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Editorial

Multiple Submissions of Scientific papers; editor's dilemma

Submission of a scientific paper to several journals simultaneously (multiple submissions) is not new. All journals discourage multiple submissions due to obvious reasons. International Committee of Medical Journal Editors (ICMJE) in 2008, stated that all authors should indicate clearly in the covering letter that the particular manuscript has not been published, accepted by another journal or is not under consideration elsewhere.

Multiple submissions lead to waste of time of editors and reviewers. Journals have limitations with regards to reviewers. Mostly reviewers work entirely on voluntary basis and it is not appropriate to waste their precious time. In addition, multiple submissions can lead to multiple publication of the same manuscript.

Editors of the Galle Medical Journal constantly remain vigilant about multiple submissions. There are no proven methods to detect multiple submissions. We request all authors and scientists who submit their work to GMJ to refrain from this practice.

Sarath Lekamwasam

Eisha Waidyarathne

Editors / GMJ

GALLE MEDICAL JOURNAL; INSTRUCTIONS TO AUTHORS

The Galle Medical Journal is published by the Galle Medical Association. The *journal* is published biannually, March and September and the submissions are accepted throughout the year. The aims of the Journal are to foster co-operation among the medical fraternity and to be a forum to make literary contributions, share experiences encountered in medical practice, update their knowledge and have debates on topics related to all aspects of medicine. Also, we attempt to cater to the educational needs especially of the postgraduate trainees. The *Journal* publishes original articles, reviews, leading articles and case reports. When an article is reviewed for publication we expect that the work it reports has not been published, submitted simultaneously to another journal or accepted for publication elsewhere. All manuscripts will be reviewed anonymously before acceptance.

Manuscripts must be submitted with the text type written in 12-point Times New Roman font double spaced. Text and all illustrative material should be submitted in two hard copies and the electronic version in Microsoft Word document format. In order to avoid delay we require authors to comply with the following requirements. **All manuscripts should accompany a covering letter indicating the number of words in the manuscript, institution where ethical clearance was granted, conflict of interests and contact details of the corresponding author.**

Types of contributions:

Review articles and Leading articles: We encourage submission of review or leading articles which are less than 3000 words in length and address topics of current interest. They should be supported by no more than 20 references. Submissions may be subjected to external review before acceptance.

Original articles: Should normally be in the format of introduction, methods, results and discussion. Each manuscript must have a structured abstract of 200 words. The text should be limited to 3000 words and maximum of 5 tables/figures taken together with no more than 15 references. Lengthy manuscripts are likely to be returned for shortening. The discussion in particular should be clear, concise and should be limited to matters arising directly from the results. Avoid discursive speculation.

Case Reports: These should not exceed 750 words and 5 references; no abstract is required. Case report should be informative and devoid of irrelevant details.

References:

These should conform to the Vancouver style. The reference in the text should be numbered consecutively in Arabic numerals in parentheses in the same line of the text in the order in which they appear. The first five authors should be listed and if there are more than five, then the first three should be listed followed by et al. Examples are given below:

1. Kumar A, Patton DJ, Friedrich MG. The emerging clinical role of cardiovascular magnetic resonance imaging. *Canadian Journal of Cardiology* 2010; **26**(6): 313-22.
2. Calenoff L, Rogers L. Esophageal complication of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 23-63.

Units/Abbreviations

Authors should follow the SI system of units (except for blood pressure which is expressed in mmHg). Authors should use abbreviations sparingly and they should be used consistently throughout the text.

Manuscripts that do not conform to these requirements will be returned for necessary modifications.

Manuscripts should be addressed to Chief Editors, Galle Medical Association, Teaching Hospital, Karapitiya and all soft copies should be sent to gmathk@gmail.com

Usefulness of Trans-Thoracic Echocardiography (TTE) in patients with acute ischaemic strokes and normal clinical cardiac examination

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ABSTRACT

Introduction: Stroke is one of the leading causes of disability and mortality in Sri Lanka. Cardiac sources of embolism account for 15 - 30% of ischaemic strokes. For optimal treatment aiming at secondary prevention it is crucial to identify the source of the embolism. We aimed to assess the influence of routine echocardiography in the management of patients with ischaemic strokes who have no evidence of cardiac abnormality on routine medical history, physical examination or 12-lead ECG.

Methods: Transthoracic echocardiography (TTE) was performed in patients admitted to Professorial Medical Unit, Teaching Hospital Karapitiya with an acute ischaemic stroke and normal clinical cardiac evaluation including a 12-lead ECG. The echo findings were categorized as therapeutically significant or insignificant by the cardiologist who performed the echo and the treating physician.

Results: Of the 110 patients with acute ischaemic stroke with normal clinical cardiac evaluation, 14.5% had therapeutically significant echo findings; left ventricular systolic dysfunction with ejection fraction <35% in 13 (11.8%), left ventricular aneurysm with intraventricular clot in 2 (1.8%), and tight mitral stenosis in 1 (0.9%).

Conclusions: In this study, TTE revealed cardiac abnormalities that need specific treatment in 16 (14.5%) patients with acute ischaemic stroke with normal clinical cardiac evaluation. TTE should be considered an essential test in the evaluation of all ischaemic stroke patients regardless of the clinical findings.

Key Words: Transthoracic echocardiography, ischaemic stroke, Sri Lanka.

Introduction

Stroke is one of the leading causes of disability and mortality in Sri Lanka. Ischaemic stroke accounts for about 70 – 80% of all strokes and is caused by embolic or thrombotic occlusions in the cerebral vessels (1). Large artery atherosclerosis is the commonest aetiology of ischaemic strokes. Further, cardiac sources of embolism account for 15 – 30% of the cases (1). The latter is associated with poor prognosis and fatal recurrences. In order to establish an optimal preventive strategy it is crucial to identify the source of the embolism.

To find the cardiac source of embolism a detailed medical history and physical examination are required. In addition, ECG and chest radiograph are routine investigations performed in order to find cardiac abnormalities which can be potential sources of embolization. There is a considerable disagreement, however, among clinicians regarding the extent of cardiac testing that should be performed in patients with ischaemic stroke, especially in less resourceful settings (2).

The routine use of echocardiography in all patients with ischaemic strokes is debatable, particularly when the detailed history, physical examination and

ECG fail to show any evidence of previous or ongoing cardiac pathology (2). Furthermore, routine echo may show the existence of cardiac abnormalities which are unlikely to be the cause of ischaemic stroke, hence have no therapeutic implications. They include degenerative changes in the cardiac valves especially mitral and aortic valves.

A recent hospital based study from Canada involving patients with ischaemic strokes reports that TTE has a low yield, diagnosing only 4% of significant cardiac abnormalities (2). A similar single centre study from Pakistan revealed 15.5% patients to have TTE abnormalities suggestive of cardioembolic aetiology (3). We were unable to find previous studies with similar objectives done in Sri Lanka.

Therefore this study was planned to assess the usefulness of routine echocardiography in patients with ischaemic strokes who have no evidence of previous or ongoing cardiac abnormality on routine medical history, physical examination or 12-lead ECG.

Methods

This study was carried out in the Professorial Medical Unit of Teaching Hospital Karapitiya which is the largest hospital in the Southern province with the highest patient turnover. Consecutive patients with acute ischaemic strokes admitted to the above unit via outpatient department were included in the study. Medical Professorial Unit receives about 30 patients with acute ischaemic stroke per month.

All patients admitted with acute focal neurological deficit underwent urgent cranial CT imaging. All the CT images were examined for the presence of cerebral bleeding that can explain the clinical presentation. Those with normal CT images as well as those with CT evidence of recent cerebral ischaemia were considered to have cerebral infarctions and were eligible for this study. They all underwent routine vascular screening and TTE. For this analysis only those patients who had normal complete clinical cardiac evaluation (history and examination) and 12 lead ECG were considered. We included 110 consecutive patients for the study. An interviewer administered questionnaire was used as the study instrument. Cardiovascular examination, ECG and ECHO findings were also included in this questionnaire.

The echo findings were categorized as therapeutically significant (those needing further cardiac investigations or interventions) or therapeutically insignificant (age-related and those not needing further investigations or interventions). Categorization was done by caring physician in consultation with cardiologist who performed the TTE.

The ethical clearance for the study was obtained from the Ethics Committee Faculty of Medicine, University of Ruhuna, Sri Lanka.

Results

Out of 110 subjects in the sample, 60 (54.5%) were males. Fifty eight (52.7%) of patients were within 50-70 year age range. Fourteen (12.7%) were below 50 years and 38 (34.6%) were above 70 years of age. Majority of the sample (62.8%) belonged to either Social class 3 or 4.

