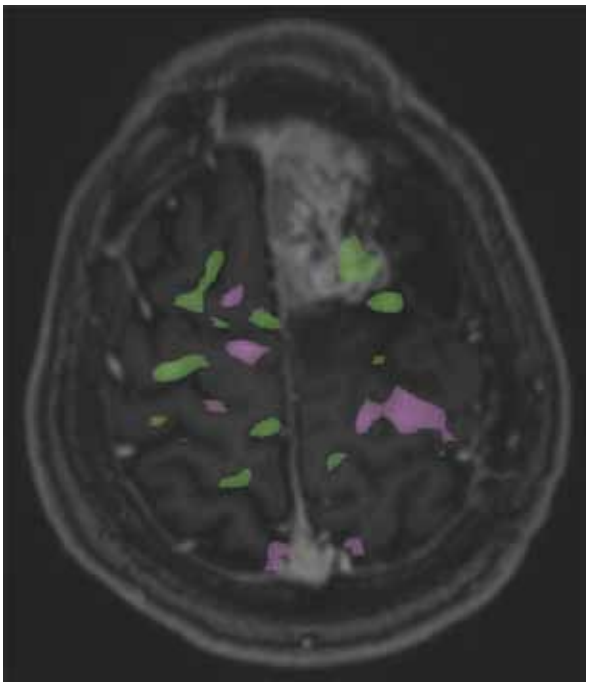

Figure 2: Functional magnetic resonance image of the hand motor task showed cortical activation in the middle part of left precentral gyrus (purple colour).

Recently, we have done fMRI with several paradigm tasks performed on a meningioma patient who had undergone surgery and radiotherapy. Figures 1 and 2 depict the patient's fMRI findings in foot and hand motor tasks, respectively.

With this advanced facility, we are aiming to boost our centre to become a centre of excellence in neuroimaging.

Authors' Contributions

Conception and design, drafting, critical revision, and final approval of the article: WMSJ, AHAK, MSA, AIAH
Analysis and interpretation of the data: WMSJ, AHAK, MCA, MSA, CMCA, SAH, WNAH, ALA, NSEMN, AIAH, HC
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References

1. Valdes-Sosa PA. Coping with brain disorders using neurotechnology. *Malays J Med Sci.* 2012;**19(1)**: 1–3.

2. Smits M, Visch-Brink E, Schraa-Tam CK, Koudstaal PJ, van der Lugt A. Functional MR imaging of language processing: An overview of easy-to-implement paradigms for patient care and clinical research. *Radiographics*. 2006;**26**:S145–158.

3. Wood JM, Kundu B, Utter A, Gallagher TA, Voss J, Nair VA, et al. Impact of brain tumor location on morbidity and mortality: A retrospective functional MR imaging study. *AJNR Am J Neuroradiol*. 2011;**32(8)**:1420–1425.

4. Haberg A, Kvistad KA, Unsgard G, Haraldseth O. Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: Clinical application and outcome. *Neurosurgery*. 2004;**54(4)**:902–914.

Comparative Cognitive Neuroscience: Non-Human Primate Study in the Understanding of Human appreciation of colours

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Dear Editor,

I read with interest the article "Coping with Brain Disorders using Neurotechnology by Pedro A Valdes-Sosa" in by Pedro A Valdes-Sosa, published in the *Malaysian Journal of Medical Sciences*, Volume 19, Issue 1, 2012 (1), where the future of neuroinformatics was presented. I would like to highlight the use of primates in cognitive neurosciences, where the aims of cognitive neuroscience research are to improve understanding of normal and pathological functions and to develop therapeutic strategies and tools that eventually will help cure and control disease progression in humans.

Cognitive neurosciences utilise a variety of elegant techniques including electrophysiology, magnetic resonance imaging, neuroinformatics, and computational modelling, and these techniques interact with clinical studies in a transdisciplinary manner. Non-human primates are probably the closest species to humans in terms of physiological, biological, and major neurological characteristics; these similarities provide a reason for utilising the non-human primates in important biomedical studies

following the conventional ethics in animal research. The brains of non-human primates are like the human brain; they share similarities in terms of physiological characteristic and functioning. This makes non-human primates—for example, those found in Malaysia such as macaques (*Macaca fascicularis*)—accurate models of neurological as well as psychiatric diseases. Non-human primate models offer a unique contribution in the translation of fundamental research findings into clinical applications and in the development of new treatments for neurological diseases (2).

