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MJMS at the Dawn of Its Electronic Era

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Abstract -

This special editorial assessed the recent developments in *Malaysian Journal of Medical Sciences (MJMS)* and examined the characteristics of the submission, peer review, and publication processes for MJMS. This retrospective analysis used information about the manuscripts submitted to MJMS during the one-year period (from 1 June 2010 to 31 May 2010) since the start of current online submission and review system (ScholarOne[™] Manuscripts, Thomson Reuters). In addition, we also discussed the future directions of *MJMS*. Finally, we would like to recommend an annual internal audit for *MJMS*, which is very useful to monitor the growth of this journal progressively.

Keywords: editorial policies, peer review, publishing, quality control, statistics

The past year has been one of great change for the *Malaysian Journal of Medical Sciences* (*MJMS*). We have progressed from a print journal to an electronic journal, from traditional hardcopy submission via postal mail to fully electronic submission and speedy correspondence via emails, and from a monotonous cover and layout to a visually stimulating and impressive appearance.

This major progress primarily stemmed from the "Accelerated Programme of Excellence" (APEX) status awarded to Universiti Sains Malaysia (USM). This award has brought more funding to the journal, which is managed under the Research Management and Creativity Office (RCMO). MJMS is targeted as one of the journals that is most likely to succeed on the international platform. USM Press took over the publication of MJMS from the School of Medical Sciences in January 2009 with the understanding that the School would continue to provide editorial assistance by selecting quality articles in accordance with the MJMS' objectives, while the USM Press would offer administrative help and would internationalise the journal by increasing exposure though ISI and PubMed. Since this transition, we have been able to utilise more resources, which allowed our recent developments.

Our Guidelines for Authors have been refined. The latest version (updated September 2010) offers more comprehensive guidelines meant to facilitate manuscript preparation and to expedite the subsequent editorial process by avoiding unnecessary hiccups. It is not our intention to lay a burden on authors with these seemingly "stricter" requirements, but rather we are adopting MEDLINE's requirements for manuscripts in hopes of receiving a positive outcome from the MEDLINE evaluation. To facilitate MEDLINE's evaluation of *MJMS*, we sincerely hope that authors will follow the Guidelines as closely as possible.

This special editorial will assess the recent developments in *MJMS* and examine the characteristics of the submission, peer review, and publication processes for *MJMS*. This retrospective analysis used information about the manuscripts submitted to MJMS during the one-year period (from 1 June 2010 to 31 May 2010) since the start of current online submission and review system (ScholarOneTM Manuscripts, Thomson Reuters).

The Electronic Evolution

Electronic submission to *MJMS* started in June 2009. We have been accepting manuscripts via ScholarOneTM Manuscripts (formerly Manuscript Central), an online manuscript submission, tracking, and review system. Prior to the adoption of the online submission system, we relied on submission by post, in person (usually from USM), and occasionally by email.

Because we no longer rely on the exchange of hard copies, we do not have to deal with stacks of paper, whose storage requires considerable physical space. This transition also obviated the need to print and file every manuscript submitted via email. This transition from paper dependence to paperless manuscript processing is in line with the sustainable campus philosophy of the USM (1) and with the global mission to save the green resources of the Earth. The paperless handling of data has been adopted and popularised by the majority of journals in the world.

Consequently, the editorial office duties have been greatly reduced—no longer must the staff mail and track hundreds of envelopes each year. With fewer envelopes to manage, the *MJMS* editorial staff can focus more on improving the quality of the journal and on getting the journal indexed in as many relevant databases as possible, importantly PubMed and ISI Web of Science.

In addition to switching to an online submission system, the journal itself has evolved into an electronic journal. Starting in January 2009, *MJMS* has been published electronically on our website, and hardcopies are only printed on demand.

Submission Trends

Our transition from a print journal to an online journal brought about a perceptible increase in our submission rate. Since we implemented the online submission system, on average, 12 manuscripts are submitted to MJMS each month (Table 1). This number is double the average number of manuscripts submitted each month before using ScholarOne[™] Manuscripts, which was 6 (unpublished data). This increase indicates that switching to electronic submission facilitates submission; it is also possible that MJMS is getting more publicity and is more visible in the local and international communities. The types of manuscripts submitted to MJMS are illustrated in Figure 1. Original articles constitute the majority (60.2%) of the manuscripts we have received. However, among these, only one-third

Table	1:	Submission of manuscripts to
		Malaysian Journal of Medi-
		cal Sciences via ScholarOne™
		Manuscripts in one year June
		2009 - May 2010 (unless indicated
		otherwise)

Submission Month	n
Jun	11
Jul	8
Aug	18
Sep	10
Oct	14
Nov	12
Dec	12
Jan	12
Feb	14
Mar	12
Apr	17
May	10
Total	150

^a One manuscript, in the format of letters to the editors, was sent via email.



Malaysian Journal of Medical Sciences in one year

(33.3%) are laboratory-based research papers, and we are aiming to attract more research papers in the future to balance the abundance of clinical papers, which encompassed two-thirds (66.6%) of original articles. Most of our submissions come from Asia: Malaysia, unsurprisingly, is the top contributor, followed by India and Iran. Classifying the origin of submissions by region, most of our submission comes from Southeast Asia (60.7%). This is followed by South Asia (14.7%), Middle East (12.0%), Africa (9.3%), Oceania (1.3%), North America (1.3%), and South America (0.7%). The breakdown of submissions by country is shown in Table 2. These data indicate that *MJMS* is successful in attracting authors from developing nations; this trend is in line with the journal's aim, which is to publish and disseminate information on biomedical and health sciences research pertinent to developing nations.

Table 2:Submission of manuscripts to
Malaysian Journal of Medical
Sciences by country in one year via
ScholarOne™ Manuscripts (unless
indicated otherwise)

Region	n
South East Asia	
Malaysia	88
Singapore	2
Indonesia	1
South Asia	
India	14
Pakistan	7
Bangladesh	1
Middle East	
Iran	11
Turkey	4
Palestinian Territory, Occupied	11
Saudi Arabia	1
Iraq	1
Africa	
Nigeria	13
Sudan	1
North America	
United States of America	2
South America	
Cuba	1 ^a
Oceania	
Australia	2
Total	150

^a One manuscript, in the format of "letters to the editors", was sent via email.

Peer Review Trends

Accept-reject ratio

On average, MJMS rejected half of the manuscripts after peer review (Table 3). The average rejection rate has increased from approximately 20.0% (2) to 51.7% (Table 3). The rejection rates of original articles and review articles are higher than the average rate, at 61.5% and 71.4%, respectively. Review articles have the highest rejection rate; the most common reasons for rejection were the lack of novelty of the review topic and the poor structure of the manuscripts. These high rates of rejection are compensated for by the low rejection rate of editorials and special communications, as these solicited articles are unlikely to be rejected. The average rejection rate is considered high for a small scientific journal like MJMS. This situation indicates that although MJMS receives many manuscripts, the quality of most manuscripts is unsatisfactory. We sincerely thank all of our reviewers who, by their commendable efforts in reviewing, have contributed to improving the quality of the manuscripts published in MJMS.

Only a small proportion (16%) of the average rejection rate is attributed to rejection prepeer review. Some of the reasons for this early rejection by MJMS are as follows: the topic is of low priority for publication due to the lack of new or useful knowledge; major language errors; failure to comply with the Guidelines for Authors; or the topic is not within the scope of MJMS, for example, veterinary sciences and agriculture. Screening at the early stages (pre-peer review) should be implemented more rigorously to remove unsuitable manuscripts. A study by Johnston et al. (3) indicated that early screening is favourable, as it lessens the burdens on reviewers and shortened the time taken to reach a final decision. For MJMS, the median time taken to reach the final decision to reject a manuscript using the pre-peer review screening is 8 days, which is significantly shorter than the 44 days taken for the post-peer review process.

Publication Trends

Language

We realise that most of the papers sent to *MJMS* are from authors for whom English is their second language. Although language problems should not be the main reason for rejection (4), we have had to reject manuscripts that are so poorly written or presented that they were hard comprehend. We felt that these manuscripts were

		Final decision					
Manuscript Type	n	Accept	Acception Ratio (%)	Reject	Rejection Ratio (%)		
Brief communication	4	4	100.0	0	0.0		
Case report	22	15	62.5	9	37.5		
Editorial	2	2	100.0	0	0.0		
Original article	52	20	38.5	32	61.5		
Review article	7	2	28.6	5	71.4		
Total/Average	89	43	48.3	46	51.7		

Table 3: Malaysian Journal of Medical Sciences acception and rejection ratio of different manuscript types^a

^a Manuscripts with an original submission date from 1 June 2009 to 31 May 2010 and a final decision date of on or before 31 May 2010.

not even understandable and therefore had to be rejected pre-peer review. To ensure that our published articles are well written, we send all accepted articles to a professional English editing service, *American Journal Experts (AJE)*. After the articles are returned by AJE, the accepted articles are refined carefully with respect to format and style by our in-house copyeditors.

Waiting time of publication

The waiting time of publication of an accepted manuscript has been reduced from 6 months (5) to a median of 4 months (Figure 2). The waiting time of articles accepted to MJMS depends on (a) the order of acceptance; (b) the type (original articles get higher priority than case reports, and editorial articles are solicited and do not undergo peer review; hence they are almost immediately accepted and published in the next upcoming issue of the journal); and (c) the subject area of the article. The Editor will select articles representing a variety of subject areas for each issue; therefore, if we have an abundance of otorhinolaryngology papers (which did happen!), we would publish these articles in separate issues. Within a particular subject area, articles that are more appealing, that is, offering new knowledge and are informative and exciting, get prioritised.

Future directions

MJMS is still developmental in character, and certainly there is more room for improvement. However, we are content with the current progress; we have made a small start, which is nonetheless important in setting the journal's pace.

We hope that the Editorial Board members will be active contributors to the journal, for example, in helping to screen the growing number of new submissions. We are also in the process of incorporating more medical-based statistics experts on the Board in addition to retaining the members with multidisciplinary areas of expertise to ensure that the published articles are not only of high quality content-wise but are also statistically sound.

At the moment, we are experimenting with the submission of video with manuscripts. Video material and animation sequences can be used to support and enhance scientific or medical research. Videos accompanying a manuscript must be innovative, provide added value, and, most importantly, not merely a rehash of the procedures described in the text. We will welcome the submission of videos (as supplements to manuscripts) starting in early 2011.

We are also striving to increase our worldwide visibility and readership by applying to be indexed in as many relevant databases as possible. MJMS is currently indexed in SCOPUS, Bioline International, the British Library, EMBASE, Index Copernicus, DOAJ, and a few more. Currently, we are under evaluation for indexing in PubMed and ISI. As a small journal from a small country, we realise that getting indexed in these databases is a herculean task; however, it is not impossible, as we are breaking slowly from the socalled "vicious cycle of inadequacy" that journals from semi-developed countries face (6). We have published papers on issues that are pertinent to developing countries, for example, articles on the unique experience of a mobile medical team during a major flood (7), the recent developments





Figure 2: Publishing time of accepted manuscripts in *Malaysian Journal of Medical Sciences*. Data was analysed from 43 accepted manuscripts in the period of oneyear. Mean = 4.7 months, median = 4.0 months.

in dengue research (8), and the H1N1 pandemic (9). Therefore, *MJMS* offers a fresh perspective on health and medical issues from the developing world.

Clearly, *MJMS* has grown in many aspects as discussed above. These achievements are the result of the hard work of a team dedicated to the development of *MJMS*. As a final note, we would like to emphasize the importance of an annual internal audit, which we hope will allow the growth of this journal to be monitored progressively.

Acknowledgements

We would like to thank *MJMS* team 2009–2010: Professor Jafri Malin Abdullah for his continuous encouragement and excellent ideas; Siti Nor Qamariah Ismail for the new and improved *MJMS* look and feel; and Fazlina Mohamed Rouse from USM Press for all the administrative help in funding, and the essential groundwork.

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Review Article

Neuroimaging in the Field of Psychoses

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Abstract -

This review looks at the recent findings in the neuroimaging of the psychoses, with a view to clarifying the question of the unitary versus the two-disorder theory of psychosis. Schizophrenia is associated with significantly more cortical grey matter loss than bipolar disorder. The distribution of these losses is different; schizophrenia is characteristically associated with loss of the medial and middle frontal, the superior temporal gyri, and the dorsolateral prefrontal cortex, while bipolar disorder has particular loss in the medial frontal gyrus and the anterior cingulate cortex. Both disorders were associated with extensive white matter deficits. In summary, neuroimaging indicates different patterns of grey matter loss for schizophrenia and bipolar disorder. However, neuroimaging of white matter reveals a good deal of overlap between these two disorders. Thus, neuroimaging does not suggest a unitary psychosis or a two-psychosis model, instead it suggests a two-dimensional psychosis field, on which disorders are located according to two dimensions, the degree of grey matter loss and the degree of white matter abnormality.

Keywords: bipolar disorder, magnetic resonance imaging, psychoses, schizophrenia, tomography

Introduction

Schizophrenia and bipolar disorder are common, disabling disorders. They were known as "functional" (by which was meant, no organic basis has been demonstrated) as opposed to the "organic" disorders (such as dementia, for which a structural basis can be demonstrated at autopsy). However, the term "functional" says more about the technology of the day than about a particular disorder, and in recent years, neuroimaging has begun to illustrate the structural abnormalities of these disorders.

In 1893, Emil Kraepelin divided the extant single category of psychosis into two (the modern equivalents being schizophrenia and bipolar disorder). His concept has guided much of the psychiatric research and clinical work for the last century. However, there have been repeated calls to return to the unitary theory of psychosis (1). Recent neuroimaging may inform this debate.

Coaxial tomography became available in the 1970s, and was immediately used to demonstrate increased cerebral ventricular size in people with schizophrenia (2), but limited progress was achieved. Magnetic resonance imaging (MRI) then revolutionized neuroimaging. This review will be limited to structural MRI, with some mention of its use in diffusion tensor imaging (DTI; which depends on water diffusing more rapidly in the direction aligned with the internal structure of white matter).

In MRI, voxel-based morphometry (VBM) is a technique in which neuroanatomical differences are detected by comparing voxels across the entire brain. This method has some technical difficulties (3,4). Small abnormalities may go undetected, and perhaps the best use of VBM is the identification of candidate regions (5). In region-of-interest (ROI) MRI, candidate regions are examined in greater detail.

Patient factors also introduce comparison difficulties. Diagnostic criteria may vary, and different disease stages may have different pathological features. Furthermore, some medications are known to alter grey matter volume.

A comprehensive assessment of the literature was conducted in PubMed using "neuroimaging, schizophrenia" and "neuroimaging, bipolar disorder" as the search terms. A selection of papers were examined and reported under these headings: 1) schizophrenia, 2) bipolar disorder, and 3) comparisons of schizophrenia and bipolar disorder.

Schizophrenia

In a meta-analysis of whole brain volumes in first-episode, medication-naïve patients with schizophrenia, Steen et al. (6) found a 2.7% reduction in comparison with healthy controls. In VBM studies of schizophrenia, reduced grey matter has been described in the frontal, temporal, and thalamic regions. Similar changes have been reported in first-episode and chronic schizophrenia, but the differences are more marked in the latter (7).

In a longitudinal ROI study (8) people with chronic schizophrenia and healthy controls were examined at two points, 4 years apart. The course of the illness was charted using the Brief Psychiatric Rating Scale (BPRS) and periods of hospitalization. People with chronic schizophrenia demonstrated significantly accelerated lateral ventricular expansion and frontal cortical grey matter loss. Rates of loss were greater in patients with higher BPRS scores and longer periods of hospitalization.

Much interest has been directed toward early brain changes. This approach may perhaps avoid complications introduced by medication and the chronic disease process. An understanding of early brain changes may also assist in early diagnosis, and eventually, in prevention. To this end, people at risk of schizophrenia (either by a change in the premorbid mental state, or possible genetic disposition) have been identified and serially investigated.

Pantelis et al. (9) examined young people at increased risk for schizophrenia. In this crosssectional study, subjects who developed psychosis compared with those who did not, showed less grey matter in the right lateral temporal, medial temporal, and inferior frontal neocortex and in the cingulate cortex bilaterally. Subjects who developed psychosis were re-scanned 1 year later, at which point, there was a loss of grey matter in the left fusiform, parahippocampal, orbitofrontal, and cerebellar cortices. Therefore, some grey matter abnormalities predated the onset of psychosis, and others came later. A similar study (10) found reduced grey matter in posterior and anterior cingulate areas, lateral and medial temporal lobes, and lateral frontal cortex in young patients prior to the development of psychosis in comparison with at-risk individuals who did no develop psychosis and healthy controls.

A recent VBM study (11) compared a group of patients with formal thought disorder with healthy controls. Thought disorder was gauged using the Scale for the Assessment of Thought,

Review Article | Neuroimaging in psychoses

Language, and Communication. The severity of thought disorder was negatively correlated with the grey matter volume of the left temporal pole, left superior temporal gyrus, the right cuneus/ lingual gyrus, and the right middle orbital gyrus. These findings support an analysis of 15 VBM studies (12) which indicated the left medial temporal lobe the left superior temporal gyrus as key regions of anatomical difference between people with schizophrenia and healthy subjects.

A DTI study of people with schizophrenia (13) revealed significant white matter disruption compared to healthy controls in the uncinate fasciculus, arcuate fasciculus, cingulum, and corpus callosum.

Bipolar Disorder

Bipolar disorder may feature psychosis, which makes comparison with schizophrenia interesting. The whole brain volume in bipolar disorder appears to be preserved (14). However, moderate ventricular enlargement has been frequently demonstrated (15), suggesting some tissue loss. VBM studies in bipolar disorder have vielded variable findings. Some studies have failed to find grey matter differences in patients relative to healthy controls, suggesting that these changes in bipolar disorder are less pronounced than those found in schizophrenia (16). ROI studies in bipolar disorder have described ventricular enlargement and white matter hyperintensities as the most robust changes, with grey matter differences generally being small (17). VBM studies of early stage bipolar disorder have been few and contradictory. Janssen et al. (18) found reductions specific to the medial prefrontal cortex. ROI studies of early stage bipolar disorder have also been few and inconsistent. Koo et al. (19) found reduced left subgenual cingulate cortex; however, Fornito et al. (20) reported increased right subgenual cingulate cortex in male patients.

Koo et al. (19) performed a longitudinal study of bipolar disorder, conducting scans at the first episode of psychosis, and again about 3 years later. A reduction was demonstrated in the volume of the anterior cingulate cortex. Moorhead et al. (21) studied people with chronic bipolar disorder for over a 4-year period and found progressive grey matter reduction in the fusiform, hippocampal, and cerebellar cortex, but not in the anterior cingulate cortex.

Savits et al. (22) compared two groups of patients with bipolar disorder (medicated and unmedicated) with healthy controls. The unmedicated patients had significantly smaller amygdalae and the medicated patients had larger amygdalae (trending towards significance) compared with the healthy controls. The disease process was believed to account for the reduced size of the amygdalae in the unmedicated group, and the medication was believed to account for the increased size of the amygdale in the medicated group.

Heng et al. (23) reviewed 18 DTI studies of the white matter of people with bipolar disorder. They concluded a loss of white matter connectivity (involving prefrontal and frontal regions), projection, associative and commissural fibres was a feature of bipolar disorder.

Comparisons of Schizophrenia and Bipolar Disorder

Some recent studies have directly compared images of patients with schizophrenia and bipolar disorder, in particular, where there have been psychotic features.

Kasai et al. (24), in a ROI study, compared the grey matter volume of the left superior temporal gyrus of a group of people with firstepisode schizophrenia, a group of people with first-episode affective psychosis, and a group of healthy controls, at two points in time, 1.5 years apart. They found progressive loss of the left superior temporal gyrus in schizophrenia in contrast to patients with affective psychosis and controls.

Coryell et al. (25) studied patients with major depressive disorder with psychotic features, patients with schizophrenia, and healthy controls, at two points, 4 years apart. The people with major depressive disorder with psychotic features had significantly smaller grey matter volumes on the left side of the posterior subgenual prefrontal cortex. The volumes of this region for patients with schizophrenia were also smaller than for the healthy controls. Four years later, the relative size relationship was unchanged; however, for the depression group, the size of this region had increased. This suggested (to the authors) that for this disorder, this anatomical deficit is reversible, and that medication may have played a role.

McDonald et al. (26) used VBM to compare the grey and white matter volumes throughout the brain of groups of individuals with schizophrenia, bipolar disorder with psychotic features, and healthy controls. The group with schizophrenia had generalized grey matter loss (predominantly involving frontotemporal neocortex, medial temporal lobe, insula, thalamus, and cerebellum). The group with bipolar disorder did not have regions of significant grey matter loss. The authors observed that the majority of the bipolar patients were on lithium, which may have increased the volume of the grey matter of this group, and hence reduced any differences in grey matter volume, which might otherwise have existed. The pathological groups had anatomically overlapping white matter abnormalities in regions occupied by major longitudinal and interhemispheric tracts (including the superior longitudinal fasciculus, inferior longitudinal fasciculus, and orbitofrontal fasciculus, as well and the anterior and posterior parts of the corpus callosum).

Nakamura et al. (27) conducted a ROI study of the neocortical grey matter of groups at first hospitalization for schizophrenia, first hospitalization for affective disorder with psychosis, and no mental disorder. Patients were scanned at intake and 1.5 years later. At first hospitalization, both the schizophrenia and affective disorder groups demonstrated significantly less neocortical grey matter than the healthy control groups; however, there was no significant volume difference between the pathological groups. Longitudinally, however, the schizophrenia group showed a neocortical grey matter reduction (-1.7%; mainly in the frontal and temporal regions) and the affective disorder group showed a neocortical grey matter increase (+3.6%), which the authors suggested may reflect the neurotrophic effects of mood stabilizers.

Koo et al. (19) studied initial and progressive grey matter volume of cingulate gyrus subregions in patients with first episode schizophrenia, patients with first episode affective psychosis, and healthy controls. Subjects were scanned twice, 1.5 years apart. Patients with affective psychosis, at initial assessment, showed significant loss of the subgenual cingulate, which was progressive. Patients with schizophrenia, on the other hand, had more widespread cingulate deficits, which were less progressive. This suggested (to the authors) that these disorders had different initial grev matter deficits and progression over time. In addition, this group looked at the morphology of the paracingulate sulcus. Cerebral folding occurs during the 2nd and 3rd trimester and is stable thereafter, and consequently, the paracingulate can be used as a marker of neurodevelopment. The authors found less fissuration of the paracingulate sulcus in people with schizophrenia than healthy controls, suggesting neurodevelopmental factors contribute to this disorder.

Janssen et al. (18) conducted an MRI study of early onset first-episode psychosis. For inclusion, onset was prior to 18 years of age and the psychosis had persisted for less than 6 months. Three diagnostic groups were identified: schizophrenia, bipolar disorder, and other psychiatric conditions. Schizophrenia was associated with grey matter volume loss in the left medial (superior) and left middle frontal gyrus. Bipolar disorder, however, was associated with grey matter volume loss of the left medial frontal gyrus only. The psychotic individuals who at follow-up did not have a diagnosis of either schizophrenia or bipolar disorder displayed different patterns. The authors noted that the schizophrenia and bipolar psychosis both appeared associated with medial frontal gyrus, suggesting some shared pathophysiology.

White matter hyper-intensities had been considered to be a characteristic feature of mood disorder (17). However, Zanetti et al. (28), in a large and well conducted study using MRI, found that white matter hyper-intensities were equally represented in psychotic bipolar disorder and schizophrenia spectrum disorders. Doubt about the specificity of white matter hyper-intensities in bipolar disorder has been recently expressed by Gunde et al. (29). Interestingly, McIntosh et al. (30) demonstrated DTI abnormalities in the uncinate fasciculus in both schizophrenia and bipolar disorder, but Walterfang et al. (31) found MRI differences between the corpus callosum of the first-episode affective psychosis and schizophrenia spectrum patients.