When risk factors were assessed, hypertension was the most common risk factor identified in this study. Seventy (63.6%) had hypertension, 29 (26.4%) had diabetes mellitus and 31 (28.2%) had evidence of dyslipidaemia.

Thirty five (31.8%) were smokers.

Past history of stroke and transient ischaemic attacks was observed in 9 (8.2%) and 7 (6.3%) of individuals, respectively. Twenty (18.2%) participants had family history of ischaemic heart disease and 20 (18.2%) had family history of stroke.

In the sample, 62 (56.4%) had normal BMI while 47 (42.7%) were either overweight or obese and only 1 (0.9%) had low BMI.

Of 110 patients, CT evidence of cerebral infarction was evident in 69 (62.7%) of individuals.

Therapeutically significant echocardiographic findings were detected in 16 (14.5%) of study participants. They were, left ventricular ejection fraction < 35% in 13 (11.8%), left ventricular aneurysm with a thrombus in 2 (1.8%) and tight calcific mitral stenosis in 1 (0.9%).

Discussion

In our study sample, 14.5% of patients with acute ischaemic stroke, with complete clinical

cardiac evaluation, had therapeutically significant transthoracic echocardiographic findings: left ventricular systolic dysfunction with an ejection fraction <35% (11.8%), left ventricular aneurysm with a thrombus (1.8%) and tight calcific mitral stenosis (0.9%).

A recent hospital-based study from Canada reports that transthoracic echocardiography has a low yield, diagnosing only 4% of ischaemic stroke patients with abnormalities suggesting cardio embolic aetiology (2). In contrast, another single centre study from Portugal reveals 37.2% of ischaemic stroke patients with transthoracic echocardiography abnormalities suggestive of cardio embolic aetiology and the authors recommended the use of echocardiography as a routine procedure in all stroke patients(1).

There was an 11.8% of patients with asymptomatic left ventricular systolic dysfunction with ejection fraction < 35% in our study. Literature review revealed that the prevalence of stage B heart failure (reduced left ventricular ejection fraction without symptoms of heart failure) varied between 12.9% and 21.4% in the community and also increased with age (4, 5). Furthermore, diabetes and hypertension have been identified as the most important underlying causes of heart failure and they were prevalent among our study participants (5,7). Tight calcific mitral stenosis is usually clinically inaudible and left ventricular aneurysm with an apical thrombus also cannot be diagnosed on clinical evaluation.

Current guidelines do not recommend transthoracic echocardiography as a routine test to evaluate patients with stroke with low risk of embolic aetiology. However, in this study, TTE findings changed the management plan of 14.5% of patients with acute ischaemic stroke with normal clinical cardiac evaluation. Therefore, we believe that these findings support the idea that transthoracic echocardiogram should be a compulsory investigation in the evaluation of all acute ischaemic stroke patients regardless of the clinical findings.

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Assessment of aesthetic and functional improvement of patients with mid-facial hypoplasia corrected using mid maxillary osteodistraction (MMOD) with a tooth-borne distractor

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ABSTRACT

Introduction: A method of mid maxillary distraction osteogenesis using tooth borne custom-made device is being performed on cleft patients in Oral and Maxillofacial unit, Teaching Hospital, Karapitiya, Sri Lanka, over the past ten years. The technique is simple, inexpensive and less time consuming. Aims of this study were to assess the level of improvement of maxillary unit length, facial appearance and quality of speech of patients following correction of mid facial hypoplasia using MMOD.

Methods: Patients with midfacial hypoplasia (n : 10, M : F – 1 : 1, Age range : 14-22 yrs) surgically corrected with MMOD technique during 2013 were included. Increase of maxillary unit length, SNA & ANB angles and over-jet were assessed with study-models and cephalometric analysis pre-surgically and one year after surgery. The quality of speech was assessed using resonance, nasal air emission and consonant production error pre and post surgically.

Results: All patients showed positive over-jet increase (mean: 4.3 mm) and improved anterior-posterior dimensions of maxilla (SNA mean increase: 8.5° , ANB mean increase: 8.8° and average increase of Maxillary Unit Length/ANS - PNS: 6.2 mm). Findings were statistically significant ($p < 0.05$). All patients accepted their current facial appearance. 60% of patients showed reduced hyper-nasality and nasal air emission in speech.

Conclusions: MMOD is a less expensive, less invasive orthognathic surgical procedure where adequate distraction is possible with minimum relapse. Bone formation on either side of osteotomy cuts expand soft tissues as well, to improve facial aesthetics and reduce velo-pharyngeal insufficiency to improve speech.

Key words: Mid-maxillary distraction osteogenesis, tooth- borne appliance.

Introduction

Congenital oro-facial clefts and related growth defects are prime causes of maxillary/ mid facial hypoplasia (1). Repaired cleft lip and palate itself have a negative impact on mid-facial growth. Sixty percent of children with surgically corrected cleft lip and palate will require correction of maxillary hypoplasia and 25% of them are beyond the boundaries of conventional orthodontic treatments (1). Class III skeletal base, crowded upper-arch with insufficient alveolar space and clefts causing

malocclusion, facial profile defects in all three planes(mainly due to mid facial retrusion) and altered soft tissue harmony in nose, orbit and upper lip have negative functional and aesthetic/social impact on these patients. Under-developed and insufficient length of soft palate causes speech and swallowing problems due to velo-pharyngeal insufficiency (VPI). Moderate maxillary hypoplasia usually associated with oro-facial clefts can be managed with mid maxillary osteo-distraction (MMOD) technique.

Distraction osteogenesis (DO) is the surgical technique in which new bone formation is induced by gradual separation of bony segments after a precise osteotomy. The method produces unlimited quantity of living bone directly by controlled mechanical distraction of the bony segments. The concept of bone lengthening by distraction was described by Codivilla in 1905 and proven by Ilizarov a Russian surgeon in 1951 by applying it to lengthen limbs (2). The use of DO on craniofacial skeleton was introduced by McCarthy in 1992 to correct a congenital hypoplastic mandible (3).

DO comprise of four basic steps as osteotomy phase, latency phase, distraction phase and consolidation phase. Gradual expansion of surrounding soft tissues, muscles and mucosa adapt to the bony changes causing increase in the size of soft tissue envelope. This is known as distraction histogenesis which enables minimum relapse comparing to advancement osteotomy procedures (4,5).

Le Fort I level osteo-distraction was initially used for correction of moderate maxillary hypoplasia in cleft patients (6), but jutting out activation devices on maxillary vestibules cause continuous intra-oral trauma and not aesthetically pleasing to wear for a long time.

Anterior-posterior unidirectional tooth-borne intra-oral distraction device (1) was invented to over-come the situation. This technique is being practiced at Oral and Maxillofacial Unit (OMFU), Teaching Hospital Karapitiya, Sri Lanka since 2002; at present about 15-20 patients per year are treated using MMOD for correction of mid-facial hypoplasia. It is a definitive surgery mostly performed at the age of growth completion to gain aesthetic and functional improvement on patients who underwent initial surgical corrections for mid facial defects (cleft palate with or without cleft lip).

Aim of this study was to emphasize the importance and validity of this less invasive and inexpensive specific surgical procedure, which is a favorable option with utilization of available facilities in Sri Lanka.

Methods

Patients with mid-facial hypoplasia secondary to repair of cleft palate with or without cleft lip (n-10, M : F – 1 : 1, Age range : 14 - 22 yrs) surgically

corrected with MMOD technique during 2013 were included in this series. Over-jet and increase of maxillary unit length [distance between anterior nasal spine (ANS) to posterior nasal spine (PNS)] assessed with cephalometric analysis and study-models pre-surgically and one year after surgery. The quality of speech was assessed using resonance, nasal air emission and consonant production error pre and one year post surgically by a speech and language therapist. Patients' appearance and acceptance were assessed by a short interview.

Surgical procedure

All patients had undergone pre-operative orthodontic treatments to create surgical space in the maxillary arch for osteotomy cuts. Nickel-Titanium coil springs were used to achieve the desired root separation for osteotomy cuts preferably between the maxillary second premolar and first molar teeth. Where this was not achievable, a space created between the first and second maxillary molar teeth became the alternative choice (1).

Custom-made tooth-borne distractor was constructed with orthodontic guidance on study model (Figure: 1). Molar and premolar bands were soldered to orthodontic hyrax screw for construction of the distraction device. The screw was aligned in the sagittal plane to achieve an antero-posterior vector with slight inclination anteriorly.