Basic cognitive neuroscience aims to integrate cellular biology (neuron structure and functions) and experimental therapeutics for psychology, neuroanatomy, neurophysiology, and neuropharmacology researches. The study of primates is also an area of interest in fundamental research that bridges the studies of rodent and human cognitive as well as physiological characteristics. Understanding visually based processes that rely on perception, learning, motor response, and behaviour as well as their relationships with regions of the primate brain is the focus of comparative neuroscientists in the next few years (3,4).

The study of colour visual system has brought the interest of neuroscience and psychology researchers to explore how the colours can improve perception, learning, and memory retention in both human and non-human primates. Studies on how animal visual system reacts to a specific type of colour have revealed interesting findings similar to the visual pattern of interaction in human cognition system. Warm colours such as red or yellow were found to have greater impact on attention, which later lead to better retention of information (5). Besides the type of colour used, a recent research on this area has suggested that the combination of colours and the contrast level are also vital to produce such as an effect (5). A study by Osorio et al. (6) on colour and memory in chicks found better memory accuracy when the chicks were given attentive colour and higher level of contrast stimuli. The colour that was used to train the chicks was likely to be chosen in the test phase; the pattern with higher contrast was found to attract the chicks better than the familiar pattern that was used in training. A comparative study of non-human primate (6) also disclosed the similar pattern of interaction in higher-level vision tasks such as visual recognition. An improvement of 6%–8% as well as impairment in visual recognition were observed in both human and non-human primate when the manipulation of the experimental stimuli was conducted using colour noise (6). Specific area of the non-human primate brain responsible for colour information has been revealed, and it matches the colour area in human brain. The posterior inferior temporal cortex and the region of ventromedial occipital of non-human primate were activated in colour discrimination task (7). Even though comparison is difficult, this finding might correspond to the human brain areas related to the knowledge of colour, which was recently found in the ventral temporal lobe (7). These studies have shown that the non-human primate system is comparable to that of humans, and its understanding is crucial in order to present an extensive comprehension of the human cognitive system.

These are some of the areas where non-human primate or animal studies can be very useful in neurosciences. Even though it is not easy to make a comparison between human and non-human primate, I believe this approach of using non-human primate models has a huge potential in understanding the complicated functions and disorders of the human brain so that preventive actions can be put in practice.

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References

1. Valdes-Sosa PA. Coping with brain disorders using neurotechnology. *Malays J Med Sci*. 2012;**19(1)**: 1–3.

2. Capitanio JP, Emborg ME. Contributions of non-human primates to neuroscience research. *Lancet*. 2008;**371(9618)**:1126–1135.

3. Busse L, Katzner S, Treue S. Temporal dynamics of neuronal modulation during exogenous and endogenous shifts of visual attention in macaque area MT. *Proc Natl Acad Sci U S A*. 2008;**105(42)**:16380–16385.

4. Westendorff S, Klaes C, Gail A. The cortical timeline for deciding on reach motor goals. *J Neurosci*. 2010;**30(15)**:5426–5436.

5. Hall RH, Hanna P. The impact of web text-background color combination on readability, retention, aesthetics and behavioural intention. *Behav Inform Technol*. 2004;**23(3)**:183–195.

6. Osorio D, Jones CD, Vorobyev M. Accurate memory for colour but not pattern contrast in chicks. *Curr Biol*. 1999;**9(4)**:199–202.

7. Liebe S, Fischer E, Logothetis NK, Rainer G. Color and shape interactions in the recognition of natural scenes by human and monkey observers. *J Vis*. 2009;**9(5)**:14.1–16.

Introducing Physician Assistants to Thailand's Rural Health

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Dear Editor,

We read with interest the paper by Thira and Patarawan Woratanarat, titled "Assessment of Prospective Physician Characteristics by SWOT Analysis", published in the *Malaysian Journal of Medical Sciences*, Volume 19, Issue 1, January 2012 (1). It reports outcomes of a SWOT analysis conducted among 568 medical students at Chulalongkorn University with the objective of becoming "a good physician in the future". In the last cohort measured (i.e., 2010), it turned out to be that 12.56% of the surveyed students did not want to be a doctor at all. The authors further indicate that despite the growth towards 18 medical schools in Thailand, still, the demand for medical doctors cannot be supplied. Can these results be extrapolated to the Thai medical student population in general? If so, which more measures, besides increasing the number of medical schools, would finally halt the medical workforce shortage? As shown, not only will there be an absolute shortage of physicians (i.e., due to a lower influx of junior doctors and retirement of seniors), but also in the relative count (i.e., due to feminisation of the profession and maldistribution of the medical workforce throughout Thailand). Even though not statistical significant (P = 0.553), a positive trend had been demonstrated from 2008 to 2010 (25.00%, 25.95%, and 29.65%, respectively) that 5th year medical students were increasingly not willing to work in rural area or community after graduation (1). Herewith, Thailand has a looming (rural) health care crisis at hand.