El-Sayed et al. (32) studied young people with early onset schizophrenia spectrum disorders, young psychotic people with mood disorders, and young healthy controls. They found significantly lower total brain volume in those with schizophrenic spectrum disorders compared with the other two groups. They found the schizophrenia spectrum disorder patients had significantly reduced grey matter volume, particularly in the frontal and parietal lobes, but found no difference in white matter volumes.

Discussion

This paper does not mention every study in the field of neuroimaging in psychosis. However, a good representative sample is presented, with particular attention applied to the most recent studies.

In 1893, Emil Kraepelin divided the psychoses into two categories, schizophrenia and bipolar disorder. However, some still question whether they are two distinct disorders, or a single disorder which is expressed differently (the unitary theory of psychosis). This paper asks whether neuroimaging can contribute to this discussion.

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Neuroimaging of schizophrenia finds a significant reduction in whole brain volume (2,6). Grey matter loss has been consistently described in the anterior and lateral prefrontal regions and the medial, lateral surfaces, and the superior gyrus of the temporal lobe (8,10,33). A DTI study in schizophrenia (13) showed significant white matter disruption throughout the brain compared with healthy controls.

Neuroimaging of bipolar disorder finds the whole brain volume to be relatively preserved (14), although there are reports of increased size of the lateral ventricles (15), which can be attributed to white matter loss. In general, grey matter loss has been described as relatively slight (16), and most marked in the medial prefrontal cortex (18) and particularly the anterior cingulate cortex (19). A review of DTI studies (23) in bipolar disorder found extensive white matter deficits.

Direct comparison studies of schizophrenia and bipolar disorder are of particular interest in addressing the question.

El-Sayed et al. (32) found significantly lower total brain volume in people with schizophrenia spectrum disorders compared with people with mood disorders with psychotic features.

McDonald et al. (26)found that schizophrenia was associated with greater grey matter loss (predominantly involving frontotemporal neocortex, medial temporal lobe, insula, thalamus, and cerebellum) compared with bipolar disorder with psychotic features. Similar finding was made by El-Sayed et al. (32). Others (27) conducted a longitudinal study and found that the grey matter in schizophrenia continued to reduce (mainly in the frontal and temporal regions), while in bipolar disorder, neocortical grey matter increased (which they attributed to mood stabilizer effect). Janssen et al. (18) found schizophrenia was associated with grey matter volume loss in the left medial (superior) and left middle frontal gyrus, while bipolar disorder was associated with grey matter volume loss of the left medial frontal gyrus only.

Kasai et al. (24) found progressive left superior temporal gyrus loss in schizophrenia in contrast to patients with affective psychosis. Coryell et al. (25) found significantly greater loss of subgenual prefrontal cortex in major depressive disorder with psychotic features, compared to schizophrenia. Koo et al. (19) made similar findings and concluded that patients with these disorders had different initial grey matter deficits and progression over time.

McDonald et al. (26) found that patients with schizophrenia and bipolar disorder with psychotic

features had similar white matter abnormalities in all regions. McIntosh et al. (30) demonstrated DTI abnormalities in the uncinate fasciculus in people with both schizophrenia and bipolar disorder.

In summary, the evidence suggests that schizophrenia, compared with bipolar disorder, is associated with more extensive grey matter loss, and white matter deficits appear to be a feature of both conditions.

Conclusion

Neuroimaging indicates different patterns of grey matter loss for schizophrenia and bipolar disorder. However, neuroimaging of white matter reveals a good deal of overlap in these two disorders. Thus, neuroimaging does not suggest a unitary psychosis or a two-psychosis model, instead it suggests a two-dimensional psychosis field, on which disorders are located according to two dimensions, the degree of grey matter loss and the degree of white matter abnormality.

Authors' Contributions

Conception and design, critical revision of the article, final approval of the article: SP Analysis and interpretation of the data, drafting of the article: SP, GB

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Special Communication

Modelling of Cerebral Tuberculosis: Hope for Continuous Research in Solving the Enigma of the Bottom Billion's Disease

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Abstract

Cerebral tuberculosis is a severe type of extrapulmonary disease that is highly predominant in children. It is thought that meningeal tuberculosis, the most common form of cerebral tuberculosis, begins with respiratory infection followed by early haematogenous dissemination to extrapulmonary sites involving the brain. Host genetic susceptibility factors and specific mycobacteria substrains could be involved in the development of this serious form of tuberculosis. In this editorial the different animal models of cerebral tuberculosis are commented, highlighting a recently described murine model in which BALB/c mice were infected by the intratracheal route with clinical isolates, which exhibited rapid dissemination and brain infection. These strains were isolated from the cerebrospinal fluid of patients with meningeal tuberculosis; they showed specific genotype and induced a peculiar immune response in the infected brain. This model could be a useful tool to study host and bacilli factors involved in the pathogenesis of the most severe form of tuberculosis.

Keywords: experimental models, infectious diseases, meningeal tuberculosis, mice, Mycobacterium, virulence

Tuberculosis and the Central Nervous System

Tuberculosis involvement of the central nervous system (CNS) is a significant and serious type of extrapulmonary disease. It constitutes approximately 5%-15% of the extrapulmonary cases, and in developing countries, it has high predominance in children (1). There are different clinical/pathological manifestations of cerebral tuberculosis; the most common is tuberculous meningitis, followed by tuberculoma, tuberculous abscess, cerebral miliary tuberculosis, tuberculous encephalopathy, tuberculous encephalitis, and tuberculous arteritis (2). Cerebral tuberculosis is often fatal and mainly caused by Mycobacterium tuberculosis; other non-tuberculous mycobacteria such as M. avium-intracellulare can also produce CNS tuberculosis, mainly in human immunodeficiency virus (HIV)-infected persons (2).

It is believed that cerebral tuberculosis, like any other forms of tuberculosis, begins with respiratory infection followed by early haematogenous dissemination to extrapulmonary sites, including the CNS. On the basis of their clinical and experimental observations, Rich and McCordock (3) suggested that cerebral tuberculosis develops in two stages. Initially, small tuberculous lesions (Rich's foci) develop in the brain during the stage of bacteraemia of the primary tuberculosis infection or shortly afterwards. These early tuberculous lesions can be located in the meninges, the subpial or subependymal surface of the brain, and may remain dormant for long time. Later, rupture or growth of one or more of the small lesions produces development of various types of CNS tuberculosis. Rupture into the subarachnoideal space or into the ventricular system produce meningitis, the most common form of cerebral tuberculosis.

Modelling of Cerebral Tuberculosis

Experimental animal models of cerebral tuberculosis have been established in rabbits (4,5), mouse (6,7), and pigs (8). Although they reproduce in some extend the human lesions, these models are artificial because they use the direct intracerebral or intravenous route of infection, instead of the natural respiratory route. Thus, it is important to establish an experimental model which reproduces more closely the human disease, including the initial respiratory natural route of infection. However, such model is difficult to achieve because of the highly efficient CNS protection conferred by the bloodbrain-barrier (BBB). BBB is composed of tightly associated brain microvascular endothelial cells covered by pericytes and outgrowths of astrocytes (cytoplasmic end feet). This structure efficiently prevents CNS infection by many microorganisms, including mycobacteria. Thus, to produce CNS infection, some microorganisms have evolved specific virulence factors that permit, first, endothelial attachment and internalization, followed by brain parenchyma invasion (9). This is the case of bacterial proteins IbeA, IbeB, AslA, YijP, and OMPA expressed by neurotropic Escherichia coli, or meningococcal surface proteins Opa, Opc, and PiIC among others.

Recent in vitro studies have shown that tuberculosis can adhere, invade, and М. traverse endothelial cells (10), and clinicalepidemiological studies have shown distinct genotype in strains isolated from tuberculous patients' cerebrospinal fluid (CSF) (11), which suggest strain-dependent neurovirulence and neurotropism. We recently informed the results from an experimental study in which, using a model of pulmonary tuberculosis in BALB/c mouse infected by the intratracheal route, three different M. tuberculosis clinical isolates obtained from CSF of meningeal tuberculous patients were able to rapidly disseminate and infect the mouse brain (12). These clinical strains were isolated from patients with meningeal tuberculosis in Colombia, and they showed a distinctive genotype. They extensively disseminated by haematogenous route after one day of intratracheal infection and rapidly produced tuberculous lesions in the mice brain. As mentioned before, it has been established that mycobacteria reach the CNS by the haematogenous route secondary to pulmonary infection (3). This experimental model is the first one that reproduced this situation, confirming that the strain type is directly related with the ability to disseminate by the haematogenous route, and add *M. tuberculosis* to the list of microorganism families in which some members or substrains have certain ability to infect the CNS.

Comprehensive clinical-epidemiological studies have identified several risk factors for meningeal tuberculosis; these include age less than 40 years, (HIV) infection, and certain ethnic populations. The latter factor suggests significant interplay between host genetic background and specific strains of mycobacteria (11). In fact, it has been recently shown association between the development of tuberculous meningitis and single nucleotide polymorphism in the Tollinterleukin-1 receptor domain containing adaptor protein (TIRAP) and Toll-like receptor (TLR-2) genes (13).

Our strains are from the Euro-American lineage which was recently reported to be more pulmonary than meningeal. It has been proposed that Euro-American strains are less capable of extra pulmonary dissemination due the lack of pks 15/1 intact gene. Pks gene participates in the production of phenolic glycolipid (PGL), which inhibits the innate immune response and may be responsible for dissemination and CNS infection. Our Euro-American isolates are unable to express PGL; however they efficiently disseminate and produced brain infection, suggesting that other mycobacterial molecules could participate in this process. We consider mycobacterial heparin-binding haemaglutinin adhesin as a good candidate because this molecule triggers receptor-mediated bacilli adherence and invasion to epithelial cells, and extrapulmonary dissemination. Another potential participating molecule is histone-like protein (HLP), which permits to M. leprae interacts with laminin on the surface of Schwann cells, facilitating its invasion. HLP is also expressed by M. tuberculosis, and could participate in the infection of the nervous cells after endothelial barrier traverse. This study is now in progress in our laboratory.

The first step required for certain neurotropic microorganisms to cause CNS infection is to penetrate the BBB. The basic and first element of BBB is microvascular endothelial cells that differ from those in other tissues by tight junctions with high electrical resistance and a relatively low number of pinocytotic vesicles. Recently, an in vitro model using human brain microvascular endothelial cells showed that the reference strain M. tuberculosis H37Rv can invade and traverse these cells, using a process that requires active cytoskeleton rearrangements. By microarray expression profiling, the authors found 33 genes that were overexpressed during endothelial cells invasion, suggesting that the products of these genes might participate in this process (10). Perhaps different gene profile could be expressed by our strains than the laboratory reference strain H37Rv used in the in vitro system that our experimental model showed limited ability to infect the brain.

Intravenous infection of C57Bl mice with *M*. *avium* induces brain infection, and the number of bacteria increases with the duration and level of bacteraemia, which depend of the inoculum size (7). One of our strains (code 209) was highly virulent; it induced more rapid animal death and high bacilli burdens in the lung, liver, spleen, and particularly in the blood. In order to study if hypervirulence could be related to dissemination and brain infection, we infected animals with other highly virulent strains isolated from the sputum of patients with pulmonary tuberculosis. Interestingly, these pulmonary strains produced minimal brain infection, suggesting that hypervirulence is not always related with the ability to CNS infection. Moreover, infection of mice with the other CSF-isolated strains (codes 136 and 28), which efficiently infected the brain, produced higher or similar mice survival and bacilli loads than infection of mice with mild, virulent pulmonary strains.

The most distinctive histological features were small or middle size nodules constituted by lymphocytes and macrophages located in the cerebral parenchyma near to piamadre or below the ependimal cell layer (Rich's nodules). During late infection these nodules were larger and connected with the subarachnoideal space producing mild or extensive inflammatory infiltrate in meninges. Another interesting histological observation was the presence of extracellular positive acid fast bacilli or intracellular in astrocytes or microglia cells without inflammatory response. Immunohistochemical detection of mycobacterial antigens showed strong positivity in activated microglia, astrocytes, ependimal cells, and meningothelial cells, indicating that all these cell types are able to phagocytose mycobacteria or their debries. Indeed, under physiological conditions, basal expression of significant innate immunity receptors involved in mycobacteria phagocytosis (such as TLR-2 and TLR-4) were detected in the meninges, choroids plexus, and circumventricular brain area, which lack BBB and are more exposed to pathogens. Microglia and astrocytes can also express these receptors. Thus, in brain mycobacterial infection specific bacterial antigens and their host cell receptors, as well as innate immunity receptors are involved.

In many areas where we found strong mycobacterial-antigen immunostaining in CNS cells, there were not inflammatory infiltrate. Thus, an efficient modulation of inflammation is produced in the brain which could avoid or delay tissue damage and signs of neurological lesion, even in the presence of high amount of bacilli. Th-2 cells could participate in this process, due to its efficient activity to suppress Th-1 high activity that induces excessive inflammation and

tissue damage. Indeed, the Th-2 response also has beneficial activity for CNS, favouring healing and supporting neuronal survival. We found progressive IL-4 expression in the brain of mice infected with either of the three different clinical strains isolated from the CSF of meningeal tuberculous patients, while reference strain H37Rv induced low expression of Th-2 cytokine. Another significant anti-inflammatory cytokine localized in activated microglia is transforming growth factor beta (TGF β). We found high gene expression of TGF β in the brain of mice infected with CSF clinical isolates, and our histological studies showed positive immunostaining in macrophages located in Rich's nodules, as well as in activated microglia and capillary endothelial cells from distant areas of the inflammatory response. Thus, neuroprotection and suppression by specific cytokines should be a significant factor to avoid excessive inflammation and tissue destruction in mycobacterial CNS infection. This is in agreement with the observation that during late infection, when high bacilli loads in the brain were determined, none of the infected mice developed evident clinical signs of neurological damage, such as seizures or paralysis. The same situation has been reported in mice infected with high doses of *M. avium* by the intravenous route (7), or even in mice infected directly in the brain (6). However, we observed significant histological damage in the hippocampus area, where many neurons showed acidophilic necrosis and extensive gliosis in completely absence of inflammation. These histological abnormalities should be related with memory and cognocitive disturbances.

We consider that this experimental model, which demonstrates for the first time the existence of apparently neurotropic mycobacterial strains, could be a useful tool to study host and bacilli factors involved in the pathogenesis of the most severe form of tuberculosis.

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Original Article

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Psychiatric Intervention Improved Pregnancy Rates in Infertile Couples

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Abstract

Background: Infertility has mental, social, and reproductive consequences. The aim of this study is to evaluate the effect of psychiatric intervention on the pregnancy rate of infertile couples.

Methods: In an experimental and intervention-control study, 638 infertile patients who were referred to a university infertility clinic were evaluated; 140 couples (280 patients) with depression (from mild to severe) in at least one of the spouses were followed. All couples provided informed consent and were randomly numbered from 1 to 140. Those with even numbers were assigned to the psychological intervention before infertility treatment, and those with odd numbers were assigned to the psychological intervention during infertility treatment. Patients in the experimental group received 6-8 sessions of psychotherapy (individually) before beginning infertility treatment and were given Fluoxetine (antidepressant) at 20–60 mg per day during the psychotherapy period. The control group did not receive any intervention. Three questionnaires, the Beck Depression Inventory (BDI), the Stress Scale (Holmes-Rahe), and a sociodemographic questionnaire, were administered to all patients before and after treatment. The clinical pregnancy rate was compared between the two groups based on sonographic detection of gestational sac 6 weeks after the last menstrual period. The data were analysed by *t* test, X² and logistic regression methods.

Results: Pregnancy occurred in 33 (47.1%) couples in the treatment group and in only 5 (7.1%) couples in the control group. There was a significant difference in pregnancy rate between the treatment and control groups (X^2 = 28.318, P < 0.001). To determine the effectiveness of psychiatric interventions on pregnancy, a logistic regression analysis was used. In this analysis, all demographic and infertility variables were entered in a stepwise manner. The results showed that in the treatment group, Pregnancy in the treatment group was 14 times higher than the control group (95% CI 4.8 to 41.7). Furthermore, cause of infertility was an effective factor of pregnancy. The adjusted odds ratio in male factor infertility was 0.115 (95% CI 0.02 to 0.55) and in both factors (male and female) infertility was 0.142 (95% CI 0.03 to 0.76) compared with the unexplained group. In this study, no other variables had any significant effect on pregnancy.

Conclusion: Based on the effectiveness of psychiatric interventions in increasing pregnancy rate, it is crucial to mandate psychiatric counselling in all fertility centres in order to diagnose and treat infertile patients with psychiatric disorders.

Keywords: behaviour therapy, depression, fertility, infertility, psychotherapy, pregnancy

Original Article | Psychiatric intervention in infertility

Introduction

According to investigations, approximately 50 to 80 million people worldwide are currently experiencing infertility (1). Although the rate of infertility differs across studies, the average rate seems to be approximately 20%. Additionally, the inability to conceive a child may be the most difficult life experience that infertile couples have encountered (2).

Infertility has mental, social, and reproductive consequences, including depression, anxiety, aggressiveness, feelings of guilt, lack of self-esteem, lack of confidence, psychosomatic complaints, obsessions, relationship difficulties, and sexual dissatisfaction (3). Infertility is bio-psycho-social phenomenon, meaning a that it involves psychological, physiological, environmental, and interpersonal relation aspects. Consequently, infertility is not considered an organ function disorder and its other dimensions demand precise attention. In fact, infertility is a complex crisis of life that is a psychological threat and an emotional pressure. Perhaps due to this reason, psychological consequences of infertility had previously been assimilated into general grief reactions (4). Mental problems and even suicide attempts due to failure of infertility treatment have been described in many studies. Several investigations have found that stress levels are high in infertile couples and the negative effects of stress are considerably higher in infertile women than in their spouses. This finding could be interpreted as the result of the high pressure associated with diagnostic and treatment interventions as well as women's responsibilities in regards to pregnancy and childbearing (5).

Today, there is a commonly held assumption that psychological illnesses and treatments may Psychological cause infertility. dimensions, physiological processes, environment. and interpersonal relations interact with each other and can predispose an individual to illness or health. Psychological treatment techniques including psychotherapy and cognitivebehavioural therapy (CBT) are known to not only prevent and lessen various mental problems such as anxiety, depression, and phobia, but also to play a positive role in physical health and a successful pregnancy (4).

Sarrel et al. (6) reported that the psychiatric interview uncovered psychological conflicts. After 18 months of follow-up, 6 of the 10 women in couples who had been interviewed had become pregnant, and 1 of the 9 women in the control group had become pregnant. Domar et al. (7) suggested a model of psychological strain that reflects an acute stress reaction to the initial diagnosis and treatment overlaid with a chronic strain response to longer-term treatment. Behavioural treatment is associated with significant decreases in negative psychological symptoms (8). The psychological interventions have been found to be useful in alleviating depression in infertile couples before they received infertility treatment. The necessity of psychological counselling and interventions for infertile couples has been expressed with different indications (9,10).

The recognition of quality of life with specific attention to the effect of psychiatric interventions on the pregnancy rate of infertile persons is a recent development in Iran. The psycho-social model of illness may be an effective tool for approaching the problem of infertility.

Subjects and Methods

The study population included all infertile couples that visited Vali-Asr Infertility Clinic, Tehran University, for the first time between March 2003 and February 2006. Infertility was defined as at least 1 year of unprotected coitus without conception. The study was conducted in 2 stages. First, 638 infertile couples were assessed for depression in a cross-sectional study (Step 1 of the study).

The Beck Depression Inventory (BDI), which includes 21 aspects of depression, was created by Beck in 1961 and the reliability (0.96) and validity (0.89) of this test was confirmed for Iranian people. Scores range as follows: no depression, mild depression, 17–27; moderate 0-16: depression, 28-34; and severe depression, 35-63 (11,12). In 1976, Holmes and Rahe created the Social Readjustment Rating Scale (SRRS), a scale to measure stress, from a list of 43 stressful life events. In addition, the rate of stress was further determined using a 6-point assessment scale that classifies psychosocial factors that cause stress (13,14). In the current study, the BDI, the SRRS, and demographic-social questionnaires were used for data collection. When the BDI score was 17 or higher, an interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (15) was conducted by a clinical psychologist to confirm the diagnosis of depression.

All couples with a diagnosis of depression were asked to participate in Step 2 of the study. The 140 couples who agreed to participate provided informed consent and were randomly numbered 1–140. Those with even numbers were assigned to the psychological intervention before infertility treatment (Group 1) and those with odd numbers were assigned to the psychological intervention during infertility treatment (Group 2).

In Group 1, infertility treatment was postponed until completion of a 6-month psychological treatment with CBT, supportive psychotherapy by a clinical psychologist (individually), and 20 to 60 mg per day of fluoxetine depending on the severity of the depression and the participant's condition. In Group 2, the same psychological treatment was provided during infertility treatment.

CBT included the recognition of negative thinking to help the participants distinguish phobia from reality and thereby change their cognitive structure. For example, infertile women often believe that they will never be able to have a child. Through exercises, this negative pattern was changed to "I will do anything to have a child of my own". The behavioural techniques used included physical activity (including daily walking), muscle relaxation exercises, imagination exercises, expressing feelings, keeping a balanced diet, and planning free time according to one's interests. After 6 months, both groups completed the BDI again.

Supportive psychotherapy assessed (a) the suitability of the psychological treatment, the cause of infertility, and the most suitable infertility treatment for each couple; (b) the depressed participants' psychological and emotional responses to family, friends, and others; and (c) the depressed participants' selfesteem in their relation to their partner, friends, colleagues, and others. Information regarding economic and other forms of social support was obtained using a semi-structured questionnaire that was modified for infertile couples. A testretest analysis showed that the reliability of the questionnaire was 0.92. Data were analysed using the SPSS version 13 (SPSS Inc., Chicago, IL) and logistic regression was performed to eliminate the effects of confounding factors.

Statistical analysis

Data are presented as frequency (percentage) or mean (standard deviation). An independent sample t test was used to compare age, infertility, and marriage duration between control and treatment groups. Other demographic data were compared between study groups using a Chi-square test. A paired *t* test was used to compare the BDI at the beginning and end of the study.

To eliminate the confounding effect of demographic and other variables, a logistic regression analysis was used. In this analysis, study group, all of the demographic variables (age, education, occupation, marital duration), and all of the infertility variables (infertility duration, stress level, infertility cause, and treatment) were entered into a stepwise model. The criterion for entering a variable was a P value less than 0.05 and the criterion for removing a variable from the model was a P value greater than 0.1. All analyses were conducted in SPSS 13 (SPSS Inc., Chicago, IL).

Results

The current study included 70 infertile couples in the treatment group and 70 infertile couples in the control group. Table 1 demonstrates the demographic characteristics of the study groups. There was no significant difference in occupation between the treatment and control groups for men (P = 0.844) or women(P = 0.586). In addition, education level was similar in the treatment and control groups for men (P = 0.253). Among females, 38 (54.3%) in the treatment group and 51 (72.9%) in the control group experienced high levels of stress (P = 0.067). Among males, 39 (55.7%) in the treatment group and 41 (58.6%) in the control group suffered from stress (P = 0.805).

The age of women ranged 19– 41 years, with a mean of 26.57 (SD = 4.14) in the treatment group and 26.09 (SD = 4.69) in the control group (P = 0.517). The men's age ranged 22–53 years, with a mean of 30.99 (SD = 4.42) in the treatment group and 31.24 (SD = 5.56) in the control group (P = 0.762). The average (SD) infertility duration in the treatment and control group was 5.81 (SD = 3.42) and 5.84 (SD = 4.42) years, respectively, with no significant difference between the two groups (P = 9.66). The duration of marriage also did not significantly differ between the study groups (P = 0.715) (Table 2).