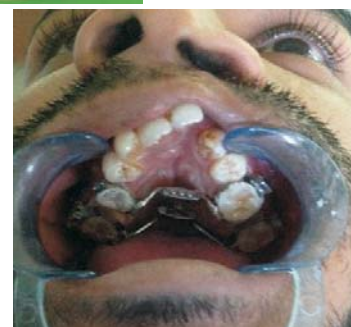


Figure 1: Distraction device on model and in situ

Osteotomy phase was performed under general anesthesia. Anterior le-fort I level osteotomy combined with transverse mid-maxillary osteotomy cut through orthodontically created spaces of upper arch was done (Figure 2).

Minimum periosteal stripping and preservation of palatal muco-periosteum is highly desirable to nourish separated anterior maxillary segment. Maximum amount of maxilla was incorporated to osteotomized segment.



Figure 2: Osteotomy cuts marked on skull

Distraction was delayed for 5-7 days (**Latency phase**) until soft callus formation to bridge the bony segments after the bone healing was commenced. Intra-oral distracter was cemented to preplanned teeth.

During **Distraction phase**, intra-oral distracter was activated 1 mm per day (two turns in the morning and two in the evening). One turn opens 0.25 mm of the device. Maximum distraction of 13 mm (vary with the type of screw) was achieved by two weeks.

Consolidation phase is theoretically twice as distraction phase (four weeks). The device was kept in situ for three months after maximum activation until callus get matured and remodeled to minimize relapsing.

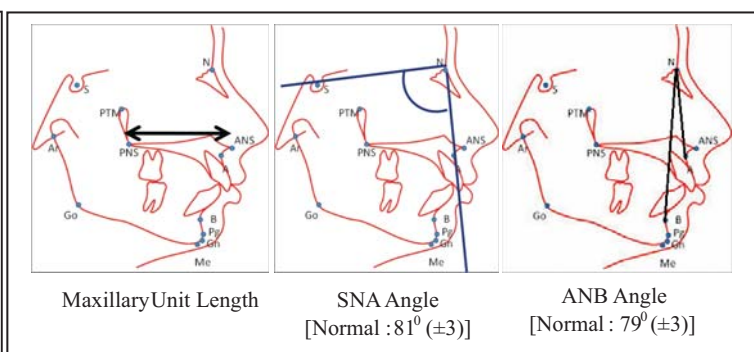
Results

Improvement of maxillary deficiency was assessed using following cephalometric measurements, pre surgically and after one year post surgically.

All patients showed increase of maxillary unit length (distance between ANS to PNS) with average increase of 6.2 mm. All the study subjects showed increase of SNA (Sella-Nasion-A point Angle) and ANB (A point-Nasion-B point Angle) angles with the mean increase of 8.5° and 8.8°, which improved the anterior-posterior dimensions of maxilla. Mean increase of 4.3mm was observed in positive over-jet increase in all patients. These findings were statistically significant (P<0.05) (**Table 1**).

Table 1: Improvement of facial dimensions

Cephalometric analysis	Average Increase	t value	p value
Maxillary Unit Length	6.2 mm	9.7	< 0.001
SNA angle	8.5°	9.89	0.001
ANB angle	8.8°	9.99	0.001
Over jet	4.3 mm		< 0.001



With the above positive changes, facial profile was changed from concave to convex, with correction of skeletal class III mal-occlusion to class II. Naso-labial angle was reduced. All patients accepted their current facial appearance than previous but preferred to have more nasal prominence (Figure 3).

According to the pre operative and one year post operative speech assessment, 60% of patients showed reduce hypernasality and nasal-emission after treatment with an improvement of VPI.



Pre-operative profile Post-operative profile

Figure 3: Improvement of facial appearance

Discussion

Hypoplastic maxilla due to oro-facial clefts results in functional problems as dento-alveolar discrepancy, insufficient space for teeth in alveolar process and clefts, speech and swallowing defects due to fistulae and VPI. Facial profile may alter in all three planes as facial soft tissue harmony of nose; orbit and upper lip are disturbed. Alteration of facial growth causes psychological and social impact.

The patient's main request in dento-facial deformity treatment is a new aesthetical balance of the face involving good occlusion, masticatory function, aesthetics of the smile and facial profile (7).

Among variety of treatment options for correction of maxillary hypoplasia of patients with oro-facial clefts, Le Fort I maxillary advancement osteotomy is widely used as it is accomplished of correcting maxillary hypoplasia in all three dimensions (6).

Depending on the severity of the discrepancy, the management protocol may vary but mostly performed in mild localized cases where as modified Le Fort III osteodistractor and Rigid External Devices (RED) are used in severe maxillary hypoplasia as in syndromic cases (8). Maxillary osteodistractor is often employed for correction of maxillary hypoplasia in patients with cleft lip and palate (9). The degree of correction and stability with DO is better than conventional osteotomies, rigid fixation, and bone grafting (10). Bone anchored internal distractors are more aesthetically acceptable and easy to wear but the main disadvantage is the need for a second surgery for removal at the end of treatment. Further, they have poor vector control and the distraction achievable is limited by the length of the screw incorporated in the device. Both, external and internal devices are expensive and need adequate bone above the root apices for safe placement to ensure good anchorage (1).

A relatively new approach for maxillary advancement by maxillary distraction using a combined surgical and modified orthodontic technique with tooth-borne custom-made osteodistractor (1) is a versatile treatment option on moderate mid facial hypoplasia patients with oro-facial clefts. Histogenesis is the main advantage of MMOD over Le Fort I maxillary advancement osteotomy as it creates bone as well as soft tissues that minimize relapses. The maxillary arch alveolar space created was effectively utilized for orthodontic correction of maxillary crowding. Since the posterior maxilla is not involved in surgical procedure, potential bleeding risk is minimum. Length of maxillary unit increase in anterior-posterior direction (ANS to PNS distance) improves VPI (II). Comparatively lesser reciprocal distraction of posterior maxillary segment improves the structural defect of the velopharyngeal sphincter by increasing the palatal length resulting in reduction of VPI. As a result there is a 60% reduction of hypernasality and nasal-emission in speech after treatment which would get worsened by le fort I advancement osteotomy. Adequate distraction is possible with multiple surgical attempts with provision of sufficient time intervals for bone remodeling and maturation. The method of DO can be used as an alternative to bone grafting and osteotomies. DO in contrast appear to provide low operative and post operative morbidity.

With this technique tipping movements of premolars on which distractor arms were cemented anterior to osteotomy cut would occur and have to be corrected orthodontically. Further, any unfavorable fracture of maxilla posterior to osteotomy cut would not provide desired results of the technique. Defective distraction vectors and insufficient distraction are the drawbacks of the internal distractors (9).

According to our results, we were able to achieve significant improvements in facial appearance and speech in all patients. The appliance was well tolerated with high patient compliance. In conclusion this relatively simple and cost effective technique corrects mild to moderate maxillary hypoplasia, with the utilization of available facilities and is very much suited to third world and developed countries.

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Supracondylar fracture of humerus in children; presentation and outcome in a tertiary centre of Sri Lanka

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ABSTRACT

Introduction: Supracondylar fracture is an important long bone fracture in children. It is of special concern due to the neurovascular injuries and malunion associated with it. Fracture sub-types, associated injuries and grades are important in decision making. The objectives were to assess epidemiology and closed manipulation impact on neurovascular outcomes.

Methods: Consecutive patients were included in the study. Structured questionnaire was filled denoting demography, severity, subtypes and associated injuries. All patients underwent closed reduction and initial casting. Outcome was measured objectively to decide on need of open surgery.

Results: There were 75 patients (male - 58%). Ninety two percent were extension-type while 48% and 21% were Gartland type 2 and 3, respectively. Neurological and vascular deficit was observed in 11% and 8% of patients, respectively. Major mechanisms of injury were direct fall (64%) and road traffic injuries (20%). Regression showed neurovascular deficit, need of open reduction and varus deformity was significantly higher with Grade 3 fracture ($P < 0.05$).

Oxford elbow score was not different between Grade 2 and Grade 3. Eighty seven percent of Grade 2 and 68% of Grade 3 fractures were successfully reduced with closed manipulation.

Conclusions: Vascular and neurological deficits were seen in 11% and 8% of patients but they were transient in most cases. Closed reduction alone has achieved good results in a majority. Further analysis is planned in future to compare these data with, closed reduction and percutaneous pinning.

Key words: Supracondylar fracture, humerus, children, Sri Lanka.

Introduction

Supracondylar fracture is the commonest elbow fracture during the first decade of life with rates ranging from 58% (1) to 75% (2) of all fractures around the elbow.

Mechanism of injury is an acute hyperextension load on the elbow from falling on outstretched arm. The central thinning of the humeral bone along with narrow surrounding bony columns predispose this

region to fracture (3). It warrants proper and prompt management to prevent complications like cubitus varus, elbow stiffness and Compartment syndrome (4).

There are several treatment modalities available to treat this fracture. Skin traction, closed reduction with casting alone, closed reduction and percutaneous pinning, and open reduction with internal fixation are some of them (5).