With the knowledge that the majority (i.e., > 60%) of Thailand's population largely resides in rural areas (2) and an increasing number of students appear not willing to work in these areas, it may be suggested that it is time to consider reforming the supply of medical health care by introducing a new type of medical care provider. This new provider, who will be able to practise medicine under supervision of an attending medical doctor, may ensure a better access to care in the rural underserved areas of Thailand.

One of such a provider of interest is the physician assistant (PA). The PA profession originated from the United States, where in the mid 60's, a solution was sought to address the medical workforce shortage. A PA is trained to the medical model and is competent to take medical history, do physical examination, render diagnosis, and perform a whole range of (surgical) interventions, next to the capability of prescribing medication. The advantages of adding PAs to medical teams have caused a global movement, and increasingly more countries, such as Australia, Canada, Germany, Ghana, India, the Netherlands, the United Kingdom, and Scotland, now train and deploy PAs to enable medical task shifting (3). The role of PAs in rural health care has been reported and underlines the value of deploying such a provider in terms of ensuring continuous access to care to consumers whom, without PAs, would likely be deprived of medical care. The main conclusion of a systematic review (4) conducted in 2010 concerning American PAs working in rural health care shows that PA deployment is cost-efficient and their services are valued.

How can PAs solve the imbalance between demand and supply of medical care in Thailand? At the district-level health post, a PA should have the role as the provider of first medical contact. This can be an improvement of the present system of village health volunteer, who is usually a layperson with little knowledge in medicine. Factors that may contribute to the retention of PAs serving their rural communities after their training were suggested in an article by Coombs et al. (5); from their survey, it is clear that students who had a rural upbringing were more likely to practise in rural care after graduation (OR = 2.29, 95% CI = 0.89–5.85, P = 0.001). This fact could be made a condition for matriculation to minimise the risk of brain drain.

Under the presumption that PAs will be introduced to the Thai rural health care system, it should be addressed that a PA is not the sole provider but needs to collaborate with the community health nurse practitioners (CHNPs) and a certified midwife. They should work in a team-based model, in which the CHNPs are much better equipped with nursing knowledge and skills to cover the chronic care and prevention of health problems, whereas the PA practices the broad range of family medicine under supervision of an attending medical doctor from a neighboring community health center. This system can be implemented under the present universal coverage policies (6). The usefulness of implementation of PAs can be expected. However, the preparation of basic requirements, a good training curriculum adapted to the local needs, and the acceptance of this new kind of medical personnel by Thai medical society are required.

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References

1. Woratanarat T, Woratanarat P. Assessment of prospective physician characteristics by SWOT analysis. *Malays J Med Sci.* 2012;**19(1)**:60–64.

2. Sakunphanit T. *Thailand: Universal health care coverage through pluralistic approaches* [Internet]. Bangkok (TH): International Labour Organization subregional office for East Asia; 2006 [cited 2012 Apr 1]. Available from: http://www.ilo.org/public/english/region/asro/bangkok/events/sis/download/paper31.pdf.

3. Hooker RS, Kuilman L. Physician assistant education: Five countries. *J Physician Assist Educ.* 2011;**22(1)**:53–58.

4. Henry LR, Hooker RS, Yates KL. The role of physician assistants in rural health care: A systematic review of the literature. *J Rural Health.* 2011;**27(2)**:220–229.

5. Coombs JM, Morgan P, Pedersen DM, Koduri S, Alder SC. Factors associated with physician assistant practice in rural and primary care in Utah. *Int J Family Med.* 2011;**2011**:879036.

6. Pannarunothai S, Patmasiriwat D, Srithamrongsawat S. Universal health coverage in Thailand: Ideas for reform and policy struggling. *Health Policy.* 2004;**68(1)**:17–30.