The causes and treatments of infertility are presented in Table 3. Male factor infertility was observed in 22 (31.4%) couples in the treatment group and 24 (34.4%) couples in the control group. The cause of infertility was similar in both groups (P = 0.166). Furthermore, couples in both groups followed the same infertility treatment route (P = 0.605).

Table 1: Demographic characteristics of the treatment and control groups									
		Female			Male				
	Treatment n (%)	Control n (%)	Stats	Treatment n (%)	Control n (%)	Stats			
Occupation									
Employed	9 (6.4%)	36 (4.3%)	X ² = 0.412	18 (12.9%)	16 (11.4%)	X ² = 0.693			
Housekeeper (Unemployed)	61 (43.6%)	64 (45.7%)	<i>P</i> = 0.586	52 (37.1%)	54 (38.6%)	<i>P</i> = 0.844			
Education									
Primary School	19 (27.1%)	26 (37.1%)		12 (17.1%)	22 (31.4%)				
Middle–High School	18 (25.7%)	19 (27.1%)	X ² = 4.077	26 (37.1%)	26 (37.1%)	$X^2 = 4.984$ P = 0.173			
Diploma	26 (37.1%)	23 (32.9%)	<i>P</i> = 0.253	23 (32.9%)	17 (24.3%)				
Degree and above	7 (10.0%)	2 (2.9%)		9 (12.9%)	5 (7.1%)				
Stress									
Without	32 (45.7%)	19 (27.1%)		31 (44.3%)	29 (41.4%)				
Low level	14 (20.0%)	26 (37.1%)	$X^2 = 7.148$ P = 0.067	20 (28.6%)	20 (28.6%)	$X^2 = 0.983$ P = 0.805			
Medium level	15 (21.4%)	14 (20.0%)		10 (14.3%)	14 (20.0%)	Ū			
High level	9 (12.9%)	11 (15.7%)		9 (12.9%)	7 (10.0%)				

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Each group consisted of 70 participants.

	Table 2: Age,	infertility and	marriage	duration	of the tre	atment and	control	group)S
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	Treatment Mean (SD)	Control Mean (SD)	Stats
Age (Female)	26.57 (4.14)	26.09 (4.69)	t = 0.649, P = 0.517
Age (Male)	30.99 (4.42)	31.24 (5.56)	t = 0.303, P = 0.762
Duration of marriage	6.29 (3.52)	6.54 (4.50)	t = 0.366, P = 0.715
Duration of infertility	5.81 (3.42)	5.84 (4.42)	t = 0.043, P = 0.966

Each group consisted of 70 participants.



Figure 1: Beck depression score at the beginning and the end of the study for both treatment and control groups. The depression score significantly decreased in the treatment group (P < 0.001), but there was no significant difference in the control group (P = 0.142).

Results of the BDI are presented in Figure 1. Psychological intervention in the treatment group significantly decreased the depression score from 18.7 (SD = 9.7) to 10.8 (SD = 5.8) (P < 0.001). The stress score in control group was 20.2 (SD = 11.3) before and 22.5 (SD = 10.3) at the end of the study; however, the difference was not significant (P = 0.149).

Finally, pregnancy occurred in 33 (47.1%) couples in the treatment group and in only 5 (7.1%) couples in the control group. There was a significant difference in pregnancy rate between the treatment and control groups ($X^2 = 28.318$, P < 0.001). The various pregnancy methods are presented in Table 4.

To determine the effectiveness of psychiatric interventions on pregnancy, logistic regression analysis was used. In this analysis, all demographic and infertility variables were entered in a stepwise manner. The results showed that psychiatric intervention was the greatest predictor of occurrence of pregnancy. In the treatment group, pregnancy in the treated group was 14 times higher than the control group (95% CI 4.8 to 41.7) (Table 5). In addition to the psychological intervention, cause of infertility was an effective factor of pregnancy. The rate of pregnancy in male factor infertility was 0.115 (95% CI 0.02 to 0.55) and in both factors (male and female) infertility was 0.142 (95% CI 0.03 to 0.76) which were less than in the unexplained group. In this study, no other variables had a significant effect on pregnancy.

Discussion

The present study was designed as a randomised clinical trial. A review of the literature revealed no published study of the synergistic effects of medication and psychological treatment in infertile participants in an oriental society. The results of this study showed that psychiatric and psychological intervention at middle- and high-school educated (men group), duration of infertility of less than 5 years, and unexplained cause of infertility leads to an increased pregnancy rate.

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	Trea n	tment (%)	Con n	ntrol (%)	Stats
Infertility treatment					
Induction of ovulation	18	(25.7%)	13	(18.6%)	
IUI	14	(20.0%)	9	(12.9%)	
ART	22	(31.4%)	24	(34.3%)	X ² =3.623
Laparoscopy + hysteroscopy	10	(14.3%)	15	(21.4%)	P = 0.605
Donor oocyte / embryo	3	(4.3%)	4	(5.7%)	
Surgical treatment of the husband	3	(4.3%)	5	(7.1%)	
Cause of infertility					
Male	22	(31.4%)	24	(34.3%)	
Female	25	(35.7%)	31	(44.3%)	X ² =5.079
Both	14	(20.0%)	10	(14.3%)	P = 0.166
Unexplained	9	(12.9%)	5	(7.1%)	

Table 3: Cause and infertility treatment in the treatment and control groups

Each group consisted of 70 participants.

Abbreviation: ART = assisted reproductive technology (in vitro fertilization), IUI = intrauterine insemination

	Treatment n(%)		Co n	ntrol (%)	Stats			
Pregnancy								
Not pregnant	37	(52.9%)	65	(92.9%)	$X^2 = 28.318$			
Pregnant	33	(47.1%)	5	(7.1%)	P < 0.001			
Type of Pregnancy								
Spontaneous pregnancy	9	(27.3%)	0	(0.0%)				
ART	8	(24.2%)	1	(20.0%)				
Laparoscopy-hysteroscopy	1	(3.0%)	1	(20.0%)	-			
Ovulatory stimulation	9	(27.3%)	3	(60.0%)				
IUI	5	(15.2%)	0	(0.0%)				
Surgical treatment of the husband	1	(3.0%)	0	(0.0%)				

Table 4: Pregnancy and pregnancy type in the treatment and control groups

Each group consisted of 70 participants.

Abbreviation: ART = assisted reproductive technology (in vitro fertilization), IUI = intrauterine insemination

Matsubayashi et al. (15) reported that depression was more common among infertile than among fertile or pregnant women. Furthermore, both Newton et al. (16) and Wischmann et al. (17) reported depression to be higher among infertile women than infertile men that it could be a reason for the loss of self-confidence in their depressed participants. In a recent study, 81.3% of depressed infertile participants reported that the main stressor leading to their depression was relatives' comments about their infertility (18). The results of the present study showed that the chance of pregnancy increases as levels of stress decrease. Cwikel et al. reported that psychological factors such as stress and anxiety can lead to changes in the heart and cortisol hormone (19). Moreover, the results of some investigations showed a significant correlation between the adrenaline hormone and depression. Specifically, women who were in the in vitro fertilisation (IVF) circle in the Oocyte Pick Up– Embryo Transfer (OPU–ET) time demonstrated changes in their adrenaline and noradrenaline

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		Unadjusted				Adjusted			
	OP	95.0		% CI		95.0% CI		Develope	
	OK	Lower	Upper	P value	UK	Lower	Upper	<i>P</i> value	
Psychiatric intervention	11.595	4.166	32.268	<0.001	14.071	4.750	41.677	<0.001	
Cause of Infertility									
Male factor	10.135	0.036	0.509	0.003	0.115	0.024	0.548	0.007	
Female factor	0.355	0.107	1.177	0.090	0.429	0.101	1.810	0.249	
Both	0.197	0.046	0.838	0.028	0.142	0.027	0.762	0.023	
Constant					0.249			0.063	

Table 5:	Unadjusted	and adjusted	odds ratio	of pregnancy
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hormone. A comparison between pregnant women using IVF and women who had treatment failure showed that there is a difference in the level of these hormones in their blood; this may lead to the change in the rate of pregnancy in infertile women. However, this association is complicated by the effect of social and psychological stresses on IVF-ET success (20-22). Although some studies do not confirm the relation between stress and infertility (23,24), stress can be decreased cognitive-behavioural using interventions (especially during IVF-ET), thus increasing the chance of pregnancy (25,26). The finding of this research confirms that of other research. Overall, stress may be an important element in infertility and decreasing stress may increase the chance of pregnancy among infertile couples.

The results of this study showed that 47.1% of the treatment group and 7.1% of the control group became pregnant. The increase in the chance of pregnancy in the treatment group (40%) demonstrates the effect of psychiatric and counselling interventions on these patients. Domar et al., Terzioglu, and Newton et al. showed that psychiatric and counselling interventions led to significant decreases in anxiety and depression and increases in the chance of pregnancy (6,27,28); there is a complex relation between stress and infertility. One study showed that 41.9% of those in a psychotherapy group, 13.5% of those in a control group, and 42% of those in a cognitive-behavioural consulting group became pregnant (29). Hosaka et al. and Kupka et al. reported that psychological consulting in 14% of cases is conducive to spontaneous pregnancy and that it can be a consequence of reduced stress (30,31). Other reports have also demonstrated that psychiatric and counselling interventions (behavioural, cognitive, psychotherapy)

conducted during treatment, diagnosis, and especially before IVF result in positive pregnancy tests. The use of psychiatric and counselling interventions increases the pregnancy chance in the following 6 months (32-39). Although Yong et al. did not confirm this relationship, even for people who believe that the advice in the first IVF cycle is ineffective; however, this type of study is of limited number (40). The findings of the present study confirm those of other research. Psychiatric and counselling interventions have an important role in curing infertility and lead to increased pregnancy success. Therefore, psychiatric and counselling interventions must accompany infertility treatments to increase the chance of pregnancy success and improve the mental health of infertile couples.

Conclusion

Psychological interventions to increase reproductive and infertility treatment success is related to stress reduction and treatment of psychiatric disorders (including anxiety and depression), and this approach tends to improve the quality of life in the infertile couples. Thus, it can be concluded that psychological intervention prior to infertility treatment was useful in infertile couples.

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Authors' Contributions

Conception and design, collection and assembly of data, drafting of the article: NA Obtaining of funding: AAN Provision of patients, administrative, technical, or logistic support: NA, AAN Statistical expertise Analysis and interpretation of the data: ARF, MMN Final approval of the article: FR, AAN

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Original Article

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A Prediction Equation to Estimate the Maximum Oxygen Uptake of School-Age Girls from Kolkata, India

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Abstract -

Background: The 20-metre multistage shuttle run test is a useful method for the regular monitoring of aerobic fitness. However, the validity of the test should be established in the particular population prior to application. The aim of the study was to validate the applicability of the 20-metre multistage shuttle run test in non-athlete, girls from Kolkata, India.

Methods: Thirty-six untrained girls from different schools in Kolkata (age range 14–16 years) were recruited for the study. Direct estimation of cardiorespiratory endurance (VO₂max) comprised treadmill exercise followed by expired gas analysis using Scholander micro-gas analyser. VO₂max was indirectly predicted by the 20-metre multistage shuttle run test.

Results: The difference between the mean (SD) VO₂max values of the direct measurement, 32.91 (2.66) ml.kg⁻¹.min⁻¹, and the 20-metre multistage shuttle run test, 33.79 (2.56) ml.kg⁻¹.min⁻¹, was statistically significant (P < 0.01). However, limits of agreement analysis suggested that the 20-metre multistage shuttle run test can be applied for use with the studied population. Intra-class correlation coefficients also suggested good reliability of the 20-metre multistage shuttle run data.

Conclusion: The results suggest that the use of the 20-metre multistage shuttle run test for the prediction of VO₂max is justified in the studied population. For better prediction of VO₂max, a new equation has been developed based on the present data for untrained girls from Kolkata.

Keywords: anaerobic threshold, chest and respiratory, exercise test, female adolescents, oxygen consumption, physical fitness, sedentary lifestyle

Introduction

Direct measurement of maximum oxygen uptake (VO max) is recognised as the best single index of aerobic fitness (1). However, the direct measurement of VO max is difficult, exhausting, and often hazardous to perform regardless of the type of ergometer used (2). Because the direct testing procedure is rather complicated for larger populations, several indirect running and walking tests have been dev eloped. Scientists often calculate VO max using indirect protocols (3). It has been reported that equations for predicting VO max indirectly using running and walking tests are very sensitive to the studied population. Therefore, before applying any indirect protocol for prediction of VO max, the validity of the test should be established in a particular population.

The 20-m multistage shuttle run (20-m MST) (4,5) is often used to measure aerobic capacity (6–10). Cooper et al. (11) studied the repeatability and criterion-related validity of the 20-m MST as a predictor of maximum oxygen uptake in active young men. Suminski et al. (12) established the validity of the 20-m MST for measuring the aerobic fitness of Hispanic youth 10 to 12 years of age. Chatterjee et al. (13,14) studied the validity of 20-m MST in junior taekwondo players and female university students in India.

Recent studies have suggested that sexspecific equations allow more accurate prediction of VO_2 max using 20-m MST data (15). For this reason, a combined male and female population was not used in this study; only girls were recruited as subject. The present study was undertaken to assess the applicability of the 20-m MST for the prediction of VO_2 max in untrained school-

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age girls from Kolkata, India, and to develop a regression equation for use with this particular population.

Subjects and Methods

Subjects

Thirty-six untrained girls from 3 different schools (12 girls from each) in Kolkata were selected for the study. The girls were in Standard 8 (n = 18) and Standard 9 (n = 18). The experimental protocol was fully explained to the participants. They had a light breakfast 2-3 hours before the test and refrained from any energetic physical activity for 4 hours before the test. The participants had no history of any major disease and did not follow any physical-conditioning program, except for occasional recreational sports. These recreational sports included table tennis, badminton, and volleyball. They played these games, on average, twice per week for half an hour to one hour. Considering their lifestyle and habitual activity level, these girls were considered representative of the majority of school-age girls from Kolkata. The tests were demonstrated to the subjects before actual administration. All participants signed a statement of informed consent. All institutional policies concerning human research subjects were followed. Ethical approval was granted by Research Ethics Committee of the institution.

Experimental design

The maximum oxygen consumption of each subject was determined by both indirect and direct methods with an interval of 4 days. The indirect method was completed first by half of the subjects, followed by the direct method; the other half of the subjects completed the direct method first to avoid any possibility of bias. Subjects were asked to take complete rest for at least half an hour prior to the tests so that pulmonary ventilation and the pulse rate would be at steady state before the test (16).

Indirect measurement of VO_2 max using the 20-m MST

Subjects ran back and forth on the 20-metre course and touched the 20 metre (m) line after running at an initial speed of 8.5 km.hr⁻¹. The speed of the shuttle runs became progressively faster (0.5 km.hr⁻¹ every minute), in accordance with a pace dictated by a sound signal on an audio tape. Several shuttle runs made up each stage, and subjects were instructed to keep pace with the signal for as long as possible. When the subjects could no longer maintain the pace, the last stage completed was used to predict VO₂max using the equation of Leger and Gadoury, 1989 (5):

Y = 31.025 + 3.238 X - 3.248 A + 0.1536 AX where

 $Y = VO_{2}max (ml.kg^{-1}.min^{-1})$

X = maximum shuttle run speed (km.hr⁻¹) A = age (year)

Direct measurement of VO_max

The subjects walked on a treadmill to warm up at a speed of 4 km/hr at 4.5° inclination for 5 minutes (17). The warm-up period was followed by running at a constant speed of 7 km.hr⁻¹ for a maximum duration of 5 minutes. The inclination was increased successively from 4.5° until the subject was unable to continue the task; in no case did the incline exceed 7.5°. The criteria for maximality was exhaustion and withdrawal from running within the scheduled 5-minute period, when the heart rate was approximately their predicted maximum heart rate and when a further increase in the incline did not result in any significant rise in oxygen uptake (16).

Gas analysis

A low-resistance high-velocity Collin's Triple "J type" plastic valve was used for the collection of gas using the open circuit method (16). The valve was connected to a Douglas Bag (150-L), and the expired gas was collected during the 2nd minute of the final running period, if signs of severe exhaustion were observed. No gas collection was made during the 1st minute of the run. The expired gas was measured using a wet gasometer (Toshniwal, Germany, CAT No. C G 05.10), and aliquots of the gas samples were analysed using a Scholander micro gas analysis apparatus following the standard procedure (18).

Validity of the results

The repeatability was investigated by having 21 of the subject perform the test twice. Intraclass correlation coefficients (ICC) were used to determine the test–retest reliability. The ICC was 0.81.

Statistical analysis

Paired t tests, intra-class correlation coefficients, Pearson's product moment correlations, linear regression statistics, and the Bland and Altman (19) approach for limits of agreement were adopted for statistical analysis of the data. Statistical Package for Social Sciences (SPSS) Microsoft Windows Release version 16.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

Results

The means and standard deviations of the physical characteristics, the shuttle run-predicted VO max values (SPVO max), and the directly measured VO max values of the participants are presented in Table 1. Significant variation was observed (P < 0.01) between the directly measured and predicted VO max values. The mean difference between VO max and SPVO max was -0.87 ml.kg⁻¹.min⁻¹ with a 95% confidence interval -0.59 to -1.17 ml.kg-1.min-1, indicating that the 20-m MST predicts a maximum oxygen uptake capacity between -0.59 and -1.17 ml.kg-1. min⁻¹. The intra-class correlation coefficients (ICC) for the VO₂max values obtained from direct measurement and from the 20-m multistage shuttle run test was 0.96 by using the equation of Leger and Gadoury (5).

Analysis of the data using the Bland and Altman (Bland and Altman, 1986) method for limits of agreement between SPVO₂max calculated using the equation of Leger and Gadoury and VO₂max measured by the direct method revealed that the limits of agreement were -0.83 to -2.57. These limits are small enough that the 20-m MST can be used confidently in place of the direct method (Figure 1). The limits of agreement analysis suggests that application of the present form of the 20-m MST may be justified for the studied population. A highly significant correlation (r = 0.87, P < 0.01) existed between the maximum speed of the 20-m MST and VO₂max.

The following equation, derived using the present data, can be used to predict the aerobic fitness of untrained school-age girls from Kolkata.

Y = 10.461 + 5.700 X - 2.027 A + 0.001 AX where

 $Y = VO_2 max (ml.kg^{-1}.min^{-1})$

X = maximum shuttle run speed (km.hr⁻¹)

Discussion

Better limits of agreement existed between the two methods when the newly developed equation was used to predict VO₂max from the 20-m MST data. The limits of agreement when using the new equation were 1.54 and -1.81. When using this newly derived equation, the shuttle run-predicted VO max values for 94% of the participants fell within the limits of agreement. On the other hand, when the equation of Leger and Gadoury was used to predict VO max from the 20-m MST data, the shuttle run-predicted VO max values for 89% of the participants fell within the limit of agreement. In the present study, the ICC was also assessed because Pearson's correlation measures the strength of a relationship between two measurements, not the agreement between them (19). The ICC found between the directly measured VO₂max and the shuttle run-predicted VO₂max using the new equation was 0.97. As a general guideline, ICC values above 0.75 indicate good reliability, and those below 0.75 indicate poor to moderate reliability (20). The ICC value suggests that the reliability of the 20-m multistage shuttle run test using the newly derived equation instead of direct measurement is sufficient for the studied population. The ICC value also suggests an equally good reliability of the 20-m MST when using the equation of Leger and Gadoury (5). However, as the limits of agreement analysis indicated a better agreement when using the newly derived equation, we recommend the use of the new equation for the prediction of VO₂max from 20-m MST data in the studied population.

$-\frac{1}{2}$								
Parameter	Minimum	Maximum	Mean	SD				
Age (years)	14.00	16.00	15.30	0.86				
Height (cm)	146.21	154.80	150.88	2.16				
Weight (kg)	36.00	49.60	40.91	2.73				
VO ₂ max (ml.kg ⁻¹ .min ⁻¹)	29.00	37.86	32.91	2.66				
SPVO ₂ max (ml.kg ⁻¹ .min ⁻¹)	29.42	38.66	33.79	2.56				
Shuttle run speed (km.hr ⁻¹)	8.50	10.50	9.34	0.66				

Table 1: Physical parameters and predicted and measured VO max values for the test subjects (n = 36)



Figure 1: Difference between the VO₂max values obtained from direct measurement and those obtained from the 20-metre MST data (using the equation of Leger and Gadoury; 5) plotted against their means (Bland and Altman method of approach; 19)

Conclusion

From the present observations, we concluded that the 20-metre multistage shuttle run test is a valid method to evaluate aerobic fitness in terms of VO₂max for school-age girls (age 14–16 years) from Kolkata, India. We recommend using the equation developed based on the present data. The 20-metre multistage shuttle run test is a useful method for the regular monitoring of aerobic fitness in the studied population when a large number of subjects must be evaluated without the help of a well-equipped laboratory and with a lower cost and within a short period of time.

Authors' Contributions

Conception and design: PC, AKB

Obtaining of funding, administrative, technical, or logistic support: AKB

Collection, assembly, analysis, and interpretation of the data; drafting and critical revision of the article: PC, PD

Provision of study materials or patients, statistical expertise, final approval of the article: PC, AKB, PD

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Original Article	A Randomised Control Trial on the Use of Topical Methicillin in Reducing Post- Operative Ventriculoperitoneal Shunt Infection
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Abstract

Background: A double-blind randomised control study was conducted on all patients who were admitted or referred to the Department of Neurosurgery, Sultanah Aminah Hospital, Johor Bahru, with a diagnosis of hydrocephalus where a ventriculoperitoneal shunt was indicated.

Methods: The period of study was from November 2005 to May 2007, and the follow-up period was 3 months after surgery. Randomisation was carried out in the operating room prior to the procedure. The scrub nurse selected a sealed envelope, which contained the assignment of each patient to 1 of 2 treatment groups: Group 1 patients were treated with topical methicillin, and Group 2 patients were not treated with topical methicillin. Prophylactic antibiotic, cefuroxime (25 mg/kg) was given intravenously at induction. Standard sterile operative technique was followed in preparing and draping the patients.

Results: A total of 90 patients were recruited in the study, and 13 (14.4%) patients developed an infection within 3 months post-operation. Group 1 had a 8.9% risk of infection, and Group 2 had a 20% risk; however, there was no statistically significant post-operative ventriculoperitoneal shunt (VPS) infection reduction with the use of topical methicillin in VPS surgery (P = 0.230). Multivariate analysis showed that only duration of surgery had a significant influence on the incidence of postoperative VPS infection in the non-methicillin group (P = 0.02). The non-methicillin group had an 8 times greater risk of developing post-operative VPS infection than the methicillin group if surgery lasted longer than 1 hour.

Conclusion: Topical methicillin had no significance in the reduction of post-operative VPS infection.

Keywords: methicillin, neurosurgery, post-operative wound infection, topical administration, ventriculoperitoneal shunt

Introduction

The development of effective cerebrospinal fluid (CSF) shunts represented a landmark achievement in neurosurgery. Although shunts have improved the morbidity and mortality associated with disordered CSF mechanics over the past 30 years, they are associated with many potentially avoidable complications. Of these, post-operative infection remains a major complication (1–3). A great deal of experimental and clinical research is aimed at determining ways of preventing these infections. The problem of shunt infections nonetheless remains unsolved, and widely varying, contradictory data abound on the incidence of shunt infection (4–7).

The reported shunt infection rates range 5%-27% in South America (4) with most centres reporting an incidence 5%-20% (1). Most shunt infections occur within 2 months, and 80% within 6 months post-operation. Inoculums are believed to arise from skin organisms at the time of shunt implantation, although this is not always the case (7). Factors that are most commonly implicated in shunt infections are listed in Table 1.