1) The treatment strategy opted not only depends on the particular fracture but also on available resources, experience and training of orthopaedic surgeons as well as local unit protocols. In this study our aims were to assess the epidemiological patterns and fracture characteristics in a tertiary centre of Sri Lanka and also to compare and contrast closed reduction and casting with published data of other treatment modalities in terms of structural and functional outcome.

Methods

After obtaining the approval of the local ethics review board and the hospital committee in April 2012, we recruited 75 children by the end of August as required according to the sample size. It was a consecutive sampling after proper informed written consent. All patients were recruited via Accident and Emergency service department of Lady Ridgeway hospital, Colombo 8, Sri Lanka. Patients as well as parents were educated and given sufficient time to decide whether to enroll or not. All necessary precautions were taken to ensure that the standard management of the unit was not altered by any means due to their decision on enrollment. Participants did not receive in any financial gains and their involvement was purely voluntary.

Both male and female, children under 12 years were selected. Exclusion criteria were; any previous attempts of treatment for the same pathology, ipsilateral multiple fractures, more than 5 days old fracture, and uncooperative patient/parents.

After enrollment, data were collected by trained professionals using an interviewer- administered questionnaire. Demographic features, fracture mechanism and aetiology were amongst the data collected. Clinical features such as neurovascular status, limb deformities as well as radiological features were interpreted by a Consultant Orthopaedic Surgeon together with a radiologist.

All patients received closed manipulation and long arm slab for immobilization at the initial stage. Manipulation was performed by qualified and well experienced Orthopaedic Surgeons. The technique of manipulation was a two person maneuver where elbow was kept in extension with in line traction for few minutes, followed by correction of medio-lateral translation and finally flexing the elbow while using

digital pressure to bring the fracture fragments together. Immobilization was through carefully molded long arm back slab with elbow in hyperflexion and forearm in pronation / supination according to mediolateral displacement. Flexion type of fractures was kept in extension after manipulation.

Post reduction clinical status and the radiological features were carefully interpreted by the same team to decide on further path of management. After achieving satisfactory clinical and imaging outcomes, patients were discharged from the hospital to be followed up at clinic at 1 week, 1 month and 3 month intervals.

Radiological features looked for adequacy were Baumann's angle within 10 degrees of opposite side along with anterior humeral line, one third translation of distal fragment of fracture, and less than 40 degrees of malrotation. Fracture healing, stability, neurovascular status and deformities were looked in to during clinic visits. In addition to the radiological features and clinical examination, Oxford elbow score was utilized for quantitative assessment of elbow function (Figure 1).

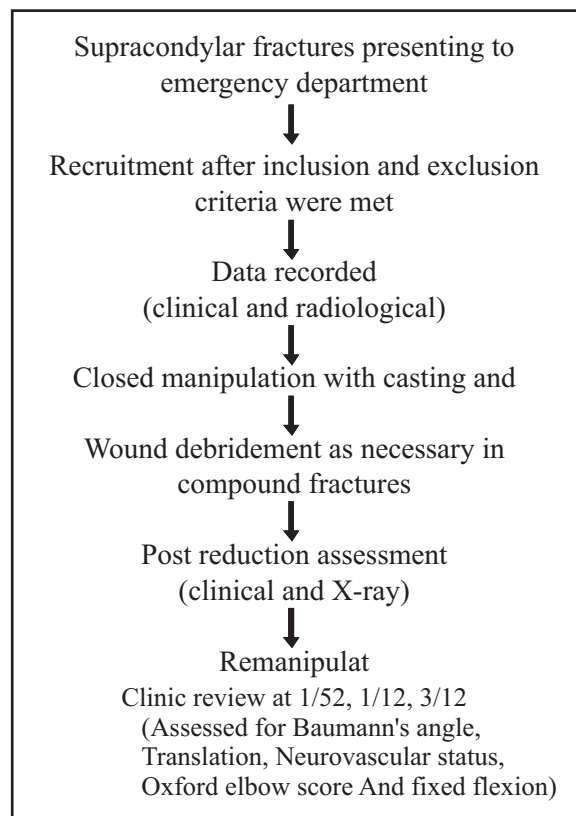


Figure 1: Methodology

Results

Our sample consisted of 75 children with mean age of 6.5 years. Male : Female ratio 1.41 : 1. Racial distribution was; Sinhalese 60%, Muslim 27% and Tamil 13%.

Fall was the main mechanism of injury where 64% (n=48) tripped and fell while 20% (n=15) suffered road traffic injuries leading to a secondary fall. There were a small number of patients who presented following other modes of injury (10%) and few with abnormal bone integrity or refracture of same site (6%).

Seven (9.33%) were open fractures and all were result of a road traffic injury. When classified according to Gartland's classification, Grade 1 severity was seen in 30.7% (n=23), Grade 2 in 48% (n=36) and Grade 3 in 21.3% (n=16).

Flexion type was seen in 6 out of 75 (8%) while rest was of extension type.

Neuropraxia, the only neurological deficit observed, was found in 8 patients (6 anterior interosseous and two radial nerve palsies). Vascular deficiency was rare and out of the 6 patients who had absent peripheral pulses none had poor perfusion status (Table 1).

Table 1: Fracture severity vs neurovascular damage

Fracture severity	Neuropraxia (n)	Pulseless hands (n)
Grade 1	Nil	Nil
Grade 2	3	Nil
Grade 3	5	6

In all fractures initial management was the closed reduction together with long arm slab for maintenance. Irrespective of fracture grade we achieved satisfactory results (acceptable Baumann's angle and humerotrochlear angle) in 87% (n=65) cases. In Grade 1 category, the success rates were 100%, 86% in Grade 2 and 69% in Grade 3. Repeat attempt was made in the reduction unsatisfactory group to achieve acceptable results in 6 out of 10. Four (5%) had to undergo open reduction and

internal fixation to reduce it after two failed attempts. Mediolateral displacement was the commonest reason (n=5) for inadequate results.

Pearson Chi-square and logistic regression analysis carried out between Grade 2 and Grade 3 fractures showed significant increase in Grade 3 patients for susceptibility to vascular deficit ($P<0.001$), Neurological sequelae ($P<0.01$, Odds ratio 10.2) and long term complications as elbow deformities ($P<0.001$, Odds ratio 5).

Patients were followed up in the clinic for 3-6 months. At one week review after fracture reduction, in-cast slipping of fracture fragments was seen in 13.3% (n=10) which increased to 18.7% (n=14) at one month including the initial number of slipped fracture children. Grade 3 had higher probability of slipping (OR 3.6 compared to Grade 2) and specially the type 3B. Neurological sequelae on average took 6-10 weeks to resolve, spontaneously. Severity of the deficit was the same in 3 out of 8 at one month review.

Functional assessment made using the validated Oxford-Elbow score showed no difference between the Grade 2 and 3. Mean score was 44.88 in Grade 1, 32.4 in Grade 2 and 30.12 in Grade 3.

Considering the long term complications of Fixed flexion (FF) and Varus deformity (VD) 4 % (n=3) had major FF by measured angle when major VD was seen in 9.3 % (n=7). All neuropraxias and vascular insufficiencies resolved by 16 weeks of initial injury.

Discussion

Supracondylar fracture is both common and an extremely important entity of paediatric long bone fractures. This is especially due to the high rate of malunion and neurovascular compromise associated with this fracture. It is important to know the data related to epidemiology and outcome of this fracture type in a particular clinical setting in order to improve treatment strategies, further.

Male to female ratio in our sample was 1.41 : 1 which is comparable to other published data such as 1.8 : 1 (6). Mean age of presentation was 6.5 years.

Higher participation in outdoor activities and contact sport may be the reason behind male predisposition. In our experience older children tend to suffer distal

radius fractures while younger ones escape with plastic deformation/greenstick fractures in similar kind of stresses while falling on outstretched hands. In keeping with literature extension type was the vast majority (91%) but flexion variety is rather prevalent (9%) in our sample whereas worldwide rates are around 4-5% (7).

Fall is the major mechanism by which injury is caused but it is alarming to see a significant proportion (20%) was due to road traffic injuries. Further, 7 out of 15 in this category suffered open type of fractures with almost uniform neurovascular compromise and risk of infection.

Severity of fracture according to Gartland classification in the sample was 31%: 48%: 21% of Grade 1, 2, 3 respectively. It contrasts with similar data series in other countries where 64%: 19%: 17% was respectively observed (1). This means higher fracture severity is seen in our population.