Syphilis Seroreactivity: Determining the Importance during Routine Screening

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Dear Editor,

There are an estimated 12 million syphilis cases worldwide, and 2 million of these cases are among pregnant women. There is paucity of data from the South–East Asia on the adverse outcomes of untreated syphilis during pregnancy and on the incidence of congenital syphilis among live-born infants. The reasons for this lack of data could be the difficulty of diagnosis, the occurrence of a high number of asymptomatic infections, or the absence of surveillance or reporting systems along with the lack of availability of trained personnel. As a result, the routine screening for syphilis starts at the district level and is not conducted at lower levels (1). According to the US Preventive Services Task Force, screening for syphilis is considered imperative during pregnancy because there is a substantial net benefit of the screening in pregnant women in the form of a reduced incidence of congenital syphilis in neonates (2). Congenital syphilis is preventable if adequate screening for syphilis is performed during pregnancy. Additionally, the prevalence of syphilis is a good indicator of the effectiveness of ongoing prenatal screening and control programmes in the area.

The present study was conducted retrospectively in the Government Medical College Hospital, Chandigarh, over a period of 6 months (January 2008 to June 2008) on 2088 non-duplicate sera received by the Microbiology Laboratory for syphilis screening. Out of the 2088 samples, 1999 were from the Department of Obstetrics and Gynaecology, 11 were from the Sexually Transmitted Diseases Clinic, and 78 were from other departments of the hospital. All sera were subjected to the rapid plasma reagin (RPR) test (using a kit procured from SPAN Diagnostics Limited, Surat, India) for qualitative and quantitative estimation. The sensitivity and specificity of the kit are equivalent to those of the classical Venereal Disease Research Laboratory (VDRL) test, according to the manufacturer. The greatest dilution of the sera at which the RPR test was positive was taken as the titre.

In the present study, 15 (0.72%) samples were found to be seroreactive for syphilis, out of which 14 were from antenatal clinics, and 1 was from the eye outpatient department. The women and their husbands were tested as a part of the normal protocol for the antenatal check-up. Among the included subjects was a woman with history of 2 spontaneous abortions who had a positive RPR with a titre of 8 dils (*Treponema pallidum* haemaglutinin positive). Her husband was also RPR positive (4 dils), and their newborn child was found to be RPR positive with a titre of 2 dils 2 days after birth. Both the husband and the wife had been treated with 3 doses of 2.4 million units of benzathine penicillin during the present pregnancy. Therefore, we assume that the RPR positivity in the newborn could have been the result of the passive transfer of antibodies from the mother (unfortunately, a specific treponemal test could not be performed for the newborn). Clinically, the newborn had no signs or symptoms of the disease. Two other couples were also found to be RPR positive. In one of the couples, both the wife and the husband had a titre of 16 dils; in the other couple, the wife and the husband had titres of 4 dils and 8 dils, respectively. Both of these women had history of abortion in their previous pregnancy. All of these individuals were

treated with 3 doses of benzathine penicillin intramuscularly at a dosage of 2.4 million units, and their RPR titres became negative. Both females delivered their babies normally, with normal birth weights and negative RPR titres 2 days after birth. Further follow-up of the babies could not be performed. Three other women had titres of 4 dils, two had 8 dils, and another two had 16 dils. Further follow-up information was not available. It is worth mentioning here that most of the cases were asymptomatic at the time of presentation. It was only the serological diagnosis and their antenatal status that led to the treatment.

The seroprevalence of syphilis in patients visiting antenatal clinics was found to be low in our study. Previously, another study from our geographic area reported similar results (3). The reason for the low prevalence of syphilis could be that the study was conducted in a well-educated city in India. These women receive informative health education and are aware of the benefits of antenatal screening. Further, the control of sexually transmitted diseases (among which syphilis is very important) is one of the main strategies for the prevention of human immunodeficiency virus (HIV) infection. It is recommended that all patients newly diagnosed with HIV infection should be tested for syphilis, and vice versa. As a result, syphilis is better monitored. Overall, in India, the prevalence is reported to vary from 2.5% to 3.4% (3). However, as congenital syphilis can be the outcome of untreated syphilis in pregnant women, screening for syphilis is an imperative cost-effective tool during pregnancy even when the prevalence of RPR positivity is as low as 2% (4).

The patient from the Eye Outpatient Department had a titre of 128 dils. He was a 44-year-old male with a history of recurrent uveitis. A study by Kunkel et al. (5) revealed that ocular syphilis could even be an indicator of previously unknown HIV infection, which emphasises that patients with ocular syphilis must be screened for HIV co-infection. Additionally, Kunkel et al. (5) were able to successfully treat all but 1 of the patients with ocular syphilis .