The most common bacteria involved in early shunt infections are *Staphylococcus epidermidis* (52.8%–88.9%) and *Staphylococcus aureus* (12.0%–40.0%). These bacteria may enter the operative field during surgery from hair follicles and sebaceous glands opened by the surgical incision. Insufficient aseptic technique and a long-lasting surgery also contribute to this risk (7,9,10). Table 1: Factors implicated in shunt infection (1,4,8)

Factors				
Poor pre-operative skin condition				
Age less than 6 months				
Reinsertion of VPS after infection				
Presence of wound dehiscence				
Proximal versus distal revision (greater risk with proximal revision)				
Presence of hydrocephalus				
Time of day the operation performed (greater risk after office hours)				
Number of staff in operating room				
Neurosurgeon's experience				
Length of operation (lower risk with shorter duration)				
Presence of airborne organisms in operating room				

In Malaysia, ventriculoperitoneal shunt (VPS) infection is the most common infection reported in neurosurgery. Although stringent rules have been applied, a successful reduction in infection rates in the operating rooms has not been achieved. There are certain neurosurgical centres that allow only consultants and senior registrars to perform VPS surgery; however, even this practice has not greatly decreased the infection rates (2,10,11).

The use of topical antibiotics and antibioticimpregnated shunt systems during VPS surgery has been widely practiced (12,13). However, there is no specific study done in the local setting to evaluate the efficacy of these procedures. Methicillin is a narrow spectrum beta-lactam antibiotic of the penicillin class. It is used to treat infections caused by susceptible Gram-positive bacteria, particularly beta-lactamase-producing organisms, such as Staphylococcus aureus, that would otherwise be resistant to most penicillin. Topical methicillin was chosen to be tested as it is cheap and do not need any special preparation. It is used in many centres and is also quoted in VPS surgery protocol by Andrew Kaye in his textbook, Operative Neurosurgery.

The main objective of this study was to evaluate the role of methicillin as a topical antibiotic during shunt insertion in VPS surgery with the aim of reducing the rate of post-operative infection. This study also evaluated factors that could play a role in post-operative shunt infection such as gender, race, age, aetiology of hydrocephalus, surgeon's experience, duration of the surgery, and time of the surgery (during or after office hours). These analyses would be helpful for developing guidelines to prevent or reduce post-operative VPS infection.

Subjects and Methods

The study included patients of all ages, races, and genders that were either admitted or referred to the Hospital Sultanah Aminah Johor Bahru. The patients were newly diagnosed with hydrocephalus of any aetiology and needed a VPS. Patients who required a revision of a VPS were excluded in this study. Patients who had poor skin condition, were undernourished, or had preoperative Glasgow Coma Scale (GCS) of less than 13 were also excluded.

If selected patients initially had an extraventricular drain inserted and were drainagedependent, then internalisation or VPS insertion was performed when CSF culture and sensitivity had no growth for 3 consecutive samples and CSF protein was less than 2 g/dL. Sample size was calculated at 90 with each arm of the study consisting of equal number of [patients: 45 patients treated with topical methicillin (Group 1) and 45 patients not treated with topical methicillin (Group 2). These designations were then sealed in envelopes and randomly selected immediately prior to surgery. The envelope was opened by the scrub nurse and the solution was prepared according to the group assignment, completely unknown to anyone else in the operation theatre, including the surgeon. The envelope then was re-sealed and attached with a questionnaire containing patient's details for record.

Because this study was conducted to observe whether post-operative infection rate of VPS could be reduced with topical methicillin, independent of the surgeon's experience, certain procedures had to be standardised and made easily attainable. In the operating room at induction, patients were given a single prophylactic dose of intravenous cefuroxime (25 mg/kg body weight). The scrub nurse then prepared the solution according to the chosen envelope. If the patient was assigned to Group 1, 1 vial of 500 mg methicillin powder was diluted in 500 mL normal saline, and if the patient was assigned to Group 2, then pure normal saline solution without any antibiotic was applied.

The surgical site was then cleaned multiple times with povidone iodine, draped and covered with opsite once the povidone iodine had dried. Surgery was then carried out with minimal manipulation and handling of the shunt system before insertion; the shunt system and all instruments used in its handling were soaked in the prepared solution. A single type of shunt system, Codman Hakim non-programmable shunt (Integra Neurosciences Inc., Plainsboro, NJ) was used in all cases. After haemostasis was achieved, the surgical site was washed with the prepared solution, and the skin was closed. The patients were subsequently followed up postoperatively with clinic appointments in the 1st and 3rd month.

Data analysis was done using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL). Cross tabulation with chi-square test was used to determine whether individual categorical independent factors were randomised fairly in each group. P < 0.05 was considered statistically significant for the univariate analysis.

The association between post-operative VPS infection and significant independent variables from univariate analysis was analysed with multiple logistic regression and adjusted for confounding factors to identify the most important determinant. The final model of factors using multiple logistic regression was examined for fitness using Hosmer–Lemeshow goodness-of-fit test. Each result was expressed as odds ratio (OR) and 95% confidence interval (95% CI). OR was used to assess the risk of the outcome (post-operative VPS infection) if a certain factor was present. The OR is considered significant if the 95% CI does not include OR of 1.

Results

Of the 90 patients studied, 13 (14.4%) patients developed post-operative VPS infection; 4 (8.9%) patients in the methicillin group and 9 (20%) patients in the non-methicillin group (Table 2). The use of topical methicillin in VPS surgery did not significantly reduce post-operative infection ($\chi^2 = 2.298$, df = 1, *P* = 0.23). However, the nonmethicillin group had a 2.5 times increased risk of developing post-operative shunt infection compared to the methicillin group (OR = 2.5, 95% CI = 0.73 to 9.03). This model was tested with Hosmer–Lemeshow tests where both Pearson and Hosmer–Lemeshow chi-square statistics were 0, hence, *P* value was 1 (*P* > 0.05). Therefore, the model fit well.

By using multiple logistic regression analysis, the forward logistic regression gave us the best model. The chi-square statistics seen in the omnibus test is significant (P = 0.006, df = 5)with 2 Log likelihood statistics was 57.904 at the final step. The Hosmer–Lemeshow test at df = 7was 0.990, which is more than the conventional value (0.05); therefore, the observed number of outcomes was not significantly different from that predicted by the model. It is concluded that this model fits well. The only significant predictor of post-operative VPS infection was duration of surgery (P = 0.02) (Table 3). The non-methicillin group had 8 times increased risk of developing post-operative VPS infection than the methicillin group in surgery that lasted longer than 1 hour (OR = 7.73, 95% CI = 1.34 to 44.78).

No significant correlation was observed between post-operative VPS infection and demographic factors, i.e., gender, race, and age (Table 4). Similarly, none of the analysed clinical factors are significant predictors of VPS infection, except for the duration of surgery in the nonmethicillin group (OR= 2.56, 95% CI = 0.73 to 9.03, P = 0.03) (Table 5).

	1 ,	· 1	•	,
Factors	Non-infected n (%)	Infected n (%)	P value	OR (95% CI)
Use of topical methicillin				
With (Group 1)	41 (91.1)	4 (8.9)	0.23 ^a	2.56
Without (Group 2)	36 (80.0)	9 (20.0)		(0.73 to 9.03)

Table 2: Univariate analysis between Group 1 (methicillin) and Group 2 (non-methicillin)

^a Chi-square test
Original Article | Trial using topical methicillin in VPS infection

Table 3:	Significant predictor from multivariate
	analysis on determining post-operative
	VPS infection

Factors	P value	OR (95% CI)
Duration of surgery	0.02	7.73 (1.33 to 44.78)

Table 4: Univariate analysis of demographic factors that influence post-
operative ventriculoperitoneal shunt surgery in both randomised
groups (Group 1: methicillin, Group 2: non-methicillin)

Factors	N inf n	lon- ected (%)	Infected n (%)		P value	OR (95% CI)
Gender						
Group 1						
Male	22	(48.9)	2	(4.4)	0.64 ^a	1.16
Famale	19	(42.2)	2	(4.4)		(0.12 to 9.03)
Group 2						
Male	15	(33.3)	3	(6.7)	0.48 ^a	1.43
Famale	21	(46.7)	6	(13.3)		(0.31 to 6.64)
Race						
Group 1						
Malay	29	(64.4)	4	(8.9)		
Chinese	8	(17.8)	0		0.45 ^a	-
Indian	4	(8.9)	0			
Group 2						
Malay	25	(55.6)	8	(17.8)		
Chinese	4	(8.9)	0		0.44 ^a	-
Indian	7	(15.6)	1	(2.2)		
Age						
Group 1						
Neonate	8	(17.8)	0			
Infant	4	(8.9)	2	(4.4)		
Child	6	(13.3)	0		0.12 ^a	2.8
Adult	23	(51.1)	2	(4.4)		(0.51 to 15.38)
Group 2						
Neonate	3	(0.7)	1	(2.2)		
Infant	4	(8.9)	3	(6.7)		
Child	2	(4.4)	0		0.36 ^a	1.28
Adult	27	(60.0)	5	(11.1)		(0.17 to 9.97)

^a Chi-square test

Table 5: Univariate analysis of clinical factors that influence post-operative ventriculoperitoneal shunt surgery in both randomised groups (Group 1: methicillin, Group 2: non-methicillin)

Factors	Non- n	infected (%)	In ז	fected າ (%)	<i>P</i> value	OR (95% CI)
Timing of surgery						
Group 1						
Office hours	23	(51.1)	2	(4.4)	0.60 b	2.86
After office hours	18	(40)	2	(4.4)	0.00	(0.27 to 29.80)
Group 2						
Office hours	16	(35.6)	2	(4.4)		-
After office hours	20	(44.4)	7	(15.6)	0.204 ~	
Duration of surgery						
Group 1						
< 1 hour	20	(44.4)	1	(2.2)	0.26 b	_
> 1 hour	21	(46.7)	3	(6.7)	0.30	
Group 2						
< 1 hour	19	(42.2)	1	(2.2)	0 03 p*	2.56
> 1 hour	17	(37.8)	8	(17.8)	0.03	(0.73 to 9.03)
Aetiology						
Group 1						
Congenital	17	(37.8)	1	(2.2)	0.37 ^a	-
Tumour	15	(33.3)	2	(4.4)		
Trauma	4	(8.9)	0			
Vascular	1	(2.2)	0	(2.2)		
Infection	1	(2.2)	1			
Others	3	(6.7)	0			
Group 2						
Congenital	6	(13.3)	2	(4.4)	0.17 ^a	-
Tumour	14	(31.1)	7	(15.6)		
Trauma	1	(2.2)	0			
Vascular	9	(20.0)	0			
Infection	6	(13.3)	0			
Others	0		0			
Surgeon's criteria						
Group 1						
Consultant	2	(4.4)	0		0.23 ^a	-
Surgeon	1	(2.2)	1	(2.2)		
Registrar	4	(8.9)	0			
Trainee	13	(28.9)	2	(4.4)		
Medical officer	21	(46.7)	1	(2.2)		
Group 2						
Consultant	0		0		0.78 ^a	-
Surgeon	1	(2.2)	0			
Registrar	4	(8.9)	0			
Trainee	13	(28.9)	6	(13.3)		
Medical officer	21	(46.7)	3	(6.7)		

a Chi-square test, b Fisher's exact test

* Significant at P < 0.05

Discussion

This was a double-blind prospective randomised control study that involved a total of 90 patients admitted to the Department of Neurosurgery, Hospital Sultanah Aminah Johor Bahru from November 2005 to May 2007. In the randomisation of the patients, certain predictors had the disadvantage of not being uniformly randomised; these were primarily the aetiology of hydrocephalus and surgeon's status. This naturally would influence the outcome, as both of these factors influence post-operative infection rate. Aetiology as an influencing factor has been reported by Vinchon et al. They concluded that age below 4 months at shunt insertion, myelomeningocele, and post-hemorrhagic hydrocephalus were significantly correlated with post-operative shunt infection (6). Cochrane and Kestle reported that the surgeon's operative experience is an important factor in determining post-operative shunt infections (14).

There were almost an equal number of male and female patients in this study with a slight preponderance towards female patients (53.3%). No specific study has shown any influence of gender on VPS infection. Race had no significant impact on post-operative VPS infection. It was not surprising that a major group of the patients studied were from the neonate age group (12 out of 90 patients, 13.3%). This was easily explained because one of the common causes of hydrocephalus is congenital hydrocephalus, which is most often diagnosed at birth and often requires VPS insertion early in life. Neonates and infants were at high risk of developing postoperative shunt infections (13); this is attributed to an immature immune system and to surgical technique (15). Therefore, many studies on VPS infection concentrated in the paediatric age group. As stated earlier, the literature shows that subgaleal collections due to large burr holes and thin dura cause CSF leakage and increase VPS infection. Bruinsma et al. showed that prematurity is an important risk factor for ventricular catheter ventriculoperitoneal reservoir and drainrelated infections, especially for patients with a gestational age of less than 37 weeks at their initial shunt placement and an extremely low birth weight (16). In this study, surprisingly, there was only 1 neonate who developed post-operative VPS infection, and the neonate belonged to the non-methicillin group. This is most likely due to awareness among surgeons of the higher risk of infection, which encourages them to be more compliant to strict sterile technique. Recently,

a study in Japan showed that clinical outcome was significantly better in full-term patients who underwent early shunt placement than in those who underwent late shunt placement (17). This clearly explains the lower infection rate in the neonate group (2.2%) and the slightly higher infection rate in the infant group (11.1%). Adults accounted for 62.2% VPS placement, mainly due to obstructive hydrocephalus secondary to tumour.

Actiology of hydrocephalus was not a risk factor in VPS infection although there are contradictory findings reported in the literature. There are studies in the paediatric age group where actiology showed no effect on VPS infection (4,5); however, recent studies reported that the most common actiologies of hydrocephalus in shunt-infected patients were congenital hydrocephalus-myelomeningocele, 32%, and meningitis, 23% (10,18).

Although most studies report that VPS is usually done in emergency situations, there were a similar number of emergent and non-emergent VPS cases in this study. This is most likely due to the protocol taken by both the neurosurgery and anaesthesia departments at Hospital Sultanah Aminah to have shunt surgery performed as the first case of the day to maximise the sterility of the operating room. This has been repeatedly suggested as a measure to reduce post-operative VPS infection in many literature reviews (8,19). Timing of surgery was not a risk factor for VPS infection: however, the duration of surgery was. Surgery that took longer than 1 hour in this study was associated with a significant increase in VPS infection as concluded in the multivariate analysis. It was the single most significant confounder that influenced the post-operative VPS infection and increased the odds 8 times in the nonmethicillin group. The duration of surgery and the surgeon's experience are correlated; the more experienced the surgeon, the shorter the duration of the surgery. Cochrane conducted a 12-year review of the relationship between the surgeon's experience, as measured by operative volume, and the outcomes of ventricular shunt treatment of hydrocephalus in children. The 6-month shunt failure risk for less experienced surgeons was 38%, compared to 31% for more experienced surgeons. The infection rate for initial shunt insertions was 7% for patients treated by more experienced surgeons and 9.4% for those treated by less experienced surgeons. The review showed a relationship between surgeon's experience and shunt outcome, which appears to be based on the operative experience that a surgeon brings to a procedure (14).

This study could not determine whether the shunt system had an influence on post-operative VPS infection because the same standard VPS system, the Codman-Hakim shunt system (Integra Neuroscience Inc., Plainsboro, NJ), was used in all cases to decrease confounding factors that might affect the outcome of the surgery.

The infection rate with the use of topical methicillin in this study was 8.9%, and the infection rate without the use of topical methicillin was 20%. Statistically, topical methicillin did not reduce post-operative VPS infection (P = 0.230). This study is comparable to a study done by Choskey and Malik in Coventry that showed a statistically significant reduction in post-operative shunt infection rates from 15.56% to 0.33% with the use of topical and intrathecal vancomycin. In their study, betadine was instilled into the exposed subcutaneous area, and intrathecal vancomycin was injected when the ventricular catheter was inserted. Even though this was a prospective study and did not have a placebo, most of the confounding factors in increasing the risk of infection were eradicated. Only a single experienced surgeon was employed in this study, surgery was done as the first case of the day, and staff in the operating room was limited to 4 personnel (1). In the current study, only topical methicillin was used; no intrathecal drugs were used because their efficacy is not fully proven in the literature and no intrathecal preparation is available in Malaysia. A placebo was used in this study; however, the confounding factors into both groups cannot be controlled. This might be influenced by the fact that there were many surgeons involved and different aetiologies of hydrocephalus. However, the main objective was to observe whether topical methicillin could reduce post-operative VPS infection rates regardless of the confounding factors. Thus, it can be clearly concluded that topical methicillin has no significant effect in reducing post-operative VPS infection.

The univariate analysis revealed that only duration of surgery in the non-methicillin group was a significant factor in determining post-operative VPS infection (P = 0.03). This was also revealed in the multivariate analysis where duration of surgery in the non-methicillin group remained as the significant factor in the model (P = 0.02).

However, this randomised study is not definitive because the results do not support the hypothesis that topical methicillin would reduce post-operative VPS infection. This could be due to the small sample size and the study being conducted in a single centre with a short followup period of 3 months. Therefore, a further multicentre, randomised control trial on a new sample size based on the infection range of this study could support the hypothesis. Where P1 = 8.9 and P2 = 20, α = 0.05, and β = 0.2, thus sample size should be 100 for each group. Study follow-up should be extended to at least 6 months because several studies have shown 80 % of shunt infections occurs in the first 6 months (20,21).

Conclusion

This study showed that there was reduced post-operative VPS infection in VPS surgery using topical methicillin, compared with VPS surgery with no topical methicillin. However, the results were not statistically significant. Thus, this concludes that the use of topical methicillin does not reduce post-operative VPS infection. The results obtained might be influenced by some factors that were not equally distributed in each group.

It seems that long duration of surgery that last more than 1 hour, when not using topical methicillin, imposed a significant risk for the development of post-operative VPS infection.

Authors' Contributions

Conception and design, critical revision of the article, final approval of the article, administrative, technical, or logistic support: JSA

Obtaining of funding, provision of study materials or patients, collection and assembly of data, statistical expertise, analysis and interpretation of the data, drafting of the article: SCT

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Original Article	Peripheral Blood Lymphocyte Subset Counts in Pre-menopausal Women with Iron- Deficiency Anaemia					
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Abstract -

Background: Iron-deficiency anaemia (IDA) is a major worldwide public health problem. Children and women of reproductive age are especially vulnerable to IDA, and it has been reported that these patients are more prone to infection. This study was done to evaluate alteration of lymphocyte subgroups in IDA.

Methods: In this prospective study, we investigated lymphocyte subsets in pre-menopausal women with iron-deficiency anaemia; 50 normal subjects and 50 IDA (hypochromic microcytic) cases were enrolled. Experimental and control anticoagulated blood samples were evaluated using flow cytometry to determine the absolute and relative numbers of various lymphocyte subgroups. Finally, the results of the patient and control groups were compared.

Results: Mean (SD) absolute counts of lymphocytes, CD₃+ cells, CD₃+/CD₄+ subsets (T helper) and CD₃+/CD₈+ subsets (T cytotoxic) in the patient group were 2.08 (0.65) x 109/L, 1.53 (0.53) x 10⁹/L, 0.87 (0.28) x 109/L, and 0.51 (0.24) x 10⁹/L, respectively. The results showed significant differences between case and control groups in mean absolute counts of lymphocytes (P = 0.014), T lymphocytes (P = 0.009), helper T cells (P = 0.004), and cytotoxic T cells (P = 0.043).

Conclusion: This study showed that absolute counts of peripheral blood T lymphocytes as a marker of cell-mediated immunity may be decreased in pre-menopausal women with iron-deficiency anaemia, and that these patients may be more prone to infection.

Keywords: flow cytometry, immunology, iron-deficiency anaemia, pre-menopause, T lymphocytes, women

Introduction

Iron deficiency is one of the most common known forms of nutritional deficiency in the world. Iron-deficiency anaemia (IDA), which occurs due to nutritional deficiency, is a major health problem in developed and developing countries. IDA is characterised by a defect in haemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of haemoglobin (hypochromic). The prevalence of IDA varies according to sex, age, and geography. Young children and menstruating women are at higher risk for IDA because of higher iron needs (1). The prevalence of IDA has been reported to be 40% of adult males and 57% of adult females in South Asia, 2%–5% of adolescent girls and women of childbearing age in the US, 19% in France, 20% in Poland, 36% in Lebanon, 28% in India, and 21% in Turkey (2–9). Although the overall frequency of IDA in Iran is not well documented, it appears to be common based on some reports. For example, in one study performed in north Iran, the prevalence of anaemia based on serum iron index and haemoglobin was 24.2% and 18.2%, respectively, in pregnant women and 21.2% and 21.0%, respectively, in non-pregnant women (10).

Altered immune responses have considerable public health significance. The relationship between iron deficiency and infection susceptibility has been investigated. There is some evidence that iron is a fundamental element for normal development of the immune system and some clinical studies have emphasised the importance of iron in the integrity of the immune system (11-14). Tang et al. observed that the incidence of infectious diseases in IDA patients was significantly higher than that in the control group (15). Furthermore, it has been suggested that iron supplementation can improve iron levels and reduce morbidity from upper respiratory tract infections in children with or without infection (16). Tang et al. (15) and Feng et al. (17) reported lower levels of immunoglobulin (Ig) G in children and pregnant women with IDA. A correlation between iron intake and IgG levels in athletes has also been reported by Kim et al. (18). Changes in serum complement levels were also observed in anaemic patients (17).

The effects of iron deficiency on cellular immune function remain controversial. Some reports indicate that iron depletion may be responsible for decreased cellular immunity while others have not reported any changes in lymphocyte subset in patients with IDA (19,20). Most studies include data obtained from anaemic children and few reports exist concerning adults with IDA. It is important to understand the effects of IDA on the immune system due to its high prevalence. Lymphocyte subsets in 50 premenopausal adult females with IDA were studied and the results were compared with those of a control group. The aim of this study was to show whether peripheral blood lymphocyte subsets change in adult non-pregnant females with IDA.

Subjects and Methods

This prospective study was conducted on non-pregnant, pre-menopausal female patients referred to the Hematology and Blood Banking Department of Ghaem Hospital, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran, from April 2008 to January 2009. The voluntary subjects were included in this study, and each patient's medical history was obtained and recent laboratory results reviewed. A

total of 50 non-pregnant, pre-menopausal women between the ages of 20-45 years old presenting with IDA as the solitary pathology were included in the patient group. The inclusion criteria were haemoglobin (HGB) level of less than 12.5 g/dL, red blood cell (RBC) count of less than $4 \times 10^{12}/L$, mean corpuscular volume (MCV) of less than 80 fL, mean corpuscular haemoglobin (MCH) of less than 27 pg, serum iron level of less than 50 μ g/dL, total iron binding capacity (TIBC) of more than 400 µg/dL, and serum ferritin level of less than 20 µg/dL. The exclusion criteria were possible thalassaemia according to the laboratory results, a history of acute or chronic infection, familial history of immunodeficiency, history of cancer, pregnancy, and a history of endocrinopathy, especially hypo- or hyperthyroidism.

Fifty healthy, asymptomatic women were selected as the control group during the same period based on recent routine laboratory results. Inclusion criteria were absence of anaemia and iron deficiency with HGB level of 13–16 g/dL, RBC count of $4-6 \times 10^{12}$ /L, MCV of 80–96 fL, MCH of 27–33 pg, serum iron level of 50–150 µg/dL, TIBC of 250–400 µg/dL, and serum ferritin level of 20–200 µg/dL. Patients in the control group had no history of chronic disease or drug consumption during the previous 6 months. The iron-deficient and control groups were comparable with respect to the sex and age.