Considering neurovascular status, 10.7% (n=8) suffered neuropraxias while 8% (n=6) had absence of distal pulses. In literature neuropraxias range from 3.2% (8) to 20% (6) while vascular insufficiency is reported in about 2.6% (9) to 14% (1). The commonest nerve that was involved in our sample was anterior interosseous branch of median nerve (6/8) whereas in most other research it was radial nerve. Pale pulse less hand with poor capillary filling of fingers is extremely rare and no such case was found in this series.

Most vascular deficits are believed to be due to traction and pressure effect of swelling and not due to transactions. Fracture reduction alone is told to be sufficient to restore filling status in most patients with pulse less hands (9).

We offered closed reduction and long arm cast slab for all the patients initially and only four needed open reduction at acute stage. But according to current evidence and general consensus all unstable and Grade 3 fractures deserve to be percutaneously pinned in view of higher elbow functional scores in long term and better immediate stability of fracture site (2,4,5,10,11).

But some researchers have shown that with regards to varus deformity and carrying angle of elbow there is no significant difference between pinning and cast alone after closed reduction (11). In some studies investigating closed reduction and unicondylar pin

fixation adequate clinical and radiological criteria were achieved in 80% of patients (10), whereas in our sample we achieved 87% irrespective of the Grade and a remarkable 69% success in unstable Grade 3 fractures. Some surgeons have even devised modified techniques of closed manipulation where elbow is throughout kept in extension and immobilized in back +/- front slabs, and speaks of even better success rates in the range of 80-100% in similar category of patients (12,13).

In-cast slipping of fracture line was a significant cause for late manipulation in our sample (10 out of 75 at 1 week). It was probably due to uneven cotton padding and initially grossly swollen elbows creating a space inside the cast when swelling subsides. But on the other hand rates of compartment syndrome and superficial skin necrosis were considerably rare in our sample compared to other published data.

Clinical cubitus varus was seen in about 21% in our sample at 3 months. Previous research with various treatment modalities resulted in similar rates of around 22%. All neuropraxias and vascular deficits were transient and did not necessitate exploration surgery at any stage.

As the main tertiary centre for children in Sri Lanka we believe our study sample is representative of the country as a whole. Being placed in such unique niche further studies with larger sample sizes and controlled study designs will surely reveal valuable information to get an insight on how this particular fracture behaves. As we are planning to introduce percutaneous pinning in very near future we would also be able to compare different treatment modalities. All this data will help immensely not only to manage the patients better but also to cut down long term disabilities and health costs to governments in the long run.

Disclosure of interest

Authors declare that there are no conflicts of interest.

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Beyond the cholinergic crisis

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ABSTRACT

Introduction: Organophosphates (OP) are the most frequently involved pesticides in acute poisoning. In Sri Lanka it has been ranked as the sixth or seventh leading cause of hospital deaths for many years. Neurotoxic effects of acute OP have been hitherto under-explored.

The aims of the studies were to assess the effects of acute OP poisoning on somatic, autonomic nerves, neuromuscular junction (NMJ), brain stem and cognitive function.

Methods: Patients following self-ingestion of OP were recruited to cohort studies to evaluate the function of somatic, autonomic nerves, NMJ, brain stem and cognition. Motor and sensory nerve function was tested with nerve conduction studies. Cardiovascular reflexes based autonomic function tests and sympathetic skin response (SSR) was used to evaluate autonomic function. NMJ function was assessed with slow repetitive supramaximal stimulation of the median nerve of the dominant upper limb. Brain stem function and cognitive function were assessed with Brain Stem Evoked Response Audiometry (BERA) and Mini Mental State Examination (MMSE) respectively. The data of the patients were compared with age, gender and occupation matched controls.

Results: There were 60-70 patients and equal number of controls in each study.

Motor nerve conduction velocity, amplitude and area of compound muscle action potential on distal stimulation, sensory nerve conduction velocity and F-wave occurrence were significantly reduced. At one week the significant impairment in autonomic function were change of diastolic blood pressure 3 min after standing, heart rate variation during deep breathing (HR-DB), SSR-amplitude and post-void urine volume. All except HR-DB were reversed at six weeks. No significant impairment of NMJ function, BERA and MMSE were noted.

Conclusions: Sub clinical somatic and autonomic nerve dysfunction was observed. There were no strong evidence of long term effects on NMJ, brain stem and higher function.

Introduction

Organophosphate (OP) compounds have become the most widely used pesticides for agricultural-pests throughout the world from the 1980s and the risk of acute and sub acute toxicity is high in humans (1). Acute pesticide poisoning is a major health problem especially in developing countries. It was estimated that one million serious, unintentional poisonings occurred and an additional two million people were hospitalized for attempted suicide with pesticides

annually (2). In Sri Lanka, the majority of poisoning cases are self inflicted and 77% of the cases are in the age range of 11-30 years (3). OP and carbamate compounds were involved in 74% of pesticide poisoning (4).

OP bind to the esteratic site on the acetylcholine esterase (AChE) molecule, phosphorylates the enzyme, and lead to inhibition of its action (5). The binding between the esteratic site on the enzyme and the phosphorus atom is stable and takes hours or

weeks to break off, depending on the compound involved. Studies have shown that a phenomenon of enzyme aging occurs which involves cleavage of a radical from the inhibited enzyme, making it resistant to reactivation. The net result is the accumulation of excess acetylcholine (ACh) at the cholinergic nerve endings all over the body resulting in the characteristic clinical manifestations. Following inhibition, recovery of this enzyme occurs at a rate of about one percent per day (5). Restoration of AChE levels occurs by spontaneous or induced reactivation of the enzyme and by new enzyme synthesis (5).

Accumulated acetylcholine at nerve endings initially stimulates and eventually leads to exhaustion of cholinergic synapses, resulting in neuromuscular junction (NMJ) dysfunction (5).

The problems occurring after OP poisoning have been identified to some extent. There are three well defined syndromes. These are acute cholinergic crisis, intermediate syndrome, organophosphate induced delayed polyneuropathy (OPIDN) and chronic organophosphate induced neuropsychiatric disorders (COPIND) (5).

Acute cholinergic crisis occurs due to accumulation of ACh, hence over activity of the nervous system. As a result the person with poisoning develops muscle twitching, narrowing of air ways, increased bronchial secretion, slowing of heart rate and low blood pressure. This cholinergic crisis is life threatening. Therefore the patient needs to be managed immediately to secure the life. Even though the patient is recovered from cholinergic crisis, the problems are not over.

Some patients develop muscle weakness, especially the proximal muscles within four days of ingestion. This entity is called the intermediate syndrome. The intermediate syndrome was first described and published by two Sri Lankans Prof. Nimal Senanayaka and Dr. Lakshman Karaliadda in 1987 and they coined the term intermediate syndrome. However problems are not yet over. There are things happening beyond the cholinergic crisis. OP can also cause polyneuropathy rarely. This occurs one to three weeks following poisoning. Patients complain of parasthesia and calf pain. Deep tendon jerks may be absent.

Therefore it is worth to look into what happens beyond the cholinergic crisis. This paper overview

the effects of OP on nervous system including central and peripheral nervous systems. Further, it will describe the function of peripheral nervous system including somatic (motor and sensory), autonomic (sympathetic and parasympathetic), the junction between nerve and muscle, brain and higher functions of the brain.

Methods

Cohort studies were conducted with matched controls with the approval of the Ethical Review Committee, Faculty of Medicine, University of Ruhuna, Sri Lanka. Informed written consent was obtained from the patients and the controls. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

The patients with self-ingestion of OP were recruited from a tertiary care hospital and a secondary care hospital in the Southern Province of Sri Lanka between June 2008 and September 2009. At the time of recruitment to the study, subjects either had features of the cholinergic syndrome or had been given atropine to counteract cholinergic syndrome in the peripheral units and then transferred to the collaborating hospitals.

OP poisoning was confirmed by the history from the patient and/or accompanying person, the cholinergic features and plasma cholinesterase activity (ChE).

The controls were recruited from the persons accompanying the patients to the tertiary care hospital. Age, gender and occupation matched healthy volunteers who did not have a history of acute pesticide exposure were recruited within one month of the recruitment of the respective case. Age of the controls was matched to ± 3 years of the patients.

Subjects with features of peripheral neuropathy, diabetes mellitus or those who were on long term medications, were excluded.

Motor nerve conduction studies (MNCS), sensory nerve conduction studies (SNCS), F-wave studies, autonomic function tests, slow repetitive nerve stimulation (RNS), brain stem auditory evoked response (BAER) and Mini Mental State Examination (MMSE) were performed at the time of discharge from the ward (the first assessment) and at six weeks (the second assessment) following

acute exposure to OP. All neurophysiological investigations done on the patients were carried out on the controls. The room temperature of the neurophysiology laboratory was maintained at 25°C.