The VDRL/RPR test has a standard cut-off value for the uniform interpretation of results. A reactive non-treponemal test indicates a present infection or a recently treated or untreated infection. Ideally, patients for whom the non-treponemal test is positive should be evaluated using a specific treponemal test. However, there are studies that indicate that caution is required when interpreting positive treponemal test results (6). Low reactivity in a treponemal test may be a false positive, which may occur in association with a low titre or a negative result for the non-treponemal tests. Low reactivity may also be observed in cases of late syphilis or adequately treated syphilis (the treponemal tests remain reactive, sometimes for life, even after treatment). The results of the study by Rajendran et al. (7) demonstrate that no single serological test for syphilis can act as a marker of ongoing acute infection in an apparently healthy population. All laboratory findings should be interpreted with regard to the medical history of the patient, including the course of infection, previous therapy, and the responses to clinical questioning (8). Recently, a new test, the colloidal gold-immunochromatography assay, has been developed, and this assay helps in identifying relapses of and infection with syphilis. This assay is fast and convenient to use and has very low biological false-positive rate. It is also inexpensive compared with other specific tests for syphilis (9).

In developing countries such as India, people are often lost during follow-up. Most of the time, they do not agree to undergo comparatively expensive specific confirmatory tests, and therefore, the results of non-specific tests are routinely used as a guide to start treatment, especially in community settings. We conclude that congenital syphilis is still prevalent and that effective surveillance during pregnancy can go a long way towards eradicating this potentially preventable disease.

Authors' Contributions

Conception and design: NS
Analysis and interpretation of the data, drafting of the article: HR
Critical revision of the article, administrative, technical, or logistic support: NS, JC
Final approval of the article: JC

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References

1. World Health Organization, Regional Office for South East Asia. *Regional strategy for the elimination of congenital syphilis* [Internet]. India: World Health Organization; 2009 [cited 2011 Jul 19]. Available from: www.searo.who.int/LinkFiles/Publications_RS-elimination-syphilis.pdf.

2. U.S. Preventive Service Task Force. Screening for syphilis infection in pregnant women: Evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2009;**150(10)**:705–709.

3. Sethi S, Sharma K, Dhaliwal LK, Banga SS, Sharma M. Declining trends in syphilis prevalence among antenatal women in northern India: A 10-year analysis from a tertiary healthcare centre. *Sex Transm Inf*. 2007;**83(7)**:592.

4. Terris-Prestholt F, Watson-Jones D, Mugeye K, Kumaranayake L, Ndeki L, Weiss H, et al. Is antenatal syphilis screening still cost effective in sub-Saharan Africa. *Sex Transm Infect*. 2003;**79(5)**:375–381.

5. Kunkel J, Schurmann D, Pleyer U, Ruther K, Kneifel C, Krause L, et al. Ocular syphilis—Indicator of previously unknown HIV-infection. *J Infect*. 2009;**58(1)**:32–36.

6. Hart G. The role of treponemal tests in therapeutic decision making. *Am J Public Health*. 1983;**73(7):** 739–743.

7. Rajendran P, Thyagarajan SP, Pramod NP, Joyee AG, Murugavel KG, Balakrishnan P, et al. Serodiagnosis of syphilis in a community: An evaluatory study. *Indian J Med Microbiol*. 2003;**21(3)**:179–183.

8. Lin LR, Fu ZG, Dan B, Jing GJ, Tong ML, Chen DT, et al. Development of a colloidal gold-immunochromatography assay to detect immunoglobulin G antibodies to *Treponema pallidum* with TPN17 and TPN47. *Diagn Microbiol Infect Dis*. 2010;**68(3)**:193–200.

9. Hagedorn HJ. Laboratory diagnosis of syphilis. In: Gross G, Tyring SK, editors. *Sexually transmitted infections and sexually transmitted diseases*. Heidelberg (DE): Springer; 2011. p. 143–149.

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> Theriault A, Caao JT, Gapor A. Tocotrienol is the most effective vitamin E for reducing endothelial expression of adhesion molecule and adhesion to monocytes. *Atherosclerosis.* 2002; **160(1)**:21-30.

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> Carlson BM. *Human embryology and developmental biology*. 3rd ed. St Louis: Mosby; 2004.

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> Rabbani SI, Devi K, Khanam S. Role of pioglitazone with metformin or glimepiride on oxidative stress-

induced nuclear damage and reproductive toxicity in diabetic rats. *Malaysian J Med Sci* [Internet]. 2010 [cited 2010 Mar 21];**17(1)**:3–11. Available from: http://ernd.usm.my/journal/journal/02-171OA1pioglitazone.pdf

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References

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   Council; 2006.
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