Four millimetres of the venous blood of controls and patients were collected in 2 sterile containing K3–EDTA anticoagulant tubes for complete blood cell count (CBC) and flow cytometry analysis. CBCs were obtained using a calibrated electronic counter, Sysmex Kx-21 (Sysmex Corporation, Kobe, Japan). Peripheral blood smears (PBS) were prepared with Geimsa staining and white blood cell (WBC) differential counting in PBS was completed to control for the absolute lymphocytes counts and percentage of lymphocytes reported by cell counters. One tube from each subject was sent to Bouali Research Center laboratories of MUMS for flow cytometric analysis of peripheral blood by a fluorescenceactivated cell sorting (FACS) count flow cytometer (Becton, Dickinson, and Company, San Jose, CA, USA) using monoclonal antibodies (Becton, Dickinson, and Company, San Jose, CA, USA) specific for CD3, CD19, CD45, CD4, and CD8 lymphocyte antigens for determining the percentage of these lymphocyte subpopulations in the samples. All samples were taken at the same time of day (usually at around 8:30 am). Specimens were kept at room temperature, transported to the Bouali Research Center laboratories of MUMS,

and analysed by flow cytometry as soon as possible (usually within 2 hours). In flow cytometry histograms, lymphocyte gating was set using linear 90° side-scatter and log CD45 fluorescence. Lymphocytes are CD45-positive cells with low side scatter. T (thymus-derived) and B (bone marrow-derived) lymphocytes were separated by CD3 and CD19 markers in the lymphocyte regions of flow cytometer histograms, then the expression of CD4 and CD8 markers were evaluated in the CD3-positive cell population. CD3 positive CD4 positive (CD3+/CD4+) and CD3 positive CD8 positive (CD3+/CD8+) cells were considered as T helper and T cytotoxic lymphocytes, respectively. The absolute lymphocyte subsets were calculated by multiplying the percentage of these lymphocyte subpopulations (results of flow cytometry) by absolute lymphocyte counts (results of CBC).

Quantitative variables were expressed as mean (SD). The percentage of lymphocyte subsets and absolute lymphocyte subset counts in two groups of IDA patients and controls were analysed with SPSS Version 11.5 (SPSS Inc., Chicago, IL, USA) by a statistician using onesample Kolmogorov–Smirnov test for evaluation normality of the data distribution and then using t test to compare mean values between case and control groups. A P value of less than 0.05 was considered statistically significant.

Results

The age range in the control group was from 20 to 45 years $(33.3 \pm 9.76 \text{ years})$ and in IDA group (case group) was from 20 to 45 years $(31.7 \pm 7.01 \text{ years})$, and *t* test analysis showed no significant differences between case and control groups (P = 0.34). The mean haemoglobin, haematocrit, red cell indices, and RBC counts were significantly lower in the iron-deficient group. In contrast, the PLT (platelet) count in IDA group was higher than that of the control group (Table 1). Statistical analysis by t test showed significant differences between these two groups for all red blood cell indexes (P < 0.001). The PLT count was significantly higher (P = 0.008) and the percentage of lymphocytes was lower (P = 0.014) in the IDA group as compared with the control group. There were no statistically significant difference between the two groups for mean relative counts of WBC (P = 0.83), or percentage of neutrophils (P = 0.10) and monocytes (P = 0.14).

The mean percentages of lymphocyte subsets were 75.38%, 58.58%, 34.04%, and 10.20% for total T lymphocytes (CD3+), T helper (CD3+/CD4+), T cytotoxic (CD3+/CD8+), and B cells

(CD19+), respectively, in the control group, and 73.20%, 58.06%, 33.10%, and 13.06% in the IDA group. Although the mean percentages of CD3+, CD3+/CD4+, and CD3+/CD8+ lymphocytes in the iron-deficient group were lower compared with those in the controls, these differences were not statistically significant with *P* values of 0.20, 0.75, and 0.53, respectively.

The absolute lymphocyte subset counts in the iron-deficient and control groups are shown in Table 2. The mean (SD) absolute CD3+, CD3+/ CD4+, CD3+/CD8+, and CD19+ lymphocyte counts were 1.80 (0.48), 1.06 (0.34), 0.61 (0.19), and 0.24 (0.11) x 109/L, respectively, in control subjects, and 1.53 (0.53), 0.87 (0.28), 0.51 (0.24), and 0.27 (0.15) x $10^{9}/L$, respectively, for the IDA group. The absolute T lymphocytes (CD3+) and subpopulations (CD4+, CD8+) in the irondeficient group were significantly lower than in the control group. Statistically significant differences in CD4:CD8 ratios and numbers of CD19+ lymphocytes between the two groups were not seen. A Pearson correlation test showed a significant correlation between the absolute T and B lymphocyte populations (r = 0.565,P < 0.001) and between the absolute CD4 and CD8 lymphocytes (*r* = 0.357, *P* < 0.001).

Discussion

Iron deficiency is one of the most common preventable nutritional deficiencies in developed and developing countries. IDA can cause irritability, headache, and fatigue that change social behaviour and impair the ability of adults to do physical work (1,3,21). An increased susceptibility to infections has been reported in some IDA patients, the aetiology of which is not well-known (11-15). Iron is crucial for cell proliferation due to its role in DNA synthesis and maturation of T lymphocytes. It is essential for enzymes such as ribonucleotide reductase, and it is involved in DNA synthesis; therefore, the proliferative phase of lymphocyte activation is an iron-requiring step and this activity can be diminished during IDA (22). Some authors have suggested that altered levels of some interleukins (IL) and cytokines (e.g. IL-2, IL-1, IL-6, TNF- α , IL-4, IL-12p40, IFN-y, and IL-10) might lead to immune system impairment in IDA patients (23-25). In addition, it has been suggested that altered cell marker expression may contribute to reduced T cell proliferation during iron deficiency (26). Cellular immunity and humoral immunity is mediated by T and B lymphocytes, respectively. T lymphocytes proliferate in the thymus and

Original Article | Lymphocyte counting in iron-deficiency anaemia

CBC indices	Con	trol	II	DA
Haemoglobin (g/dL)	13.93	(0.74)	10.8	(1.11)
Haematocrit (L/L)	41.1	(1.9)	32.96	(3.01)
MCV (fL)	86.54	(2.54)	74.85	(3.45)
MCH (pg)	29.79	(0.87)	24.27	(2.73)
MCHC (g/dL)	33.6	(0.97)	30.59	(2.46)
RBC (x 1012 /L)	4.74	(0.24)	3.81	(0.26)
PLT (x 109 /L)	232.8	(48.87)	268.0	(76.74)
WBC (x 109 /L)	6.53	(1.19)	6.60	(2.19)
Neutrophils (%)	3.74	(1.01)	4.02	(1.76)
Monocytes (%)	0.30	(0.90)	0.28	(0.10)
Lymphocytes (%)	37.20	(8.50)	32.93	(8.63)

Table 1: Complete blood cell count (CBC) result in iron-deficiency anaemia (IDA) and control groups

Data are expressed in mean (SD).

Abbreviations: MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, MCHC = mean corpuscular hemoglobin concentration, RBC = red blood cell, PLT = platelet, WBC = white blood cell

Table 2:	The absolute	lymphocytes	subset	counting	in	iron-deficiency	anaemia	(IDA)	and	control
	groups									

Sub population of		Control			P		
lymphocytes	Minimum	Maximum	Mean	Minimum	Maximum	Mean	value
CD3+ lymphocytes (x 10 ⁹ /L)	1.50	3.63	1.80	1.12	4.21	1.53	0.009
CD3+/CD4+ lymphocytes (x 10 ⁹ /L)	1.02	2.94	1.06	0.58	3.07	0.87	0.004
CD3+ CD8+ lymphocytes (x 109/L)	0.52	1.85	0.61	0.28	1.94	0.51	0.043
CD19+ lymphocytes (x 10 ⁹ /L)	0.29	1.20	0.24	0.20	1.05	0.27	0.263
CD4/CD8 ratio	0.10	0.60	1.84	0.06	1.01	1.92	0.625

released into the peripheral blood where they constitute 60% to 70% of total blood lymphocytes. Cellular immunity protects the body by the production of cytotoxic T lymphocytes, activated macrophages, and activated NK cells, and it is mediated mainly by T lymphocytes. Cell-mediated immunity is responsible for defence against intracellular microbes (27). Mature T cells are of at least three types. The T helper cells express CD3+/CD4+ cell markers, while T suppressor/ cytotoxic cells express CD3+/CD8+ cell markers. Mature T cells with γ/δ T cell receptor chains exhibit CD2+, CD3+, and CD7+, and lack CD4 and CD8; these type of T cells seem to function as another population of cytotoxic cells.

Our findings showed significant decreases in total CD3+, CD3+/CD4+, CD3+/CD8+, and T lymphocyte counts in IDA patients. These were consistent with some earlier studies (29-32). Lower levels of mature T lymphocytes (CD4+ and CD8+) were observed in 40 IDA children by Attia et al. (30). A relationship between iron deficiency and cell-mediated immunity in children was also studied by Mullick et al.; the research was done on 40 iron-deficient and 30 healthy children and the authors also reported significantly decreased mature T lymphocytes (CD3+), helper-inducer T lymphocytes (CD4+), and CD4:CD8 ratios in iron-deficient versus iron-sufficient children. Although slightly lower means of CD8+ lymphocyte counts were observed by Mullick et al. (31), these differences were not significant. In contrast to our results, no difference in the distribution of T lymphocyte subgroups was found by Ekiz et al. and Thibault et al. (33,34). The previous discrepancies may be due to different sample size, age, sex, nutritional status, and host immune responses. The majority of similar previous studies were completed with paediatric patients (29-34). We selected nonpregnant menstruating women who were prone to IDA. Furthermore, the sample size in our study was slightly greater than that reported in previous studies. Mullick et al. (31) and Attia et al. (30) reported that iron supplementation improved T lymphocyte counts. This improvement was not observed by Tsouchnikas et al. (35) or Sejas et al. (36).

The difference between the mean CD4:CD8 ratio in the iron-deficient group and control group in our study was not found to be statistically significant. Reports by other authors regarding the CD4:CD8 ratios in IDA are variable. Luraschi et al. (37) showed decreases in CD3+ and CD8+ levels and increases in the CD4+/CD8+ cell ratio. In contrast to our study, lowered levels of CD3, CD4, and CD4/CD8 ratios were reported by Mullick et al. (31). Our observations that the iron-deficient women had significantly lower mean levels of CD3+ lymphocytes in comparison with the control group were consistent with these reports.

We found that there was no significant difference for the absolute number of B lymphocytes (CD19+ cells) in IDA patients versus the control group. This finding was concordant with some earlier studies (38). In our study, an increase in platelet counts in IDA patients compared with the control group was seen and this increase was statistically meaningful and consistent with some other reports (39,40), although other studies were not in agreement with ours (41,42). Leukocyte counts in the two groups were not statistically different, where this was again consistent with some previous studies (1,27).

Conclusion

We found significant changes in the total lymphocyte counts, T lymphocyte numbers, and distribution of T cell subgroups (lower CD3+/CD4+ and CD3+/CD8+ T lymphocytes count) in women with IDA. This study showed that absolute counts of peripheral blood T lymphocytes, as a marker of cell-mediated immunity, may be decreased in pre-menopausal women with IDA and that these patients may be more prone to infection.

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Authors' Contributions

Conception and design: MRK Obtaining of funding: HT Provision of study materials: MM Collection and assembly of the data, administrative, technical, or logistic support: AB Statistical expertise: MK Analysis and interpretation of the data: MRK, MHS Drafting and critical revision of the article: MHS Final approval of the article: HA

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Original Article

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Thirteen Years' Experience of Diaphragmatic Injury in Children from the Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, India

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Abstract

Background: Diaphragmatic hernia is migration of abdominal viscera into the thoracic cavity through a defect in the diaphragm. In children, it is mostly congenital; traumatic diaphragmatic hernia being less common. This study aimed to review our experience with traumatic diaphragmatic rupture (TDR) and to identify the clinical findings and diagnostic modality that may help in early diagnosis and prompt therapy.

Methods: The study involved 11 children (1–18 years old) with TDR who were hospitalised between 1993 and 2005. In addition to clinical examination, a plain X-ray of the chest and abdomen, an ultrasound, barium studies, and a computerised tomography (CT) scan were used to evaluate the patients.

Results: All of the diaphragmatic ruptures occurred on the left side, with 10 occurring in the posterolateral part and 1 near the oesophageal hiatus. Two of our patients presented 7 and 10 days after the injury, and 1 patient presented 1 year after the trauma.

Conclusion: TDR should remain a diagnostic possibility in children. These patients are best assessed using a CT scan. New research on stem cells and tissue-engineered bioprosthetics may pave the path for better future therapies in these cases.

Keywords: acute respiratory distress syndrome, child, diagnosis, diaphragmatic hernia, medical imaging, rupture, trauma

Introduction

Diaphragmatic rupture is an uncommon but well-recognised complication of trauma that consists of 1.0%-5.8% of admissions into a trauma unit (1). It occurs in 0.5%-8.0% of adult trauma patients (2). In paediatric patients, it is estimated to occur at a rate of 4%-6%, and its presence has been reported to indicate high impact. It is associated with other severe injuries in 44%-94%of cases (3).

Traumatic diaphragmatic injuries are usually caused by blunt abdominal trauma or penetrating injuries (2); they were first described by Ambriose Paire in 1579 (4). Due to their rarity in infants and children, such injuries can be overlooked if unsuspected. Delayed presentation can lead to life-threatening complications as a result of organ herniation and strangulation (3).

Subjects and Methods

The study included children (1–18 years old) with traumatic diaphragmatic rupture (TDR) who were admitted to the Department of Pediatric Surgery of Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India, between 1993 and 2005. The following information was recorded for each patient: age, gender, duration between the trauma and hospital

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admission, type of injury, clinical/radiological findings, relevant information regarding traumatic site, herniated organs into the thorax, associated injuries, and patient's outcome.

Result

In the study duration, 11 patients were treated for TDR in our hospital; 8 boys and 3 girls. Their ages ranged from 1–18 years (mean 9.5 years). The TDR occurred following blunt trauma in 9 cases and a penetrating injury in 2 cases (elaborated in Table 1). Road traffic accidents were the most common cause. The most common clinical findings were respiratory distress and abdominal pain.

All of the ruptures occurred on the left side. The ruptures were localised in the posterolateral parts in 10 cases and near the oesophageal hiatus in 1 case. Eight of the patients were admitted soon after the trauma, while 1 patient was admitted after 7 days of injury. One patient was referred to our hospital after 10 days of injury with bilious contents from the thoracic drainage site (admitted to a peripheral hospital in the initial days following the injury). The chest tube had been inserted into the stomach because it was thought to be a case of hydropneumothorax. Another patient presented with abdominal pain after 1 year of trauma with the small and large bowels herniated into the thoracic cavity. The large bowel had strangulated and required resection and anastomosis.

Abnormalities were found in all of the chest X-rays (Figure 1), and all included an elevated or indistinct diaphragm or pleural effusion. Computerised tomography (CT) scan confirmed a diaphragmatic injury with herniation of the abdominal contents in all cases (Figure 2).

After adequate investigations and resuscitation, all of these cases were treated surgically through an abdominal approach. The defect was localised, the abdominal contents were reduced, and the defect in the diaphragm was repaired. Post-operatively, all patients had an uneventful recovery with the exception of 2 cases of post-operative bronchopneumonia, which was managed medically.



Figure 1: Chest X-ray (posteroanterior view) showing a cystic structure with an air-fluid level occupying the left haemithorax, causing collapse of the left lung and a slight mediastinal shift towards the right. The left haemidiaphragm is not well outlined (herniating stomach mimicking hydropneumothorax).



Figure 2: Axial noncontrast computerised tomography scan of the lower chest showing a herniated stomach in the left thoracic cavity in an 8-year-old boy (arrow).

Table 1: Age, gender, duration between the trauma and hospital admission, type of injury, clinical/ radiological findings, site of the trauma, herniated organs into the thorax, associated injuries

 and outcome of patients.

Case 1	Mode of Injury	Duration*	Clinical Findings	Plain X-rays
Female Age 5	Roadside accident (blunt). Bruises over left hypochondrium.	Hours.	Respiratory distress with vomiting.Bowel sound auscultated in chest.	Herniation of gut into left haemithorax.
	USG	Ba studies	CT scan	Operative Findings
	Minimal fluid in the abdominal cavity.	-	-	Small gut and stomach herniated through diaphragmatic rent near oesophageal hiatus.
Case 2	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
Male	Roadside accident (blunt). Bruises over right iliac fossa.	Hours.	Respiratory distress with vomiting. Air entry was good on both sides.	Herniation of gut into left haemithorax.
Age 12	USG	Ba studies	CT scan	Operative Findings
	-	Herniated small gut.	-	Small gut herniated through posterolateral rent in diaphragm.
Case 3	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
	Roadside accident (blunt). Contusion over hypogastrium and bruises over left iliac fossa.	1 year.	Respiratory distress.	Left pyopneumothorax.
Male	USG	Ba studies	CT scan	Operative Findings
Age 0	Tube was in the stomach. Minimal fluid in the abdominal cavity.	-	-	Spleen, small bowel, and colon herniated through posterolateral rent in diaphragm.
Case 4	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
Nr. 1	Diving in pond from about 3 m height.	7 days.	Respiratory distress with hydropneumo- thorax.	Bilious fluid from left-sided drain.
Male Age 8	USG	Ba studies	CT scan	Operative Findings
Age 8	_		TT and at a star a sh	
		-	and small intestine in left haemithorax.	Stomach, large gut, and spleen herniated through postero-lateral rent in diaphragm.
Case 5	Mode of Injury	Duration*	and small intestine in left haemithorax.	Stomach, large gut, and spleen herniated through postero-lateral rent in diaphragm. Plain X-rays
Case 5	Mode of Injury Stab injury spanning lower chest and upper abdomen on left side.	Duration* 1 year.	And small intestine in left haemithorax. Clinical Findings Severe abdominal pain and vomiting.	Stomach, large gut, and spleen herniated through postero-lateral rent in diaphragm. Plain X-rays Opacity in left lung base.
Case 5 Male Age 16	Mode of Injury Stab injury spanning lower chest and upper abdomen on left side. USG	Duration* 1 year. Ba studies	And small intestine in left haemithorax. Clinical Findings Severe abdominal pain and vomiting. CT scan	Stomach, large gut, and spleen herniated through postero-lateral rent in diaphragm. Plain X-rays Opacity in left lung base. Operative Findings
Case 5 Male Age 16	Mode of Injury Stab injury spanning lower chest and upper abdomen on left side. USG -	Duration* 1 year. Ba studies	Arefniated stomach and small intestine in left haemithorax. Clinical Findings Severe abdominal pain and vomiting. CT scan -	Stomach, large gut, and spleen herniated through postero-lateral rent in diaphragm. Plain X-rays Opacity in left lung base. Operative Findings Small gut and large bowel hernias with gangrene of large bowel; resection anastomosis performed.

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Case 6	Mode of Injury	Duration*	Clinical Findings	Plain X-rays
Male	Roadside accident (rolled over) with bruises over whole of abdomen and back.	-	-	-
Age 6	USG	Ba studies	CT scan	Operative Findings
	-	-	-	Small bowel, large bowel, and spleen hernias in left haemithorax.
Case 7	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
Female Age 11	Fall from about 2.5 m;10 days.had pneumothorax.Intercostal tube wasinserted initially;increased air andbilious drainage.Patient was thenreferred to ourinstitute.		Respiratory distress, bilious drainage through intercostal tube.	Pneumothorax; left side.
	USG	Ba studies	CT scan	Operative Findings
	-	-	-	Tube was in the stomach, which was herniating through posterolateral rent.
Case 8	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
Female Age 15	Bullet Injury with entry wound in left hypochondrium and exit wound on the lower aspect of chest on back side.	Soon after injury.	Decreased breath sounds on left side, vomiting and respiratory distress on 3rd day of injury.	Haemopneumothorax on left side.
	USG	Ba studies	CT scan	Operative Findings
	-	-	-	Stomach herniated through posterolateral rent in the diaphragm.
Case 9	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
Male	Roadside accident (rolled over) with bruises over whole of abdomen and back.	Hours.	Chest pain, abdominal pain.	Herniation of gut on left side.
Age 6	USG	Ba studies	CT scan	Operative Findings
-	Haemoperitoneum.	-	-	Stomach and small intestine herniated through posterolateral rent in diaphragm.

Case 10	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
	Roadside accident (blunt). No visible bruises over the abdomen.	Soon after injury.	Respiratory distress.	Herniation of gut into left haemithorax.
Male	USG	Ba studies	CT scan	Operative Findings
Age 18	-	-	-	Herniation of small gut through posterolateral rent in diaphragm.
Case 11	Mode of Injury	Duration *	Clinical Findings	Plain X-rays
	Roadside accident (blunt). Bruises over left lumbar area.	Soon after injury.	Respiratory distress.	Herniation of gut into left haemithorax.
Male	USG	Ba studies	CT scan	Operative Findings
Age 1	-	-	-	Herniation of large gut through posterolateral rent in diaphragm.

Post-operative period was uneventful for all cases except Cases 9 and 11; both patients had bronchopneumonia.

* Duration between occurrence of trauma and hospital admission.

Abbreviations: USG = ultrasonography, Ba = barium, CT = computerised tomography.

Discussion

The diaphragm is а complex, musculotendinous, dome-shaped structure dividing the thoracic and abdominal cavities. In blunt trauma, a diaphragmatic rupture occurs when intra-abdominal forces overcome the normally higher intrathoracic pressure and the elasticity of the contracted diaphragm. The diaphragm most frequently tears at the junction of the muscular and tendinous elements that is called the centrum tendinosum (5). Herniation of the stomach, small and large intestines, kidneys, and spleen may follow the rupture acutely or years after the original injury. Delayed herniation of the abdominal viscera may occur under a number of circumstances. In some cases, the diaphragm weakens secondary to the aggressive inflammatory response at the ruptured site. Patients are also at risk just after tracheal extubation when the intrathoracic pressure quickly becomes negative. Alternatively, visceral content herniation may occur slowly, as the physiologically negative intrathoracic pressures gently pull the abdominal contents through the diaphragmatic defect (6).

Most diaphragmatic ruptures occur on the left side. This is believed to be due to a congenitally weaker left haemidiaphragm and the protective effect of the liver on the right side (5). In our study, all of the cases were left-sided.

classic physical signs While the of diaphragmatic herniation include unilateral breath sounds, a scaphoid abdomen, and bowel sounds over the lung fields, these clues are not consistently present. Many victims simply demonstrate respiratory distress as their sole pulmonary finding. Additionally, 90% to 95% of individuals with diaphragmatic ruptures have other significant injuries. The most common associated pathologies include lacerations of the spleen, liver, and kidney; pelvic fractures; major vessel disruption; long bone fractures; and head trauma (7).

Diaphragmatic injury following blunt trauma remains rare in children and may be more difficult to assess than in adults for both anatomical and physiological reasons. The compliance of the paediatric chest wall may result in internal injury in the absence of the external evidence of major injury (8). As minor injuries have caused ruptures of the diaphragm, the timing of the impact during the respiratory cycle is possibly more important than the severity of the trauma because it creates a significant pressure gradient across the diaphragm. Chest X-ray is one of the most important methods for the detection of diaphragmatic rupture and herniation. The chest X-ray, however, is diagnostic in only 25% to 50% of cases (9). Suggestive findings on the chest Xray include an interrupted, indistinct, or elevated haemidiaphragm, bowel loops or air-fluid levels in the lung space, and a displaced nasogastric tube into the chest. Rib fractures, pneumothoraces, haemothoraces, lower lobe collapse, and pleural effusions are associated complications that are usually evident on plain films and may increase the suspicion of a more extensive injury (9).