The patients were assessed twice to explore the acute and subsequent effects on peripheral nerves. The earliest possible time to assess the patients was at the time of discharge and the earliest possible time for the second assessment with the least drop outs was at the sixth week.

The Neuropack MEB-9400A/K EMG/EP Measuring System (Nihon Koden) was used for electrophysiological assessment.

SNCS

SNCS were performed on median and ulnar nerves on both sides. The orthodromic method was used. Stimulating ring electrodes were placed on the second digit for median SNCS and on the fourth digit for ulnar SNCS. The ring cathode was placed around the digit near the metacarpophalangeal joint and the ring anode around the digit near the distal interphalangeal joint. A recording electrode was placed over the respective nerve on the anterior aspect of the wrist. Ground electrode was placed between the stimulating and the recording electrodes. The nerve was stimulated with supramaximal electrical stimulus.

Sensory nerve conduction velocities (SNCV) and the amplitude of the complex were recorded.

MNCS

MNCS were performed on median, ulnar and common peroneal nerves on both sides. Surface electrodes were used. The nerve was stimulated with supramaximal stimulation.

For the median MNCS, the recording electrode was placed over the abductor pollicis brevis, the reference electrode was placed over the proximal phalanx of the thumb and the ground electrode was attached between recording electrode and the stimulating probe. The stimulation was given on the palmar aspect of midwrist and at the elbow (antecubital fossa) just medial to the palpable brachial artery. The cathode was placed distal to the anode.

For the ulnar MNCS the recording electrode was placed on the mid portion of the abductor digiti quinti, the reference electrode was placed over the proximal phalanx of the fifth digit and the ground electrode was attached between recording electrode and the stimulating probe. The nerve was stimulated on the palmar aspect of wrist and just distal to the osseous groove in the posterior aspect of the medial epicondyle of the humerus, i.e., the ulnar groove.

For the common peroneal MNCS the recording electrode was placed over the extensor digitorum brevis muscle, the reference electrode was placed over the fifth toe and the ground electrode between the recording electrode and the stimulating probe. The nerve was stimulated on the lateral aspect of the popliteal fossa just medial to the insertion of the tendon of the biceps femoris and along the anterolateral surface of the fibula, 3 to 4 cm distal to the proximal tip of the fibular head.

Motor nerve conduction velocity (MNCV), amplitude and area of the compound muscle action potential (CMAP) on distal stimulation were recorded.

F-wave studies

F-wave studies were performed on median, ulnar and tibial nerves. Electrodes were placed as for MNCS on median and ulnar nerves. For the tibial F-wave studies, the recording, the reference and the ground electrodes were placed over the abductor hallucis muscle between the great toe and between the recording electrode and the stimulating probe respectively. The nerve was stimulated at a point slightly posterior and proximal to the medial malleolus. Sixteen stimulations were analyzed, percentage of F-wave occurrence and minimum reproducible F-wave latency were recorded.

Autonomic function tests

R-R interval based autonomic function tests (heart rate response to standing, heart rate variation during deep breathing and heart rate response to Valsalva manoeuvre), blood pressure response to standing, blood pressure response to sustained handgrip, sympathetic skin response and residual urine volume were assessed.

Heart rate response to standing

Participants were asked to stand up unaided from lying down position as quickly as possible when performing heart rate response to standing. The heart rate response was expressed by the 30:15 ratio; ratio of longest R-R interval around the 30th beat after standing to shortest R-R interval around the 15th beat after standing (6,8).

Heart rate response to deep breathing

To perform heart rate variation during deep breathing, participants were asked to breathe deeply and evenly at 6 breaths per minutes (5 seconds in; 5 second out) for three cycles (30 seconds). Maximum and minimum R-R intervals were analyzed during each cycle and converted to beats per minute. Greatest heart rate differences (expiratory-inspiratory difference; E-I difference) during each cycle were calculated and the three differences averaged (8,9).

Heart rate response to Valsalva manoeuvre

During the Valsalva manoeuvre, the participant breathed in to a mouth piece connected to a modified sphygmomanometer and maintained an expiratory pressure of 40 mmHg for 15 seconds. The ratio of the longest R-R interval within 20 beats of ending the test to the shortest interval during the test was analyzed. The test was performed three times and the ratios from three Valsalva attempts averaged (8,9).

Blood pressure response to standing

Blood pressure was measured while the participant was lying down quietly and around three minutes after standing (9) by using an OMRON SEM-1 automatic blood pressure monitor that uses the oscillometric method of blood pressure measurement. The monitor detects blood movement through the brachial artery and converts the movements into a digital reading.

Blood pressure response to sustained handgrip

In blood pressure response to sustained hand grip, the participant was asked to press a hand dynamometer with full strength. Then the hand grip was maintained at 30% of the maximum strength for five minutes.

Due to muscle contraction, sympathetic activity and vasoconstriction should lead to a rise in blood pressure. The diastolic blood pressure at the end of the effort should be at least 16 mmHg higher than before the manoeuvre. An increase in the diastolic blood pressure by 10 mmHg or less is considered as abnormal (8,9).

Sympathetic skin response (SSR)

Sympathetic skin response measures the skin potential which is evoked by stimulation (electric, auditory and visual). This potential shows the functioning of the sympathetic nerves of the sweat glands (10). Participant's skin was cleaned where the electrodes were attached to remove any moisture and gel from the skin. The active electrode was pasted on the center of the palm of the dominant hand. The reference electrode was pasted on the center of the back of the same hand. The ground electrode was attached between the active and the stimulating electrodes. The stimulating electrode was placed on the median nerve of the recording wrist and stimulated with the intensity of 25 mA. Six stimulations were administered with at least 30 sec intervals between each stimulation. The latency was measured from the onset of stimulus artifact to the onset of negative deflection. The amplitude was measured from the baseline to negative or positive peak whichever was the highest. Average latency and maximum amplitude were recorded.

Residual urine volume

Post void residual urine volume was measured ultrasonically after a voluntary void (11,12).

Exercise modified slow repetitive supramaximal stimulation

Exercise modified slow repetitive supramaximal stimulation (RNS) was used to assess NMJ function on the median nerve of the dominant upper limb. RNS was carried out administering 10 stimulations at a rate of 3Hz with a filter setting of 20 Hz – 5 kHz. Forearm and hand were fixed by straps to restrict movements and to ensure that contraction of the abductor pollicis brevis was isometric. Recording electrodes were placed over the abductor pollicis brevis, the reference electrode was pasted over the

proximal phalanx of the thumb and the ground electrode was attached between the recording electrode and the stimulating probe (13). Laboratory temperature was maintained at 25^o C during the test.

The nerve was stimulated at the wrist at rest- the first train (A), immediately after 30 seconds maximal isometric exercise - the second train (B), and two minutes after the exercise - the third train (C) (14). Participants were asked to abduct the thumb against fixed resistance for the isometric exercise (14). The post exercise facilitation and the post exercise exhaustion were calculated after the isometric exercise (13,14).

The decrement responses were quantified by calculating the percentage change in amplitude as follows: (15)

- At rest - the first train of stimuli (A)
 - percentage change in amplitude between the second and the first action potential of the first train of stimuli $((A_1-A_2)/A_1 \times 100)$
 - percentage change in amplitude between the fourth and the first action potential of the first train of stimuli $((A_1-A_4)/A_1 \times 100)$
 - percentage change in amplitude between the fifth and the first action potential of the first train of stimuli $((A_1-A_5)/A_1 \times 100)$
- Immediately after 30 seconds maximal isometric exercise - the second train of stimuli (B)
 - percentage change in amplitude between the second and the first action potential of the second train of stimuli $((B_1-B_2)/B_1 \times 100)$
 - percentage change in amplitude between the fourth and the first action potential of the second train of stimuli $((B_1-B_4)/B_1 \times 100)$
 - percentage change in amplitude between the fifth and the first action potential of the second train of stimuli $((B_1-B_5)/B_1 \times 100)$
- Two minutes after the exercise - the third train of stimuli (C)
 - percentage change in amplitude between the second and the first action potential of the third train of stimuli $((C_1-C_2)/C_1 \times 100)$

- percentage change in amplitude between the fourth and the first action potential of the third train of stimuli $((C_1-C_4)/C_1 \times 100)$

- percentage change in amplitude between the fifth and the first action potential of the third train of stimuli $((C_1-C_5)/C_1 \times 100)$

A decline of compound muscle action potential (CMAP) amplitude up to 8% with RNS is considered as normal (15).

The post exercise facilitation was assessed by calculating the ratio of the amplitude of the first action potential in the second train to the amplitude of the first action potential of the first train (B_1/A_1) (13,14) and the post exercise exhaustion by calculating the ratio of the amplitude of the first action potential of the third train to the amplitude of the first action potential of the first train (C_1/A_1) (14).

Brain Stem Auditory Evoked Response (BAER)

BAER is an electrophysiological method that can be used for neurotoxicity testing of auditory function (16). A computer based Neuropack S₁ EMG/EP measuring system MEB-9400 (Nihon Kohden) was used for the BAER. A piece of cotton moistened with alcohol was used to clean the patient's skin where the electrodes were attached and the skin rubbed with dry gauze to remove any moisture and gel from the skin. Recording electrodes (active and reference) and grounding electrodes were attached on the patient's head with Elefix paste. The patient was kept on a chair relaxed with eyes closed. To avoid EMG of the neck, patients were asked not to move their head. To avoid EMG of the chin, patient was asked to open his / her mouth slightly. The headphones were kept on the head. The hi-cut and the low-cut filters were set to 3kHz and 100Hz respectively. The skin-electrode contact impedance was kept below 5k Ω . The stimulation intensity was 90dB and 1000 stimulations were averaged. Latency was measured in msec. Interpeak latencies of I-III, III-V and I-V were measured (16,17).

Mini Mental State Examination

Cognitive function was assessed only if the educational level of the participant was at least up to year five. People who were suffering from dementia, psychiatric illness and those on medication which

have the potential to alter cognitive function (anticonvulsants; vigabatrin, gabapentin and lamotrigine, minor tranquilizers; diazepam, and antihypertensive like methyl dopa) were excluded from the study. Cognitive function was assessed once the patient had recovered from the acute cholinergic crisis.

A validated Sinhalese translation of the MMSE was used with a few modifications (18). Table 1 illustrates the modifications made in the MMSE administered in our study which reflected our need to use this in the community. A total score of less than 24 out of 30 was considered as cognitive impairment. No response or refusal to perform any item was scored as zero.

Estimation of plasma ChE activity

Generally the term acetylcholinesterase activity is referred to red blood cell acetylcholinesterase or acetylcholinesterase at the nerve tissue. However we analyzed ChE (ChE = acetylcholinesterase (AChE) plus butyrylcholinesterase (BChE)) activity in plasma. The modified Ellman method developed by Worek F et al. (1999) was used to estimate ChE activity in plasma (19). Plasma samples were obtained from EDTA blood after centrifugation (10 min, 500 * g) and stored in 1ml aliquots at -80°C until analysis.

Prior to analysis the thawed samples were kept on ice until analysis. Preparation of inhibited cholinesterase were made by incubating plasma samples with PX-ethyl, PX-methyl and obidoxime for 15 min at 37°C followed by immediate dilution of the samples (1:100 in diluting reagent) and freezing.

The activity of cholinesterase was measured with a thermostatted filter photometer (Model 1101 M, Eppendorf, Hamburg, Germany) at 436 nm and 37°C using polystyrol cuvetts.

Cholinesterase enzyme activity was calculated by using the equation,

$$Activity(\mu\text{mol/l/min}) = \frac{\text{Sample}(mE/\text{min}) - \text{Blank}(mE/\text{min})}{10.6}$$

The analysis was done at Walther Straub Institute for Pharmacology and Toxicology, Munich, Germany.

Statistical analysis

Graph Pad Prism 4 and Social Package of Statistical Software were used for the statistical analysis. Normal distribution of the data was tested with Kolmogorov-Smirnov test. Data which had no normal distribution were analyzed with non-parametric tests. The paired T-test was used to compare the results of the first and the second assessment and the unpaired T-test was used to compare the results of the patients and the controls. Correlation of neurophysiological indices with potential confounders was analyzed with Spearman's correlations. Multiple liner regression model was used to adjust for potential confounders.

Results

From a total of 163 acute OP poisoning admissions to the collaborating hospitals, 60 -70 patients participated for each study. Mean (SD) GCS on admission was 14 (2). All patients received atropine, 54 patients received pralidoxime.

Plasma ChE activity at four and/or twelve hours after the exposure was available in 33 patients. The median (inter quartile range) of plasma ChE activity at four and twelve hours was 790 (146 - 2598) $\mu\text{mol/l/min}$ and 431 (136 - 3068) $\mu\text{mol/l/min}$ respectively.

None of the patients or the controls had diabetes mellitus. The mean HbA_{1c} of patients and the controls were $5.4 \pm 0.5\%$ and $5.7 \pm 0.6\%$.

Function of peripheral nerves

The neurophysiological assessments and the results of SNCS, MNCS and F-wave studies are shown in the **Table 1**.

Impairment of peripheral nerve function was observed at both occasions in the cases compared to the controls. In the first assessment these were significant for MNCV of median, ulnar and common peroneal nerves, SNCV and CMAP amplitude of ulnar nerve and F wave occurrence of median, ulnar and tibial nerves. However no abnormality was detected when compared to the standard cut-off values for normal MNCS and SNCS except F-wave occurrence.

Table 1: Effects of acute OP exposure on peripheral nerve function

Neurophysiological assessment	First assessment of the patients	Second assessment of the patients	Controls	Difference (Controls- 1 st assessment)	95% CI/P value (Controls- 1 st assessment)	Difference (Controls- 2 nd assessment)	95% CI/P value (Controls- 2 nd assessment)	Difference (1 st assessment - 2 nd assessment)	95% CI/P value (1 st assessment- 2 nd assessment)
SNCV (m/s)									
Median	53.6 (1.0)	52.8 (1.2)	56.0 (0.7)	2.3	-0.2 to 4.7	3.2 [*]	0.6 to 5.8	1.2	-0.6 to 3
Ulnar	55.3 (0.9)	55.9 (1.0)	59.7 (0.6)	4.4 [*]	2.3 to 6.5	3.7 [*]	1.5 to 5.9	0.01	-2.5 to 2.5
Amplitude of sensory complex (µV)									
Median	14.3 (10.4)	12.9 (10.6)	13.4 (7.1)	-0.9	-4 to 2	0.5	-3 to 4	0.5	-5 to 4
Ulnar	7.4 (6.3)	7.2 (7.4)	7.7 (4.3)	0.3	-2 to 2	0.4	-2 to 3	0.8	-4 to 3
MNCV (m/s)									
Median	55.2 (0.5)	55.6 (0.6)	56.6 (0.4)	1.4 [*]	0.1 to 2.7	1.05	-0.4 to 2.5	-0.8	-1.7 to 0.06
Ulnar	53.9 (0.6)	54.4 (0.7)	56.2 (0.5)	2.3 [*]	0.7 to 3.8	1.8 [*]	0.1 to 3.5	-0.4	-1.4 to 0.7
Common peroneal	46.6 (0.6)	48.2 (0.7)	49.4 (0.6)	2.8 [*]	1.1 to 4.5	1.2	-0.7 to 3.1	-1.2	-2.3 to 0.1
Amplitude of CMAP on distal stimulation (mV)									
Median	13.4 (0.4)	14.2 (0.6)	14.4 (0.5)	0.9	-0.4 to 2.3	0.1	-1.5 to 1.7	-0.7	-1.5 to 0.08
Ulnar	9.5 (0.3)	10.0 (0.3)	10.5 (0.3)	1.0 [*]	0.2 to 1.8	0.5	-0.4 to 1.3	-0.3	-0.8 to 0.3
Common peroneal	7.7 (0.4)	7.2 (0.4)	8.7 (0.4)	0.9	-0.2 to 2.1	1.4 [*]	0.3 to 2.6	0.6	-0.2 to 1.3
Area of CMAP on distal stimulation (mVms)									
Median	32.3 (1.2)	30.9 (1.4)	33.6 (1.2)	1.4	-2.0 to 4.8	2.7	-0.9 to 6.3	0.9	-0.7 to 2.7
Ulnar	18.7 (0.8)	17.1 (0.7)	19.5 (0.5)	0.8	-1.0 to 2.6	2.3 [*]	0.6 to 4	1.3	-0.02 to 2.6
Common peroneal	15.3 (0.8)	13.1 (0.7)	16.2 (0.8)	0.9	-1.4 to 3.2	3 [*]	0.8 to 5.2	2.7 [*]	1.2 to 4.2
F-wave latency (ms)									
Median	27.2 (0.4)	26.8 (0.3)	26.7 (0.3)	-0.4	-1.3 to 0.4	-0.1	-0.9 to 0.7	0.3	-0.4 to 0.9
Ulnar	27.0 (0.3)	27.3 (0.4)	26.7 (0.3)	-0.3	-1.2 to 0.5	-0.6	-1.6 to 0.3	-0.3	-0.9 to 0.3
Tibial	50.9 (0.6)	49.4 (0.8)	49.6 (0.6)	-1.3	-3.1 to 0.4	0.2	-1.7 to 2.1	1.9 [*]	0.2 to 3.6
F-wave occurrence (%)									
Median	82 (2)	78 (3)	90(1)	9 [*]	0.005[†]	12 [*]	0.002[†]	3	0.4 [‡]
Ulnar	83(3)	84(2)	93 (1)	10 [*]	0.001[†]	9 [*]	0.002[†]	-2	0.6 [‡]
Tibial	89(2)	92 (2)	93 (2)	4	0.059[†]	1	0.6[†]	-0.3	0.8 [‡]

Values are as mean and SE, analyzed using [†]Mann-Whitney U test and [‡]Wilcoxon signed rank test, ^{*}significant at 0.05 level

In the second assessment significant worsening of peripheral nerve function was seen in common peroneal CMAP-area and reduction of tibial F-wave latency compared to the first assessment. MNCV of median and common peroneal nerves, amplitude of ulnar nerve CMAP on distal stimulation and F-wave occurrence of tibial nerve reversed to normal at the second assessment.