Other imaging modalities that are available to the emergency physician to assess the integrity of the diaphragm include ultrasonography (USG) and CT scan (7). Diaphragmatic discontinuity, diaphragmatic thickening, segmental nonrecognition of the diaphragm, intrathoracic herniation of the abdominal viscera, elevation of the diaphragm, and both haemothorax and haemoperitoneum are strong predictors of a blunt diaphragmatic rupture (10).

As diaphragmatic tears do not close spontaneously, a diaphragmatic rupture requires surgical closure (5). Laparotomy is the favoured surgical approach to acute diaphragmatic rupture, given that approximately 50% of patients with blunt diaphragmatic injuries have other intra-abdominal pathologies (9). Thoracotomy is commonly employed to repair chronic ruptures.

Successful surgical and bioprosthetic repair of TDR poses a serious challenge for surgeons. With the advent of molecular tools, proteomics, regenerative medicine and systems biology, surgeons, physicians, molecular biologists and bioengineers are now following a common translational path to reach a viable solution for successful tissue and organ reconstruction. To the best of our knowledge, there has not yet been a report of any mechanical strain-induced expression of a tendon-specific protein that leads to a visible phenotypic effect in traumatic rupture that contributes to traumatic diaphragmatic herniation. Neither is there any data available that substantiates gene or protein expression in traumatic diaphragmatic hernia or associated multi-organ complications. New strategies ranging from laparoscopic patch and intestinal sub-mucosa to stem cell and tissue-engineered bioprosthetic construct-based strategies for the repair and reconstruction of diaphragmatic hernias have been attempted in several laboratories around the world (11–15). However, most of the data for these types of studies come from congenital cases, and these remain challenging options because of high complication rates. Ongoing and future experiments in animal models for developing foetal cell-based therapies will open newer avenues towards developing a translational approach to successfully deal with traumatic diaphragm reconstruction in children.

Conclusion

TDR, though uncommon, does occur and should remain a diagnostic possibility in children because these patients do not undergo selfhealing and require surgical correction of the defect. It should remain a possibility even in cases of remote trauma, as exemplified by one of our patients who presented after one year of trauma. A CT scan is the best imaging modality because it clearly depicts the anatomy with 3-dimensional reconstructions and highlights other associated organ injuries, which is extremely helpful in treating the patient. Stem cells and tissueengineered bioprosthetics, which are being tested in several laboratories around the world, can be more relevant in such cases as they can better integrate into growing tissues.

Authors' Contributions

Conception and design, statistical expertise: DBD Obtaining of funding, provision of study patients: KNR Collection and assembly of data: RN Analysis and interpretation of the data, drafting of the article: SR Critical revision of the article: SR, DBD Final approval of the article: KNR, SR, DBD Administrative, technical, or logistic support: KNR, SM

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Original Article | Diaphragmatic injury in children

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Original Article

Factors Affecting the Outcomes in Children Post-Myelomeningocoele Repair in Northeastern Peninsular Malaysia

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Abstract -

Background: The present study aimed to evaluate the impact of multiple factors and outcomes (ambulatory function and sphincter function) on children with myelomeningocoele (MMC) following surgical repair.

Method: A retrospective chart review of children that underwent surgery for MMC in the Hospital Universiti Sains Malaysia from 1 January 1990 to 31 December 2004 was conducted. Only those children who were followed-up for at least 18 months after the operation were included in the study.

Results: A total of 42 children with MMC were included in the study. Approximately 79% of the MMC were located in the lumbosacral and sacral regions. Thirty (71.4%) of the children had hydrocephalus, and 28 (67.7%) had a cerebrospinal fluid (CSF) shunt inserted. An analysis of the association between the predictors of ambulatory status revealed that hydrocephalus (P = 0.013), the presence of a CSF shunt (P = 0.005), intact motor function at L3 and below (P < 0.001), and the presence of deep tendon reflexes (P < 0.001) were good factors of ambulatory status. Only 16.7% of the children did not have urinary or faecal incontinence. Hydrocephalus (P = 0.049) and low-level MMC (P = 0.028) were significantly associated with sphincter control.

Conclusion: Multiple factors contributed to the outcomes in post-MMC repair children in terms of ambulation and sphincter function following a repair of MMC. The Spina Bifida Neurological Scale (SBNS) should be applied during the management of these children to identify neurological deterioration.

Keywords: children, myelomeningocoele, neurosurgery, neural tube defects, spina bifida, spinal cord

Introduction

Myelomeningocoele (MMC) is the most common congenital disorder of the central nervous system. It is characterised by an exposure of the nervous system and/or meninges to the environment because of a congenital bone defect (1).

Children with MMC who survive are likely to have life-long disabilities. Functional problems may often result from the neurologic defect or the surgical repair. In addition, the functional problems may be sequelae of the neurologic deficit (1). The present study was performed to evaluate the impact of multiple factors that are associated with MMC on the outcomes that follow repair.

Subjects and Methods

Children with MMC that were operated on at the neurosurgical unit of the Universiti Sains Malaysia teaching hospital over a 15-year period (from January 1990 to December 2004) were analysed in the present study. Only those children who were followed-up for at least 18 months after the operation were included in the study.

The clinical records of all of the children with MMC were reviewed for information about sex, the mode of delivery, the parental age when the child was born, the size of the lesion, associated abnormalities, the integrity of the MMC sac, the type of imaging performed, the level of the lesion, the time point of the repair of the lesion (duration between the time of diagnosis and repair), the presence of a ventriculoperitoneal shunt, the presence of complications, and the neurological outcome based on the Spina Bifida Neurological Scale (SBNS).

Table

Ruptured lesions were defined as any lesions with a ruptured sac, which was usually accompanied by leakage of the cerebrospinal fluid. The percentage of the size of the defect in relation to the thoracolumbar region was calculated using the following formula (2): Percentage of lesion size=

Surface area of the lesion × 100 Surface area of the thoracolumbar area

The whole body surface of each patient was determined using the following well-known formula to calculate the total body surface:

$$\frac{\text{Total body surface} = (\text{Body weight} \times 4) + 7}{\text{Body weight} + 90}$$

The size of the lesion area was calculated using the following formula:

Size of the lesion (with circular base) = πr^2 Size of the lesion (with elliptical base) = $D \times d \times \pi$ 4

where r is the radius, D is the long diameter, and d is the short diameter.

The total areas of the thoracic and lumbar regions were calculated according to the "rule of nines," which states that these regions constitute 18% of the total body surface. Lesions that occupied less than 8% of the area of the thoracolumbar region were classified as Grade I, and the lesions that occupied more than 8% were classified as Grade II.

The level of each lesion was established on the basis of both the anatomical and functional levels. The anatomical level of the lesion was defined as the level of the intact posterior vertebral arch above and below the lesion on the abdominal plain radiograph, taken as a part of the ventriculoperitoneal shunt assessment or the micturating cystourethrogram. In a number of cases, the anatomical level of the lesion was determined from either the magnetic resonance imaging or the computed tomography of the spine. The functional level was determined from the lower limb motor assessments in the neurosurgical, orthopaedic, or paediatric clinic follow-ups. This level was defined as the lowest level of the intact myotome with a power of at least 3/5 on either the right or the left side. Both the anatomical and functional levels were designated by the use of 6-point scale (Table 1). The two methods of assessment were compared

Table	1:	Point	system	m	for	assessing				
		myelor	nening	ocoe	le at	functional				
		and anatomical levels								
Point	Fu	nction	al 🛛	Anat	tom	ic Level				
		Level								
	1	1 into at			0					

1	L1 intact	Cervical
2	L2 intact	Thoracic
3	L3 intact	Thoracolumbar
4	L4 intact	Lumbar
5	L5 intact	Lumbosacral
6	S1 intact	Sacral

by subtracting the anatomical level from the functional level. A negative value indicated that the functional level was higher than the anatomical level and vice versa.

The neurological outcomes of the children who had operations for spinal dysraphism were evaluated using the SBNS at 18 months postrepair. The scoring was based on the motor function, reflexes, and bladder and bowel functions; these scores are divided (according to the level of spinal function) into 6, 4, and 5 points, respectively. The clinical status is divided into 5 Grades. Spina bifida Grade I represents a normal spinal neurological function, spina bifida Grade II represents conditions in which there is a voluntary control of bladder and bowel functions, spina bifida Grade III represents problems with ambulation, spina bifida Grade IV represents a non-ambulatory function, and spina bifida Grade V indicates a bedridden status.

The main outcome was defined as the ambulatory status at 18 months after the operation. Children who were in Grades I to III were deemed to be ambulant, and those in Grades IV and V were deemed to be non-ambulant. The presence of urinary and faecal incontinence was also analysed as a part of the outcomes.

Data entry and analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 15 for Windows (SPSS Inc., Chicago, IL). The comparisons were made between the groups using the Chi-square and Fisher's exact tests, as appropriate, for the categorical variables and dichotomous outcomes. P < 0.05 was considered to be statistically significant.

The associations between the ambulatory status, urinary and faecal incontinence, and significant independent variables from the univariate analysis were analysed with multiple logistic regressions that were adjusted for possible confounding factors to determine the significant variables. The final model of the factors determined using multiple logistic regressions was examined for fitness using the Hosmer–Lemeshow goodness-of-fit test. All results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Odds ratios were used to assess the risk of the outcome (ambulatory status and urinary and faecal incontinence) if a certain factor is present. The odds ratio was considered significant if the 95% confidence interval did not include an odds ratio of one.

Results

The present study led to the review of 78 cases of children that had operations for MMC at our hospital from January 1990 to December 2004; however, only 42 cases were included in the study. The other 36 cases were not analysed due to an absence of follow-up records at 18 months or more after the repair of the MMC.

The included cases were comprised of 18 boys (42.9%) and 24 girls (57.1%) with a male to female ratio of 3:4. The mean (SD) birth weight of the children was 3.29 (0.36) kg, and the mean (SD) age of the mothers was 30.65 (5.64) years. The mean (SD) size of the lesions was 17.30 (15.30) cm². Approximately 88% of the lesions (n = 37) belonged to Grade I, and 12% (n = 5) of the lesions were Grade II lesions. There was no relationship between the Grade of the lesion size and the wound complications (P = 0.618 by Fisher's exact test).

The anatomical levels of the lesion included 1 (2.4%) thoracic lesion, 3 (7.1%) thoracolumbar lesions, 5 (11.9%) lumbar lesions, 18 (42.9%) lumbosacral lesions, and 15 (35.7%) sacral lesions. The functional levels of the cases at 18 months or more post-repair were found to be intact at L1 in 4 cases (9.5%), L2 in 5 cases (11.9%), L3 in 8 case s (19%), L4 in 7 cases (16.7%), L5 in 2 cases (4.8%), and S1 in 16 cases (38.1%). The functional level was higher than the anatomical level in 57.1% of the cases, and the functional level was lower than the anatomical level for only 23.8% of the cases. In 19.0% of the cases, there was no difference between the functional and anatomical levels.

From the 42 patients, 34 (81%) were delivered via the vaginal route and 8 (19%) were delivered via Caesarean section. Seventy-four percent of the ruptured MMC cases, and 93% of the unruptured MMC cases, were delivered by the vaginal route. It was found that the mode of delivery was not related to the frequency of the rupture of the MMC ($\chi^2 = 2.320$, P = 0.128). There were 27 (64%) cases

of the MMC rupturing at birth, and 14 (52%) of these cases were repaired within 72 hours. The Grade I lesion size was found to have a significant association with the frequency of sac rupture (P = 0.047 by Fisher's exact test).

Hydrocephalus was found in 71.4% (n = 30) of the patients. The incidence of hydrocephalus was independent of the anatomical (Fisher's exact = 1.820, P = 0.874) and functional levels of the spinal dysraphism (Fisher's exact = 5.431, P = 0.354). The presence of hydrocephalus was not a factor that predicted wound breakdown following MMC repair ($\chi^2 = 0.840$, P = 0.359).

Of the 42 patients reviewed, 28 (67.7%) were shunted. Table 2 depicts the factors that were associated with the insertion of a cerebrospinal fluid shunt in these children. The time point of the shunt insertion for hydrocephalus was not related to the time point of the MMC repair ($\chi^2 = 1.193$, P = 0.223) or to the integrity of the MMC sac (Fisher's exact = 0.565, P = 0.912). There was no relationship between complications associated with the shunt and the time point of the MMC repair ($\chi^2 = 0.016$, P = 0.615).

Complications related to the surgical wound, such as wound dehiscence, cerebrospinal fluid leaks, and wound infections, developed in 5 patients (14.3%). Sepsis and shunt complications occurred in 2 (4.8%) and 10 (23.8%) patients, respectively.

Approximately 5% (n = 2) of the patients had normal neurological function (Grade I), 16.7% (n = 7) of the patients were ambulatory but had bowel and bladder problems (Grade II), 52.4% (n = 22) of the patients were ambulatory but spastic (Grade III), 21.4% (n = 9) of patients were non-ambulatory (Grade IV), and 4.8% (n=2) of patients were bedridden (Grade V). There were 13 (31%) areflexic cases, 15 (35.7%) cases with patellar tendon reflex, 12 (28.6%) cases with ankle reflex, and 2(4.8%) cases with intact anal reflex. There was no association between reflex functioning and the anatomical level of the lesion (Fisher's exact = 12.394, P = 0.433). None of the patients with intact functional levels above L2 were ambulatory, whereas 88.2% (*n* = 15) of the patients with intact L2 to L5 levels and 100% (n = 16) of those with intact S1 and below levels were ambulating 2 years after repair. The significant positive factors for the ambulatory status at 2 years after repair included the presence of hydrocephalus ($\chi^2 = 5.961$, P = 0.013), the presence of a cerebrospinal fluid (CSF) shunt (χ^2 = 7.452, P = 0.005), intact motor functions at L3 and below ($\chi^2 = 21.917$, P < 0.001), and the presence of deep tendon reflexes ($\chi^2 = 33.246$, P **Table 2:** Factors associated with a cerebrospinal shunt insertion in 42 children with myelomeningocoele (MMC)

Factors	Num	ber (%)		
CSF shunt inserted	28	(67.7)		
Time point of the shunt insertion				
During the MMC repair	8	(28.6)		
After the MMC repair	20	(71.4)		
Shunt complications				
Yes	10	(35.7)		
No	18	(64.3)		
Shunt complications in relation to the MMC repair				
During the repair	3	(37.5)		
After the repair	7	(35.0)		
Relationship of the anatomical level of the MMC with the shunt insertion				
Thoracic	1	(100.0)		
Thoracolumbar	2	(66.7)		
Lumbar	4	(80.0)		
Lumbosacral	12	(66.7)		
Sacral	9	(60.0)		

< 0.001). No difference was observed between the ambulatory and non-ambulatory groups in terms of the mode of delivery, the presence of a ruptured sac, the level of the lesion, the time point of the repair, and the size of the MMC. Using multiple logistic regression analyses, no significant associations were established between the main effects of each of the significant predictors and the ambulatory function of the children with MMC 2 years following repair. No interactions were found among the significant predictors.

Thirty-five (83.3%) of the children had urinary incontinence, and 18 (42.9%) of the children had faecal incontinence 2 years post-MMC repair. Only 7 (16.7%) of the children had a normal sphincter. Significant associations were observed between sphincter dysfunction and hydrocephalus, occurring in 20 (83.3%) patients ($\chi^2 = 3.889$, P = 0.049), and low-level MMC (lumbosacral and sacral), occurring in 22 (91.7%) patients (Fisher's exact = 5.657, P = 0.028). From the multivariate analysis, only the presence of hydrocephalus remained significant in the model for sphincter function.

Discussion

MMC is the most severe form of a neural tube defect. Its incidence varies between countries and geographical areas. Epidemiological data about this defect from South East Asia are available for 2 cities, Kuala Lumpur and Jakarta. It is predicted that the incidence of neural tube defects in Kuala Lumpur and Jakarta is 2.4 per 1000 and 1.5 per 1000 live births, respectively (3). Because MMC has strong environmental factors in its aetiology, it will be necessary to determine the pattern, aetiological factors, associated anomalies, and factors that affect the outcome in children that have had operations for spinal dysraphism in the Hospital Universiti Sains Malaysia.

There was a mild female predominance (female to male ratio of 3:4), which is in agreement with Faraji et al.'s study (4). The majority of MMC are located in the lumbosacral or sacral areas; very few MMC are located at cervical or upper thoracic levels (5). In the present study, 78.6% of MMC were located in the lumbosacral and sacral level. Another study by Rintoul et al. also demonstrated a similar distribution of the level of the MMC (6). Maternal age has an insignificant effect on the incidence of MMC. When a correlation can be found, the risks tend to be higher in older or very young mothers (4,7). In the present study, the youngest mother was 18 years old, and the oldest mother was 40 years old.

Large skin lesions can lead to difficulties in the primary closure of the skin, leading to skin necrosis. This study revealed wound complications in 14.3% of the cases. In other series, wound complications ranged from 12% to 22.4% of the cases (8). Appropriate skin flaps and techniques can decrease the wound-related complications (9). In a published study, the authors suggested that a broad base MMC lesion that was more than 8% of the total body surface of the thoracolumbar region should be repaired with muscle-skin flaps, and that those less than 8% of the total body surface of the thoracolumbar region should be repaired primarily (2). Luce and Walsh reported that lesions with a mean area of 22.7 cm2 could be primarily closed, whereas those with a mean area of 37.3 cm2 needed skin grafting for closure (10). Our study found that MMC with less than 8% of the total body surface area of the thoracolumbar region had a higher incidence of rupture. We theorised that a smaller sac was more likely to dry quickly following birth; therefore, increasing the pressure of the CSF that was pooling underneath the dried sac might contribute to sac rupture in small MMC.

MMC repair can be performed safely up to 72 hours after birth. This allows for a full assessment of the newborn to identify any associated abnormalities. Ventriculitis had been found 5 times more frequently in infants who underwent delayed MMC closure than in those that underwent a closure that was not delayed (1). One study found that 75% of the cases developed a shunt infection and that the mortality was 13% (11). In the present study, 51.9% of the ruptured MMCs were repaired within 72 hours.

Theoretically, the functional level of the lesion should correspond to the anatomical level of the spinal lesion from a radiological examination. However, a retrospective study noted that the functional level was higher than the anatomical level in 48% of individuals and that it was lower than the anatomical level in 14% of individuals (6). Data from our study showed that the functional level was higher than the anatomical level in 57.1% of the children and that it was lower than the anatomical level in 23.8% of the cases.

The mode of delivery may have effect on the neurological outcome in children with MMC. The use of a Caesarean section has been advocated as being superior to vaginal delivery in preventing further neurological insult in foetuses diagnosed with MMC antenatally. It has been postulated that the mechanical forces of labour and vaginal delivery may aggravate any already compromised exposed nerve roots (12). This study did not find a significant relationship between the mode of delivery and the ambulatory status in children that had an operation for spinal MMC. Cochrane and colleagues found no association between the mode of delivery and the ambulatory status, except for the neonates that presented as breech. For breech neonates, the authors theorised that neurological damage may occur with vaginal delivery (13). Some authors found that the MMC sac would rupture if the diameter of the sac was more than 4 cm during labour (14). In the current study, the size of the MMC was not associated with rupture of the sac. In another study, the authors found that an elective Caesarean section before the onset of labour might result in an improved neurological outcome in foetuses with MMC, normal karyotypes, and a lack of severe hydrocephalus (15). In a large study that compared elective Caesarean sections to trials of labour, there was no significant relationship between the mode of delivery and the ambulatory status. The authors concluded that the theory that labour causes placode injury was not supported, and injury to the MMC would still take place regardless of the mode of delivery (12).

Earlier studies revealed the presence of a Chiari II malformation in nearly 90% of all children with MMC. However, some studies suggested that this malformation was only clinically significant in 10% to 20% of these children who were aged 3 months or less (16). In the present study, only 9.4% of the cases were diagnosed with a Chiari II malformation. This low incidence rate might be due to the fact that most of the children did not survive beyond infancy. As a result, they were not alive long enough to exhibit symptoms that are associated with a Chiari II malformation.

Hydrocephalus is the most common abnormality associated with MMC. Prior to the advent of shunting devices, the leading cause of death in children with MMC was uncontrolled hydrocephalus. Previous publications reported that the incidence of hydrocephalus varied from 35% to 90% (9). In the present study, 71.4% of the children with a MMC had hydrocephalus. Almost 87% of those patients with hydrocephalus had a shunt inserted. The present study revealed that for the majority of the cases (71.4%), the shunts were inserted following a repair of the MMC. Hydrocephalus may be worsened following repair because of a loss of the decompressive effect that results from cerebrospinal fluid leakage via a ruptured MMC, because of a loss of the damping effect on elevated intracranial pressure by a bulging MMC sac, and because of further impaction of a Chiari II malformation due to an acute loss of cerebrospinal fluid during operation (5). Cerebrospinal fluid shunts have allowed at least 75% of the children that are born with a MMC to reach their early adult years (17).

The timing of the ventriculoperitoneal shunt insertion in relation to the timing of the repair of the MMC remains controversial. Insertion of a shunt simultaneously with a back closure has raised concerns regarding the general susceptibility to infection because of the poor immune function in neonates with MMC. It has been argued that insertion of a shunt reverses the flow of the cerebrospinal fluid from the ruptured MMC in the lumbar region to the ventricles and leads to an infection (18). Many experts advocate simultaneous MMC repair and ventriculoperitoneal shunt insertion to reduce the incidence of cerebrospinal fluid leaks from the operation site and to lead to a shorter hospital stay (19). Alternatively, serial ventricular taps from ventricular access devices may be used initially, and a shunt may be inserted a few days later. Many studies found that comparing the complication rate for shunts that are inserted at the time of MMC repair with those inserted at a later date during a separate procedure did not reveal any differences in terms of shunt infections or shunt malfunctions. Miller and colleagues found that there was a higher rate of cerebrospinal fluid leakage in patients who had ventriculoperitoneal shunt insertion after MMC repair (19). This finding was due to an increased intracranial pressure from the evolving hydrocephalus that resulted in wound breakdown following repair. In a larger study, no difference was observed between the outcome of the shunt function and the time of its insertion in relation to the MMC repair (20,21). Approximately 10% of MMC patients do not require shunt insertion to treat hydrocephalus (18). This study found that 13.3% of hydrocephalic patients did not require shunt insertion. In the present study, shunt complications were not associated with the time point of the repair, the time point of the shunt insertion, and the integrity of the MMC.

It has been shown that the frequency of the shunt insertion for hydrocephalus in infants with MMC was associated with the level of the lesion (6,22). A larger number of cephalic lesions were associated with an increased frequency of shunting when assessed at the anatomical and functional level, as demonstrated in the present study. Therefore, foetal repair of MMC might eliminate the need for CSF shunting postnatally. However, there was no significant association between the incidence of shunt insertion and the anatomical or functional level in the present study. These findings were supported by the results from another study that did not find any relationship between the level of the MMC and the incidence of hydrocephalus (4).

In 1992, Shizuo Oi and Satoshi Matsumoto proposed a scoring system, the SBNS, that reflects a patient's clinical status and enables an analysis of the chronological changes of neurological functions (23). This scoring system is an important tool in the follow-up assessment of children who have had an operation for a MMC. This assessment is important because these children may exhibit neurological deterioration as they grow older. In the present study, the SBNS grade was determined 2 years after repair. Due to a lack of data, the pre-operative SBNS grade could not be evaluated. In the present study, 4.8% of the patients had normal neurological functioning (Grade I), 16.7% of patients were ambulatory but had bowel and bladder problems (Grade II), 52.4% of patients were ambulatory but spastic (Grade III), 21.4% of patients were nonambulatory (Grade IV), and 4.8% of patients were bedridden (Grade V). Another study that used the SBNS grade to evaluate the neurological outcome of patients with spina bifida found 21.8%, 12.7%, 40%, 10.9%, and 14.5% of the cases belonged to Grades I, II, III, IV, and V, respectively (4).

In addition paralysis in the lower extremities, almost all individuals with MMC suffer from some degree of urinary and faecal incontinence. Incontinence affects the quality of life of children with MMC. In the present study, 83.3 % of the children did not attain acceptable bladder and bowel continence. The presence of hydrocephalus and a MMC that was located at the lumbosacral or sacral area were strongly associated with poor sphincter control. Similar findings were reported in another published study (24).

The ambulatory status in patients with spinal dysraphism is an important factor for functional independence. Children with low-level lesions (low lumbar and sacral levels) are usually able to walk; however, they may need the help of braces and/or crutches. Patients with midlevel lesions (midlumbar level) typically require significant support in the form of braces, twister cables, crutches, or walkers to walk for even brief periods. Most patients with lesions at the upper lumbar level and above require wheelchairs for mobility (25). In the present study, 73.8% of the patients were ambulant at 2 years after the repair of the lesion. The present study demonstrated similar findings in which none of the patients with highly functional lesions could ambulate, and a majority of the patients with intermediate and lowfunctional lesions could ambulate (88.2% and 100%, respectively).

The present study found that the presence of hydrocephalus and CSF shunts, intact motor functions at L3 and below with the presence of knee and ankle reflexes, and a motor level that was lower than the anatomical level were significantly associated with ambulation. By using a multivariate logistic regression, however, none of the odds ratios remained significant in the model. The present study, therefore, agrees with an earlier publication that found that the presence of shunted hydrocephalus, the number of shunt revisions, and the lesion level seemed to be less important with regard to ambulation (26–28).

Other authors found several significant predictors of ambulatory status in children with spinal dysraphism. However, comparisons among these studies are difficult because different definitions were used for the level of the lesion and varying classifications were used for the ambulatory statuses (29). It has been suggested that ambulation early in life is a better than the neurological level in predicting the ambulatory status in adult life (30). Another study found that children with a high level of spina bifida who participated in a walking program during early childhood had fewer fractures and pressure sores and were more independent than those who were wheelchair-bound early in life (31). Most studies found that children with thoracic and high lumbar lesions were non-ambulatory (28). Those children who had sacral lesions were able to walk around the community. Children with MMC at other levels were not uniform in terms of the status of their ambulation (28). The present study found a similar pattern in terms of the relationship of the functional level of the lesion and the ambulatory status. It has been reported that hydrocephalus and its complications influence the intelligence of these individuals and affects their ability to recognise their potential to become mobile (28). The present study found a significant correlation of hydrocephalus and shunt insertion with the ambulatory status in the univariate analysis, but the factors was not significant in the multivariate analysis.

Conclusion

The present study demonstrated that various factors can affect the outcome of children with MMC. Because these children may develop neurological impairment as they grow older, a measuring tool such as the SBNS should be used to monitor any neurological dysfunction. In addition, a multidisciplinary team approach should be employed in the management of children with MMC. Aggressive treatments that prevent further complications should be used to facilitate socially acceptable levels of functional independence in these individuals.

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Brief Communication

Computed Tomography of Blunt Spleen Injury: A Pictorial Review

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Abstract -

The spleen is one of the organs most frequently injured in blunt abdominal trauma. Computed tomography (CT) scanning can accurately detect splenic injury and is currently the imaging modality of choice in assessing clinically stable patients with blunt abdominal trauma. The CT features of spleen injury include lacerations, subcapsular or parenchymal haematomas, active haemorrhage, and vascular injuries. We present a pictorial review of the spectrum of CT findings for blunt splenic injuries. This article will be a useful reference for radiologists and surgeons as CT scan is widely used for the assessment of splenic injuries and contributes to the current trend towards nonsurgical management of this injury.

Keywords: abdomen, blunt injuries, computed tomography, medical imaging, spleen, trauma

Introduction

The spleen is one of the organs most frequently injured in blunt abdominal trauma, accountingforupto49% of all visceral injuries (1.2). Physical examination and laboratory data are often nonspecific in the diagnosis of splenic injury (3). Contrast-enhanced computed tomography (CT) scanning is currently the diagnostic imaging tool of choice for the assessment of haemodynamically stable patients with spleen injury due to its speed, widespread availability, diagnostic accuracy, and relatively noninvasive nature (4). CT scanning can also provide an accurate appraisal of coexisting abdominal injuries, such as injuries to the retroperitoneum and the abdominal wall, and can exclude the presence of lesions requiring surgery, such as bowel or pancreatic injuries (5). The use of CT scanning has influenced the current trend in the management of spleen injuries towards nonsurgical managements (6,7). Even though the decision to use a surgical intervention is usually based on clinical criteria rather than on imaging findings, data from CT scans frequently increase the diagnostic confidence of surgeons and play an important role in decreasing the frequency of unnecessary exploratory laparotomy (7,8).

Over a 2-year period (2008–2009) in our hospital, there were 44 cases of spleen injury out of 151 cases for which an abdomen CT scan was performed for blunt abdominal trauma. All of these spleen injury cases were retrospectively

4-row multislice Somatom Siemens Volume Zoom CT scanner (Siemens Medical Systems, Erlangen, Germany) with a 10-mm slice width, 2.5-mm collimation, 0.75-s rotation time, 15-mm table feed, and 3-mm reconstruction interval. Pre- and post-contrast scans were routinely performed. Patients received 2 mL/kg of intravenous contrast medium (iohexol 300 mg I/mL). Oral contrast agents were not routinely given. The postcontrast scans were acquired during the portal venous phase, approximately 80 seconds after contrast injection. Multiplanar reconstruction (MPR) images in the sagittal and coronal planes were acquired when necessary. In this article, we present a spectrum of the CT findings for blunt splenic injuries. The spleen injury grading system was applied according to the classification system of the American Association for the Surgery of Trauma (AAST). **CT Features of Blunt Splenic Injury**

reviewed. Of these 44 cases, 12 patients had Grade

I injury, 9 patients had Grade II injury, 11 patients had Grade III injury, 4 patients had Grade IV

injury, and 8 patients had Grade V injury. For all

patients, the CT scans were performed using a

The major CT features of blunt splenic injuries are lacerations, a non-perfused region, subcapsular and parenchymal haematomas, active haemorrhage, haemoperitoneum and vascular injury. Lacerations and intraparenchymal haematomas or contusions can be clearly observed using contrast-enhanced CT (Figures 1 and 2) (9). Subcapsular haematomas appear as an elliptic collection of low-attenuation blood between the spleen capsules and enhanced splenic parenchyma that causes the indentation or flattening of the underlying spleen margin. Free intraperitoneal blood in the perisplenic space does not cause this effect on the underlying spleen parenchyma (Figure 3) (4).

Haemoperitoneum be can accurately detected on a CT scan (10). When a patient is in the supine position, blood from the splenic injury passes via the phrenicocolic ligament to the left paracolic gutter and the pelvis. Blood can also pass into the right upper quadrant (Figure 4). Previously, the volume of haemoperitoneum has been considered to be a predictor of the need for surgery in patients with blunt splenic injury; however, recent reports have detailed the successful nonsurgical management of patients with a large amount of haemoperitoneum (11,12). Active haemorrhage appears as an area of high attenuation on a CT image with Hounsfield units value ranging 85-350 due to extravasated contrast material (Figure 5) (13). Contrast extravasation occurs in approximately 17.7% of patients with splenic injury and is a significant predictor of nonsurgical management failure (2).

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CT-based Injury Grading System

Various CT-based grading systems have been developed for the assessment of splenic injury, with the goals of standardising reporting, planning appropriate management, and enabling comparisons between institutions and studies. However, none of the grading systems correlates well with the need for surgical intervention (7,11,14). Recently, a better correlation between a newly proposed CT grading system and surgical intervention was achieved if important CT findings such as active haemorrhage, pseudoaneurysm, arteriovenous fistula, and the severity of haemoperitoneum were included in the grading system (15). Radiologists should be familiar with CT-based grading systems to facilitate research and communications with the surgeons. The most widely used CT grading system for splenic injury in trauma patients is based on the AAST scale (Table 1) (16). The injuries covered in this study were categorised as Grade I (Figures 6 and 7), Grade II (Figures 8-10), Grade III (Figures 11-13), Grade IV (Figure 14), or Grade V (Figures 15 and 16).



Figure 1: Splenic laceration seen on contrastenhanced computed tomography scan as linear irregular hypodense area (arrow). It was proven intraoperatively in this 15-year-old boy who was injured when his motorcycle skidded. He had an uneventful recovery after splenectomy.



Figure 2: Parenchymal haematoma (arrow) seen on contrast-enhanced computed tomography scan as focal hypodense area within the enhanced splenic parenchyma with an intact capsule. This patient was injured in a motor vehicle collision and was managed conservatively.

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Table 1: Classification of splenic injuries as proposed by the American Association for the Surgery of
Trauma (AAST), 1994 revision (16)

Grade	Injury	Criteria
Ι	Haematoma	Subcapsular, <10% of surface area
	Laceration	Capsular tear, <1-cm parenchymal depth
II	Haematoma	Subcapsular, 10-50% of surface area Intraparenchymal, <5-cm diameter
	Laceration	1-cm to 3-cm parenchymal depth that does not involve a trabecular vessel
III	Haematoma	Subcapsular, >50% of surface area or expanding Subcapsular or intraparenchymal, ruptured Intraparenchymal, ≥5-cm diameter or expanding
	Laceration	>3-cm parenchymal depth or involving trabecular vessels
IV	Laceration	Laceration involving segmental or hilar vessels producing major devascularization of >25% of the spleen
V	Laceration	Completely shattered spleen
	Vascular	Hilar vascular injury that devascularizes the spleen

Advance one grade for multiple injury (up to Grade III)



Figure 3a: Subcapsular haematoma (arrow) seen as perisplenic collection that indents the underlying parenchyma.



Figure 3b: Perisplenic blood collection (arrow) seen as collection surrounding the spleen with no mass effect to adjacent parenchyma.

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Figure 4: Haemoperitoneum from splenic injury in a 30-year-old man after being assaulted. Computed tomography scan showed massive haemoperitoneum (arrows) due to laceration at splenic hilum. This was confirmed intraoperatively with blood loss of 1L. There was no other intraabdominal injury.



Figure 5: Active haemorrhage from splenic injury seen as contrast extravasation (arrow) in 18-year-old boy injured after motor vehicle accident. Blood loss of 2L was noted intraoperatively and splenectomy was done for this patient.



Figure 6: Grade I spleen injury in a 17-year-old girl involved in motor vehicle accident. Coronal reformatted computed tomography showed a capsular tear less than 1 cm in the lower pole (arrow). She was managed conservatively with uneventful recovery. Note the minimal perisplenic collection.



Figure 7: Grade I spleen injury in a 35-year-old male injured in an industrial accident. Axial contrast-enhanced computed tomography scan showed subcapsular hemorrhage (arrow) less than 10% of surface area. He was managed conservatively and recovered well. Malaysian J Med Sci. Jan-Mar 2011; 18(1): 60-67



Figure 8: Grade II splenic injury in a 13-year-old boy injured after a fight. Computed tomography scan showed subcapsular haematoma involving 30%–40% of splenic surface area (arrow). He was managed conservatively with uneventful recovery.



Figure 9: Grade II splenic injury in a 14-year-old girl injured in motor vehicle accident. Computed tomography scan was done 2 days after the accident demonstrated intraparenchymal haematoma (arrow) less than 4 cm in diameter with no capsular tear. Surgery was performed in this case for continuous blood loss. There were lacerations of left broad ligament with bleeding from branches of left ovarian artery (images not shown). Splenic capsule was intact.



Figure 10: Grade II splenic injury in a 30-year-old man after being assaulted. Computed tomography scan showed a 2-cm laceration at the hilum (arrow) which was confirmed intraoperatively.



Figure 11: Grade III splenic injury in a 15-yearold boy injured during football match. Axial contrast-enhanced computed tomography scan showed multiple lacerations and intraparenchymal haematoma (arrow). He was managed conservatively and recovered fully

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Figure 12: Grade III spleen injury in a 32-year old man injured in motor vehicle accident. Axial contrast-enhanced computed tomography scan showed multiple intraparenchymal lacerations with subcapsular haematoma (arrow). Splenectomy was done with blood loss of 300 mL.



Figure 13: Grade III splenic injury in an 18-yearold boy, injured when his motorcycle hit a buffalo. Axial contrastenhanced computed tomography scan showed a laceration at upper pole (arrow). Intraoperative findings confirmed a 6-cm laceration with haemoperitoneum of about 1L. Splenectomy was performed.



Figure 14: Grade IV splenic injury in a 17-yearold boy injured in motor vehicle accident. Coronal reformatted computed tomography showed multiple lacerations causing major devascularisation of the spleen. Splenectomy was performed for this patient.



Figure 15: Grade V splenic injury in an 18-year old man after his motorbike hit a lorry. Axial contrast-enhanced computed tomography scan showed shattered spleen with large-volume haemoperitoneum which was confirmed intraoperatively. Note the focal high attenuation (arrow) due to active hemorrhage. Splenectomy was done for this patient.



Figure 16: Grade V splenic injury in a 17year old boy involved in motor vehicle accident. Axial computed tomography showed non-perfusion of the spleen on this post contrast image. Perisplenic hyperdensity (short arrow) was due to contrast extravasation. He also had left renal injury (long arrow).



Figure 17: Splenic abscess as a complication of splenic injury in a 43-yearold man. He presented about 1 week after trivial trauma due to persistent abdominal pain. Computed tomography scan showed intraparenchymal haematoma with multiple air pockets within; this was confirmed intraoperatively.

CT Features of Delayed Complications

There are few complications related to splenic injury. Delayed complications of splenic injury occur at least 48 hours after the initial injury and include pseudocysts, abscesses, pseudoaneurysms, and delayed rupture (17,18). Delayed splenic rupture has been reported to occur in approximately 5%-6% of nonsurgically managed adults. Post-traumatic pseudocysts were reported in 0.44% of splenic injury patients (18). Splenic abscess formation is a rare complication of blunt trauma (Figure 17). However, as the trend towards nonsurgical management continues, this rare complication may become more prevalent. Post-traumatic splenic artery pseudoaneurysm is also a rare complication that may develop after splenic injury of any grade.

Role of Follow-up CT in Splenic Injury

Follow-up imaging can provide valuable information about healing patterns (17,19). CT scanning demonstrates apparent complete healing of half of all splenic injuries after 6 weeks. Complete healing of all grades is observed 3 months after injury (20). However, this information has not been shown to significantly influence the management of the injury or affect patient outcome, and thus, follow-up CT scans are not currently recommended (18,21).

Conclusion

A shift towards nonsurgical management of blunt splenic injury in clinically stable trauma patients has been made possible by the widespread use of CT scanning as the initial imaging evaluation. CT scans accurately depict various patterns of splenic injuries and other associated surgically important findings. Knowledge of CT findings of spleen injury is important for both radiologists and surgeons for optimal patient care.

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Abstract -

Knowledge of muscular, vascular, and neural variations in the axilla is of great clinical importance, especially in mastectomies, breast reconstruction, and axillary bypass operations. In the present paper, we report unilateral variations observed in the axillary region of a male cadaver. A fibromuscular axillary arch was observed on the right side. On the same side, there was a bifurcated axillary vein; a medial cutaneous nerve of the arm passed through and later ran beneath this axillary vein. In addition, the intercostobrachial nerve was absent on the right side. The clinical significance of the variations observed and their embryological basis are discussed in this paper.

Keywords: axilla, axillary vein, intercostal nerve, lymph nodes, mastectomy, surgery

Introduction

Anatomic variations may remain undetected until they are discovered during surgical intervention or after local complications have occurred. Knowledge of muscular, vascular, and neural variations in the axillary region is of clinical importance in mastectomies, breast reconstruction, and axillary bypass operations (1,2). In the present paper, we report unilateral variations in the axillary vein and the intercostobrachial nerve in a male cadaver with an axillary arch.

The axillary arch muscle (Langer's axillary arch) is an accessory muscle that extends between the pectoralis major and latissimus dorsi (3). Accessory muscle slips connected with pectoralis muscles or occurring in the axilla may have variable origin (from the latissimus dorsi or the pectoralis major) and insertion (4). The axillary arch can cause thoracic outlet syndrome and shoulder instability (5). Entrapment of the neurovascular bundle within the arch can lead to entrapment syndrome. In addition, the axillary arch hides a small group of lateral axillary nodes, which can mislead the surgeon during breast surgery (1,2).

The major blood vessels found in the axillary region are the axillary artery and the axillary vein. The axillary vein extends from the lower border of the teres major muscle to the outer border of the first rib, where it is surrounded by nerves from the distal brachial plexus (6). The axillary vein is an alternate route for venous access during pacemaker and cardioverter defibrillator (ICD) implantation, treatment of severe burns, evaluation of central thoracic venous thrombosis caused by thoracic outlet compression, and treatment of breast carcinoma (7,8). Therefore, variations in this vein are of great clinical significance.

The nerve supply to the axillary floor is through the intercostobrachial nerve (ICBN), which is the lateral cutaneous branch of the second intercostal nerve (T₂). It also supplies the lower third of the medial side of the arm via communication with the medial cutaneous nerve and the posterior strip of skin over the forearm (9). A second intercostobrachial nerve is often present, and it is the lateral branch of the third intercostal nerve (9). Knowledge of variations in the branching pattern of the ICBN is important for avoiding complications during mastectomies (10-12) and axillary lymph node clearance during surgery for breast carcinoma (13). Toressan et al. (14) reported that preservation of the ICBN is feasible and leads to a significant decrease in alteration of pain sensitivity of the arm without altering the total time of surgery, the number of dissected nodes, or local relapse rates.
Case Report

During routine dissection in the axillary region of a 40-year-old male cadaver, a fibromuscular band, the axillary arch, was observed on the right side. It extended from the lower border of the latissimus dorsi to the tip of the coracoid process, where some fibres mingled with the pectoralis minor. The axillary arch was 8.9 cm in length; it was partly muscular and partly fibrous. The muscular slip at the base originated from the latissimus dorsi, which was 1.6 cm wide and 3.2 cm long. The fibrous part of the arch, measuring 5.7 cm in length and 0.5 cm in width, was attached to the tip of the coracoid process (Figure 1). The latissimus dorsi had a normal nerve supply from the thoracodorsal nerve. Moreover, on the same side, the axillary vein bifurcated for a short distance and then rejoined the axilla. The medial cutaneous nerve of the arm originated from the medial cord and passed through the bifurcated part of the axillary vein, and thereafter it ran beneath the axillary vein for a short distance and then lay medial to the axillary vein. Beyond this point, the nerve had a normal course and supplied the medial aspect of skin in the lower third of the arm. However, it did not communicate with the lateral cutaneous branch of T_o (intercostobrachial nerve), which was absent. The lateral cutaneous branches of intercostal nerves T₁ and T₂ were seen in their respective intercostal spaces, and they supplied the axillary skin and medial aspect of the arm, respectively. The medial cutaneous nerve of the arm did not communicate with the lateral cutaneous branch of T_1 and T_2 (Figure 2). However, on the left side, none of these variations were observed.

Discussion

The axillary arch, an infrequent and often overlooked variant of the latissimus dorsi, has been recognised in 0.25%–37.5% of subjects, depending on the population studied (15). Earlier studies have reported that the muscular slip of the axillary arch may arise from the latissimus dorsi or the pectoralis major and may insert into fascia (axillary and brachial), muscles (biceps brachii, teres major, long head of triceps brachii, and pectoralis minor), or bones (coracoid process and medial epicondyle of humerus) (4,15).

In the present case, the male cadaver had a unilateral axillary arch on the right side. A major part of the axillary arch was made up of a fibrous band, which is rarely reported in the literature.

Case Report | Multiple variations in axillary region



Figure 1: Photograph showing the fibromuscular axillary arch and bifurcated axillary vein and abnormal course of medial cutaneous nerve of arm on the right hand side



Figure 2: Schematic representation of variation in axillary vein and course of medial cutaneous nerve of arm

The most widely accepted view of embryological development of the axillary arch suggests that it is a remnant of the panniculus carnosus found in mammals (16). During the embryonic period, limb muscles arise in situ from the mesenchyme, which in turn is derived from the somatic layer of lateral plate mesoderm that surrounds the developing bone. As described by Cihak et al. (17), the ontogenesis of muscle has 4 fundamental phases. During phase 3, muscle primordia from different layers fuse to form a single muscle, while some muscle primordia disappear through cell death in spite of differentiated myofilaments (18). In phase 4, connective tissue elements develop and start their integration with muscle fibres. In the present case, the anomaly probably arose during phases 3 and 4, during which the majority of muscle fibres must have undergone apoptosis (during phase 3). The fibrous slip of the axillary arch might be persistent connective tissue formed between the latissimus dorsi and the coracoid process.

Identification of the axillary arch and its variations may help avoid accidental injury to axillary vessels and the brachial plexus during surgical procedures. The axillary arch can pose difficulty during sentinel lymph node biopsy because the slip stretches in the hyperabducted position and shifts the node higher (19). The latissimus dorsi is of clinical significance, especially in breast cancer surgeries, because the deep fascia surrounding the muscle is continuous anteriorly with the axillary fascia, and the nerve supply to this muscle traverses the axilla (20). The anterior edge of the latissimus dorsi marks the dorsal extent of a total mastectomy (21). Preservation of thoracodorsal nerves and vessels is of utmost importance in the preservation of muscle for reconstructive purposes (22).

Variations in the axillary vein have been reported previously. They have been observed surgeries during axillary and cadaveric dissections (23,24). A large number of invasive procedures, both diagnostic and therapeutic, use veins of the upper limb, particularly in and distal to the axillary region. The axillary vein develops in the limb bud mesenchyme during embryonic life as a dense capillary plexus that persists as a superficial capillary plexus due to different hemodynamic influences. In this plexus, some anastomoses persist to form deep vessels, while others regress. The axonal growth cones for the cutaneous nerves also traverse through the undifferentiated mesenchyme, intermingling with the developing vascular channels. The medial cutaneous nerve of the arm, which passes through the bifurcated axillary vein, could be the result of entrapment of the persistent axonal growth cone within the venous plexus during embryological development. This variation has not been reported previously. A similar observation was reported by Hovelacque (25) in 2 cases in which it was the medial cutaneous nerve of the forearm (MCF) or a collateral branch of the MCF that perforated the axillary vein. The venous anomaly described in this case has a number of implications for medical practice. Formation of 2 narrow venous channels in place of a single vein may enhance the incidence of thrombi and emboli in cases of prolonged hyperabduction, trauma, and surgery (26).

In the present case, the lateral cutaneous branch of the first intercostal nerve and the third intercostobrachial nerve supplied the upper part of the arm independently. However, there was no contribution from the ICBN of T_2 . Several variations of ICBN have been reported in the literature. Cunnick et al. (27) observed 6 different variations of the ICBN during axillary dissections of 45 patients, whereas Loukas et al. (27) observed 8 different arrangements in the ICBN in 200 axillae.

Few surgeons choose to sacrifice the ICBN during segmental mastectomy because this nerve carries a T_2 contribution to the brachial plexus, and its preservation is important. Damage to this nerve may have additional consequences beyond the deficits described for the axillary and pectoral regions (28,29). Block dissection of axillary lymph nodes and venipuncture procedures can induce nerve injuries resulting in chronic pain in the upper limb (30). Therefore, identification of this nerve and its variations is essential for its preservation as well as the avoidance of pain and paraesthesias.

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Case Report

Metallic Foreign Body Penetrating the Carotid Sheath: A Case Report

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Abstract -

Foreign bodies are a common problem seen in otolaryngological practice. Of the reported foreign bodies, metallic foreign bodies are a rare entity. One of the least common complications of foreign body ingestion is penetration and migration. We describe a case of a migrating metallic foreign body in a 50-year-old woman with a history of accidental ingestion causing odynophagia. In the present case, the foreign body migrated extraluminally into the carotid sheath. Our review of literature revealed that few such cases have been reported.

Keywords: : foreign bodies, foreign-body migration, medical imaging, metals, neck, otolyngology; head neck

Introduction

Ingested foreign bodies (FBs) are a common problem encountered in otolaryngological practice (1). However, only a small number of FBs perforate the wall of the aero-digestive tract, and an even smaller fraction migrate extraluminally (2). Although a migrating foreign body may remain quiescent, they may cause life-threatening suppurative or vascular complications; hence, location and removal is essential. Removal of embedded FBs can be quite challenging and frustrating because location of the FB is often quite difficult.

We present a case report of a migrating metallic foreign body that was found to be present lateral to the carotid sheath, with a relevant review of the literature.

Case Report

A 50-year-old female presented to the Otolaryngology Outpatient Department, St John's Medical College and Hospital (a tertiary care centre in Bangalore, South India) with complaints of a pricking sensation in her throat for 4 days. She had been examined at a district hospital, and serial radiographs were taken, which showed a foreign body in the right retropharyngeal area. The patient was referred to our centre for further management. An initial radiograph taken at the time of admission confirmed the presence of the foreign body in the right retropharyngeal area (Figure 1).



Figure 1: Foreign body visualised on a radiograph at the time of admission.

A rigid Hopkins endoscopy showed congestion in the region of the vallecula, with no foreign body (FB), casting doubt on extraluminal migration. Computed tomography (CT) of the neck with contrast showed the presence of a foreign body in the right lateral pharyngeal wall (Figure 2).

Case Report | Metallic foreign body penetrating the carotid sheath



Figure 2: Computed tomography image showing the foreign body in the lateral pharyngeal wall.

A careful search was made for the foreign body under general anaesthesia with intraoperative radiographic aid. The FB could not be located; thus, an open lateral cervical approach was used. Two needles were placed below the skin in the neck, and intra-operative radiographs were taken to locate the foreign body (Figure 3). An oblique incision was made from the hyoid bone to the thyroid cartilage, and the lateral pharyngeal wall was exposed. Another attempt was made to visualise the foreign body using direct laryngoscope-assisted trans-illumination from the oral cavity. This again proved to be unsuccessful.

On further neck exploration, the foreign body (a metallic wire) was found to be embedded in the carotid sheath (Figure 4) and was removed (Figure 5). The neck wound was closed in layers, and a size 16 nasogastric tube was passed. The patient's post-operative recovery was uneventful, except for throat pain, which persisted for 2 weeks post-operatively.





Figure 3: (a) Needles placed below the skin to help locate the foreign body.

(b) Foreign body with the two needles seen on an intraoperative radiograph.



Figure 4: Foreign body found embedded in the carotid sheath.



Figure 5: Foreign body post-removal.

Discussion

Impaction of foreign bodies in the upper aero-digestive tract has been reported since early history. Foreign bodies can be lodged in the tonsils, the base of the tongue, pyriform the fossa, and the cervical oesophagus. Only rarely do foreign bodies penetrate the wall of the aero-digestive tract, and even more rarely do they migrate into the soft tissue and viscera of neck (3).

Larger and sharper FBs get stuck in the pharynx or oesophagus, causing symptoms that require their removal by oesophagoscopy. In the pharynx, FBs usually become lodged in the vallecula or lymphoid tissue, particularly the hypertrophied tonsil or tongue base. Those FBs in the oesophagus commonly remain stuck below the upper oesophageal sphincter. Foreign bodies that are sharper and those that are more horizontally oriented have a higher chance of penetrating the wall of the aero-digestive tract (4).

The possible mechanisms for penetration of foreign bodies include a combination of oesophageal peristalsis and neck movements or careless manoeuvres used when trying to remove it, for example, using fingers for balloons (4,5). Foreign bodies may also introduce bacteria into the soft tissue of the neck and cause suppurative complications such as parapharyngeal or retropharyngeal abscess (2).

A barium swallow is of limited value in locating migrated foreign bodies but can be useful in detecting oesophageal leaks (5). The most commonly used tool for foreign body identification is radiography of the soft tissues of the neck. However, images of the foreign body and calcified cartilage of the upper airway may overlap, making location of the foreign body difficult. Thus, radiographs lack sensitivity in diagnosis (2,6). A CT scan of the neck utilising 1-mm cuts is the investigative method of choice. CT scans are invaluable in confirming the exact location of the foreign body and its relationship to the vital structures in the neck.

However, CT scans are not without their drawbacks. The soft tissues of the neck are mobile in relation to the bony and cartilaginous structures; thus, at the time of surgery, the foreign body may not be situated exactly as where it is seen in the CT, as in our case (1,5).

Direct laryngoscopy may be done for confirmation. A finding of oedema, laceration or ulceration on direct laryngoscopy should raise the level of suspicion of a penetrating foreign body (2). Exploration and removal of the foreign body via an external approach is recommended if the foreign body is confirmed to be extraluminal. Surgery may be supplemented with intraoperative radiography for accurate location of the foreign body. However, due to their poor image quality, intraoperative radiographs are not routinely used, but they come in handy as a last resort in cases in which the foreign body cannot be found after an extensive search (2).

Foreign body fixation to organ walls may lead to perioesophagitis or peripharyngitis, which can result in an abscess. Perforation may lead to fever, chest pain, subcutaneous emphysema, dyspnoea, and dysphagia. Migrating foreign bodies may rupture large vessels such as the carotid or aorta, and foreign bodies can damage neighbouring organs such as the thyroid gland. In some cases, the long duration of symptoms may be the only hint of the presence of an intraluminal foreign body (4).

Conclusion

Our case highlights the need for a high index of suspicion to detect perforation and migration of an ingested foreign body into the soft tissues of the neck. Prompt diagnosis is needed to prevent the high morbidity that can occur in such cases. The majority of the upper aero-digestive foreign bodies are intraluminal and can be removed by endoscopy; therefore, it is cost effective to do CT scans in cases of foreign bodies that could not be located and removed endoscopically or in which the symptoms have persisted for long duration. A systemic approach to neck exploration via an external approach, with the use of intraoperative radiography, will decrease the chances of an unsuccessful exploration.

Authors' Contributions

Conception and design: HV Drafting of the article: ABN Final approval of the article: NR

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Case Report

Acute Acalculous Cholecystitis after Laparoscopic Appendicectomy that Responded to Conservative Management

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Abstract

Inflammation of the gallbladder without evidence of calculi is known as acute acalculous cholecystitis (AAC). AAC is frequently associated with a poor prognosis and a high mortality rate. Thus, early diagnosis and prompt surgical intervention has been recommended to improve the outcome of AAC. Herein, I present a case report of AAC complicating laparoscopic appendicectomy. Unlike previous studies that have reported the need for urgent intervention in patients with AAC, in this study, our patient responded to conservative management. Therefore, the management of AAC after laparoscopic appendicectomy should be individualised.

Keywords: acalculous cholecystitis, acute disease, appendicitis, gut, laparoscopic surgery, appendicitis, disease management

Introduction

Inflammation of the gallbladder without evidence of calculi is known as acute acalculous cholecystitis (AAC). Inflammation of the gallbladder without evidence of calculi is known as acute acalculous cholecystitis (AAC); this condition occurs in 5%-15% of all cases of acute cholecystitis (1). AAC is frequently associated with gangrene, perforation, and empyema. Due to these associated complications, AAC can be associated with high morbidity and mortality (2-3). AAC has been reported in critically ill patients after cardiac surgery, abdominal vascular surgery, trauma, burns, prolonged fasting with or without total parenteral nutrition, sepsis, or atherosclerotic vascular disease (2-3). Here I present a case of AAC arising as a complication of laparoscopic appendicectomy.

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A 53-year-old woman with previously good health presented with an acute onset of abdominal pain. The acute abdominal pain initially occurred at the umbilical area and migrated to the right lower quadrant after 12 hours. Examination of the abdomen on presentation revealed tenderness over McBurney's point with rebound and rigidity. Computerised tomography imaging of the abdomen and pelvis revealed an inflamed appendix in the right iliac fossa with a diameter of 1.5 cm. The appendix had a fluffy border with surrounding soft tissue strands. Wall thickening in the caecum was also present. Laboratory studies performed on admission were unremarkable except for an elevated C-reactive protein (CRP) level of 14 mg/L (normal range less than 10 mg/L).

The patient was started on intravenous tigecycline, and a laparoscopic appendicectomy was performed within 2 hours of admission. The procedure was uncomplicated with no episodes of haemodynamic instability during the pre-, intra-, and post-operative periods. Microscopic examination of the appendix revealed features of acute appendicitis, with focal mucosal erosions, suppurative changes, and serositis. The patient resumed a fluid diet on Day 1 post-laparoscopic appendicectomy. As she tolerated the fluid diet well, she resumed a soft solid food diet on Day 2 post-laparoscopic appendicectomy.

However, on Day 3 post-laparoscopic appendicectomy, the patient developed right upper quadrant discomfort. Physical examination of the abdomen revealed tenderness over the right upper quadrant, but there was no evidence of rebound or rigidity. Although she remained afebrile, her CRP had increased to 56 mg/L. No

Case Report | Acute acalculous cholecytitis

other abnormality was detected in the complete blood work-up or in the amylase and liver biochemistry.

Computerised tomography imaging of the abdomen was repeated, and a small amount of fluid was seen in the gallbladder fossa. The gallbladder wall was also thickened with prominent contrast enhancement (Figure 1). However, no radiopaque stone was seen in the gallbladder or bile ducts. The common bile duct and the intrahepatic tree were normal in size. No abnormal mass, focal fluid collection or abscess was seen in the right iliac fossa. There was also no abnormal free fluid in the lower abdomen or pelvis. Therefore, based on her right upper quadrant discomfort, right upper quadrant tenderness, the presence of fluid in the gallbladder fossa, and the thickened gallbladder wall with contrast enhancement, she was diagnosed with AAC arising as a complication of laparoscopic appendicectomy.

As the patient was haemodynamically stable, she was managed conservatively. In addition to intravenous tigecycline, which had been commenced on the day of admission, the patient was also started on intravenous meropenem and amikacin. On Day 6 post-laparoscopic appendicectomy, her symptoms started to improve. Her CRP on Day 6 post-laparoscopic appendicectomy had decreased to 32 mg/L. On Day 7 post-laparoscopic appendicectomy, her CRP normalised to 9 mg/L. As she remained asymptomatic with a normal CRP, the patient was discharged on Day 14 post-laparoscopic appendicectomy. Her liver biochemistry and amylase levels were normal throughout the course of her hospitalisation.

Discussion

AAC following surgery was first reported in 1844 (4). Since then, AAC has been reported to occur following cardiovascular surgery, aortic reconstruction, non-biliary tract procedures, and breast reconstruction (5–8). To the best of my knowledge, this is the first report of AAC complicating laparoscopic appendicectomy.

The pathogenesis of AAC is postulated to be diverse and has been called "a paradigm of complex inter-relationships" by Barie et al. (9). However, the common denominator for this set of disease states is visceral hypotension (3). As de novo AAC has been reported in healthy patients without any co-existing illness, I believe that in this woman, the AAC complicating laparoscopic appendicectomy was due to biliary stasis that worsened as the result of a spasm of the cystic



Figure 1: Computerised tomography images showing (A) a normal gallbladder on the day of admission for acute appendicitis and (B) a small amount of fluid in the gallbladder fossa with thickened gallbladder walls with prominent contrast enhancement.

duct, as postulated by Becker et al. (10). The administration of morphine during the immediate post-operative period may have aggravated the spasm of the cystic duct in this patient (10).

AAC is frequently associated with a poor prognosis and a high mortality rate (1,2). Thus, investigators have recommended early diagnosis and prompt surgical intervention to improve the outcome of AAC. However, this recommendation was based on studies in which the subjects had multiple co-morbidities or severe illness, or they were elderly patients (1,2).

The patient described in this case report recovered with conservative management and did not require surgical intervention. Therefore, the management of AAC in post-operative patients should be individualised. The clinical condition and pre-morbid condition of the patient must be considered in the formulation of the treatment strategy.

In conclusion, this is the first case report of AAC complicating laparoscopic appendicectomy in a patient with no existing co-morbidity. The management of AAC in post-operative patients with no co-morbidity should be individualised.

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Case Report

Knee Joint Pain May Be an Indicator for a Hip Joint Problem in Children: A Case Report

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Abstract [·]

Knee joint pain is one of the most common complaints related to the skeletal system encountered by paediatricians. Knee joint pain generally occurs as the result of hypermobility and growing pains, though disorders manifesting as arthritis/arthralgia and orthopaedic problems should be considered in the differential diagnosis. A thorough and careful physical examination and laboratory and radiological findings are of importance for an accurate diagnosis. Although treatment should be based on the aetiology of the knee pain, non-steroid anti-inflammatory drugs can be used to alleviate the pain. A 7-year-old male patient presented with recurring pain in the left knee. Physical examination of the patient, laboratory tests, and radiological examination of the knee joint were normal; roentgenograms performed for a presumed hip joint problem revealed a focal cortical defect on the left femoral head and an increased effusion in the left hip joint space compared with the right counterpart. With this case report, we would like to highlight that paediatric health and diseases specialists (paediatricians) should consider hip joint pathologies when patients present with knee pain, particularly knee pain with an unidentified aetiology.

Keywords: : children, diagnosis, hip, joint pain, knee, referred pain

Introduction

Complaints relating to the musculoskeletal system represent the reasons for 6.1% of visits to paediatric clinics, and the complaint of knee pain accounts for approximately 33% of these visits (1). Anterior knee pain defines a complaint of pain in the anterior part of the knee. This complaint typically arises from the patellofemoral joint and the surrounding tissues that reinforce this joint; however, with regard to the epidemiology of and the approach to knee pain, it may occur in association with hypermobility of the knee joint (2) and osteochondrosis during adolescence (3).

Knee pain seen in children may have several orthopaedic causes. Sinding-Larsen–Johansson syndrome (SLJ), Osgood–Schlatter syndrome (OSS), patellar tendinitis, patellofemoral syndrome, fat pad syndrome (FPS), plica syndrome, lateral retinacular pain (LRP), iliotibial band syndrome (ITBS), osteochondritis dissecans, joint mouse, meniscus tear, ligament tear, and chondral injuries can cause anterior knee pain leading to internal irregularity in the knee (4). Other causes of knee pain may be diseases causing inflammation such as juvenile rheumatoid arthritis, infection, and neoplasms. Childhood knee pain may be a sign of an orthopaedic disorder or a systemic disease, or it may be referred pain. It should be kept in mind that the actual reason for paediatric knee pain may be referred hip joint pain. In the patients with no identifiable pathology on knee examination, hip examination must always be performed. The pathologies of the hip that may lead to knee pain are developmental dysplasia of the hip, transient synovitis, slipped capital femoral epiphysis, septic arthritis of the hip, sickle cell anaemia, stress fractures of the hip, and Legg–Calve–Perthes disease (4).

Case Report

A 7-year-old male patient presented to our polyclinic with the complaints of the pain in the left knee and impeded walking beginning 2 weeks prior. His pain became worse with activity; however, sometimes he also suffered from pain during rest. The medical history of the patient revealed that he had visited an orthopaedic clinic 9 months earlier; the roentgenograms of the knee and laboratory tests were normal, and he was

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prescribed non-steroid anti-inflammatory (NSAI) drugs. His pain was relieved by these drugs within 1 week. The previous medical history of the patient was unremarkable, and no other person in his family had similar complaints. On physical examination, vital signs were stable. There was no recognisable warmth, hyperaemia or swelling in the joints, but movements of the left knee and the left hip were painful. Examination of other areas was normal.

Laboratory test results were as follows: haemoglobin 12.9 g/dL, white blood cell count 11 300/mm³ (on peripheral blood smear, 58% neutrophils, 33% lymphocytes, 9% monocytes), erythrocyte sedimentation rate (ESR) 8 mm/h, antistreptolysin O titre <25 U/mL, rheumatoid factor (RF) negative, C-reactive protein (CRP) <1 mg/dL, alkaline phosphatase 243 U/L, calcium 8.4 mg/dL, and tube agglutination tests for the presence of the antibodies against Salmonella and Brucella were negative. On the radiological examination, two-sided radiographs of the left knee were normal. Anteroposterior comparative radiography of the hip was performed, followed by magnetic resonance imaging (MRI) of the left hip because of a focal lytic lesion observed on the left femoral head (Figure 1). A focal cortical defect on the left femoral head and an increased effusion in the left hip joint space compared with the right counterpart were identified (Figure 2). A specific diagnosis was not made radiologically. Needle biopsy was not suitable because of the anatomic location of the lesion, the technical difficulty, and the necessity of anaesthesia. Surgical biopsy was not performed because of the risk of avascular necrosis of the femur. The patient was recommended for follow-up for an assumed benign bone tumour (e.g., chondroblastoma or eosinophilic granuloma) in early initial stage, and the use of crutch was recommended. Treatment with NSAI drugs was started to alleviate his pain. Two months later, on clinical evaluation of the patient, his complaints had regressed; however, no change was observed on the plain radiographs. He is being followed for the hip joint pathology.

Discussion

Knee pain is a commonly encountered problem in children and adolescents, with a prevalence ranging 4%–30% (5). Diagnosis requires obtaining a careful medical history and doing physical examination because knee pain is a non-specific complaint. Localisation, character, time of onset, duration of the pain, association with activity or resting, factors that aggravate



Figure 1: Anteroposterior radiograph of the hip revealing a focal lytic lesion on the left femoral head



Figure 2: Magnetic resonance image of the left hip confirmed a focal cortical defect on the left femoral head and revealed an increased effusion in the left hip joint space

or relieve the pain, mechanical symptoms, neurological symptoms, trauma, inflammatory changes, haemorrhagic diathesis, and the response to analgesics must be determined. For the differential diagnosis, it is important to do a thorough and detailed examination for systemic diseases as well as local signs such as swelling, redness, and tenderness of the joint affected.

For diagnosis, complete blood count, CRP, and ESR are laboratory tests that should be completed initially; however, the results of these tests may not always be instructive. Microbiological and rheumatological tests directed to aetiology may be done using both blood and synovial fluid, when needed (6,7). The imaging method that should be used first for the diagnosis is plain radiography. In some cases, magnetic resonance imaging may be required.

Much of childhood knee pain results from hypermobility of the joint, transient synovitis, slipped capital femoral epiphysis (SCFE), or growth-related factors in adolescents (2). SCFE can present with vague knee pain in adolescents, and hip radiographs should be obtained to rule out this disease. Joint hypermobility and growthrelated factors are generally self-limiting and have good prognoses. Growing pains occur in children aged between 4-8 years; occur bilaterally in the thighs, calves or behind the knee; and are generally intermittent. Physical examination and laboratory tests were normal (6). Although our patient was in the proper age range for pain relating to growth or joint hypermobility, non-organic pathologies were ruled out in the differential diagnosis because of painful movements of the left knee.

Organic causes of childhood knee pain result from orthopaedic, infectious, or rheumatologic disorders or malignancies. Septic arthritis of the knee joint, osteomyelitis, brucellosis, tuberculosis, viral infections, enteric infections, and subacute bacterial endocarditis are examples of knee pain with an infectious aetiology (8). On physical examination, systemic symptoms and arthritis signs are generally present. In laboratory tests, acute phase reactants are noticeably increased. In our patient, knee pain of an infectious aetiology was not considered because arthritis signs were not present, and the results of laboratory tests were normal.

Almost all connective tissue disorders, especially juvenile rheumatoid arthritis, vasculitis, certain systemic diseases (such as rheumatic fever, lupus erythematosus, and familial Mediterranean fever), leukaemia, lymphoma, and bone and soft-tissue tumours may manifest as knee pain, leading to arthritis/arthralgia. All of these diseases may manifest as multi-systemic symptoms that can easily be distinguished from other pathologies by physical examination, laboratory tests, and radiological studies (6). For our patient, infectious and rheumatological diseases and malignancies were not considered because the physical examination, laboratory test results, and radiological results were normal.

Childhood knee pain may be an indicator of orthopaedic problems involving the knee and surrounding structures. Trauma is a commonly encountered problem. Patient history and radiological imaging are helpful for the diagnosis. SLJ, OSS, patellar tendinitis, patellofemoral syndrome, FPS, plica syndrome, LRP, and ITBS may also cause knee pain. In these diseases, tenderness of the tendon or at its attachment site is present, and pain occurs especially during sportive activities. Osteochondritis dissecans, meniscus tear, ligament tear and chondral injuries also cause knee pain (4). In these diseases, generally a severe trauma has occurred, and symptoms such as stiffness and locking of the knee occur. When these diseases are suspected, MRI must be done for diagnosis. Our patient had no history of trauma, he could not localise the pain exactly, and pain occurred during rest as well as during activity. Because of the characteristics of the pain, the physical examination, and the normal radiological findings, orthopaedic problems involving knee were ruled out.

Knee pain may originate from a hip pathology. Because the knee joint is a more superficial joint than the hip joint, and because the nerves of the anterior knee consist of the articular branches of the femoral, common peroneal, and saphenous nerves, a painful and tender knee joint usually indicates an anomaly in the knee (7,9). The actiology of pain referred from the hip to the knee may be the innervation of the anterior branch of the obturator nerve or of the articular branches of the femoral, common peroneal, or saphenous nerves. However, pain referred from hip may be perceived as knee pain (10). Hip pathologies that may lead to knee pain include developmental dysplasia of the hip, septic arthritis of the hip, sickle cell anaemia, SCFE, stress fractures of the hip and Legg-Calve-Perthes disease (4). Legg–Calve–Perthes disease-an idiopathic avascular necrosis/osteonecrosis of the femoral epiphysis-usually affects 4- to 10-year-olds and peaks between 5- and 7-year-olds. Children usually present with a limp or pain in the hip, thigh, or knee. Examination of the knee is normal, but there is limited and painful rotation and abduction of the ipsilateral hip. Radiographs vary with the stage of the disease but may show evidence of bone necrosis, fragmentation,

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reossification, or remodelling and healing (10). SCFE—displacement of the proximal femoral epiphysis off of the femoral neck—usually affects 11- to 14-year-olds, is more common in obese children and boys, and is bilateral in 20%–40% of cases (10). Anteroposterior (AP) and frog-leg radiographs of the hip may show widening and irregularity of the physis with posterior inferior displacement of the femoral head. On the AP view, a line drawn from the superior femoral neck (Klein's line) should intersect some portion of the femoral head (10).

In the literature, 2 childhood cases presenting with the complaint of knee pain resulting from hip pathologies have been reported. In 1 case, a 3-year-old child presented with pain localised medially on the left knee, as reported by Van Ommeren et al., and hip dislocation secondary to trauma was found (11). Similarly, Meek et al. found chondrolysis of the hip secondary to septic arthritis caused by Pseudomonas aeruginosa during the examination of a child who presented with knee pain (12). In our patient, recurrent knee pain was the reason for the visit to the doctor; an orthopaedic consultation was requested because the result of the physical and laboratory examinations were normal. The knee pain of the patient was related to the pathology of the hip joint; MRI revealed a focal cortical defect on the left femoral head. The patient's weight-bearing was restricted to movements supported by the clutch, and his complaints were relieved. He is still under follow-up for the hip joint pathology.

Conclusion

Childhood knee pain is a condition that requires a multidisciplinary approach. Knee pain may originate from the knee and the surrounding tissues; however, it may also be an indicator of a systemic disease or an unrelated orthopaedic problem. We conclude that examination of a patient complaining of knee pain is not complete without hip examination. We presented this case to remind physicians that hip joint pathologies can lead to knee pain and that this fact must be considered when evaluating the complaint of knee pain, which is commonly encountered by paediatricians.

Authors' Contributions

Conception and design: AEY Provision of patients: MB Analysis and interpretation of the data: HA Critical revision of the article: SK Final approval of the article: TT

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