Seventeen patients were admitted to Intensive Care Unit. Among them seven patients died. Four of the 10 (40%) survivors underwent neurophysiological assessment at median (range) of 24 (6-40) days after the exposure.

Correlation of neurophysiological indices with potential confounders was looked into. None of the neurophysiological indices significantly correlate with plasma ChE activity. However MNCV of ulnar; SNCV of median and ulnar, MNCV of ulnar; MNCV of median, ulnar and tibial F-wave occurrence showed significant negative Spearman's correlations with smoking habits, PAM therapy and alcohol consumption respectively.

When multiple liner regression models were used to adjust for potential confounders, effects on SNCV of median nerve, area of CMAP of median nerve and F-wave latency of tibial nerve with prlidoxime therapy and the area of CMAP of ulnar nerve with the type of OP ingested showed statistical significance.

To determine whether any multicollinearity were present, and to understand whether there is a strong linear association between each predictor variable and all other remaining predictors, the Variance Inflation Factor (VIF) and condition indices were examined. None of the VIF exceeds 10 and a condition index exceeds 30 (20).

Function of autonomic nerves

Statistically significant autonomic dysfunction was seen in the first assessment of the patients compared to the controls in change of diastolic blood pressure (DBP) 3 minutes after standing, HR-DB, SSR-amplitude, SSR-latency and post-void urine volume (**Table 2**). At six weeks recovery of autonomic dysfunction was observed except in HR-DB (**Table 2**).

When the number of patients with abnormal autonomic function test was compared with the number of controls with abnormal autonomic function tests (by Chi-Square test) in relation to standard cut-off values of autonomic function tests, no statistically significant difference was observed.

Sixteen patients were not able to perform blood pressure response to sustained hand grip due to painful cannula site on their dominant hand. Twenty-four patients were not able to complete the test. Twenty-one patients in the second assessment and 15 controls were also not able to complete the test. Participants (26 in the first assessment, 30 in the second assessment and 55 in the controls) who could complete the test were within the normal limits. However odds ratio of the number of patients who were able to complete the test in the first assessment (vs controls) and the second assessment (vs controls) were 3.4 and 2.3 respectively.

The complex of SSR was almost flat in seven patients in the first assessment and in one patient in the second assessment. None of the controls showed flat SSR complex.

The urinary bladder of most patients was catheterized. The catheter was removed only at the time of discharge from the hospital. Hence residual urine volume was measured in 27 patients on discharge and 24 matched controls (**Table 2**).

In the correlation matrix, it was observed that none of the bivariate correlations are highly correlated except alcohol consumption and smoking habits, GCS on admission and smoking habits. To determine whether any multicollinearity were present, and to understand whether there is a strong linear association between each predictor variable and all other remaining predictors, the Variance Inflation Factor (VIF) was examined. None of the VIF exceeds 10.

Adjusted multiple linear regression revealed significant effects of alcohol consumption on change of SBP 3 min after standing ($B = 4.4$, $SE = 1.6$, $p = 0.009$) and size of the pupil ($B = -0.6$, $SE = 0.3$, $p = 0.04$); and the effects of smoking on residual urine volume ($B = 11.8$, $SE = 5.1$, $p = 0.03$) and size of the pupil ($B = 0.5$, $SE = 0.2$, $p = 0.04$) (21).

Table 2: Assessment of autonomic function

Autonomic function	Patients		Control group n = 70	Controls vs 1 st assessment		Controls vs 2 nd assessment		1 st assessment vs 2 nd assessment	
	First assessment n = 66	Second assessment n = 51		Mean change (patients - controls)	95% CI (patients - controls)	Mean change (patients - controls)	95% CI (patients - controls)	Mean change (2 nd - 1 st assessment)	95% CI (2 nd - 1 st assessment)
<i>Blood pressure response to standing</i>									
Change of SBP 3min after standing (mmHg)	-4 (-3 to 10) [†]	-3 (-4 to 7) [†]	-2 (-3 to 7) [†]	-2.6	-5.5 to 0.4	1	-4.1 to 2.5	1.3	-4.0 to 1.4
Change of DBP 3min after standing [†] (mmHg)	-3 (-8 to 1) [†]	-6 (-11 to -1) [†]	-7 (-12 to -4) [†]	4.6 [‡]	2.4 to 6.7	0.9	-3 to 1.3	-3.2 [‡]	1.1 to 5.3
<i>Heart rate variation during</i>									
Standing ratio	1.31 (0.31)	1.27 (0.19)	1.34 (0.28)	-0.04	-0.06 to 0.13	-0.07	-0.02 to 0.2	-0.07	-0.02 to 1.7
Deep breathing (breaths/min)	22 (12)	22 (8)	27 (10)	-5 [‡]	-1.6 to -8.8	-5 [‡]	2 to 8	-0.98	-4.1 to 2.2
Valsalva ratio	1.59 (0.34)	1.64 (0.36)	1.69 (0.32)	-0.10	-0.02 to 0.22	-0.07	-0.06 to 0.02	0.05	-0.2 to 0.1
<i>Sympathetic Skin Response</i>									
Latency (ms)	1639 (234)	1596 (196)	1543 (152)	96 [‡]	28 to 163	-53	-126 to 2	-56	-39 to 152
Amplitude (mV)	0.51 (0.49)	0.99 (0.69)	1.25 (0.98)	-0.7 [‡]	-1.01 to -0.46	-0.3	-0.005 to 0.6	0.5 [‡]	-0.7 to -0.3
Residual urine volume [†] (ml)	22 (0 to 10) [†]	-	5 (0 to 10) [†]	17 [‡]	9 to 25	-	-	-	-
Pupil size (mm)	4.1 (1.1)	3.1 (0.6)	3.1 (0.3)	1 [‡]	1.30 to 0.72	0.1	-0.3 to 0.09	-1 [‡]	0.6 to 1.4

Values are in mean (SD) except[†] median (interquartile range), [‡] significant at 0.05 level (2tailed)

Slow repetitive nerve stimulation

Table 3 shows decrement response at rest, immediately after isometric exercise, two minutes after the exercise, post exercise facilitation and post exercise exhaustion. Statistically significant difference of decrement response was observed at rest (A_4) and two minutes after the exercise (C_4 , C_5) in the second assessment compared to the controls.

The decrement response was significant at rest (A_4 , A_5) and two minutes after the exercise (C_4) in the second assessment compared to the first assessment.

Seven occasions in the patients in the first assessment and five occasions in the controls showed more than 8% decrement response either to the second, fourth or fifth stimuli.

BAER

The differences of the mean latency of I – III, III – V and I – V were prolonged in the test group compared to the controls except in right side I – III difference in the first assessment of the test, right side I – III and I - V difference in the first and the second assessment in the test group compared to the controls. None of the differences were statistically significant (**Table 4**) (22).

MMSE

There were 60 patients and 61 controls. The mean age (SD) of the patients and controls were 31.5 (11.6) years and 31.3 (11.8) years respectively. Forty-two patients turned-up for the follow up assessment at six weeks following the exposure. Three out of 60 patients required Intensive Care Unit (ICU) admission.

Seventeen out of 60 patients in the first assessment and 9/61 in the controls scored less than 24 in the MMSE ($X^2 = 3.3$, $p = 0.06$). Seven patients out of 42 showed MMSE score less than 24 in the second assessment. There was no significant difference between the number of patients with impaired MMSE in the second assessment vs controls ($X^2 = 0.07$, $p = 0.7$) and the second assessment vs the first assessment ($X^2 = 1.8$, $p = 0.17$). All three patients who had ICU admissions had MMSE score more than 26.

Table 5 indicates mean (SD) score of individual domains of MMSE in the patients and the controls. The total score of MMSE, orientation and the language domains of MMSE showed significant impairment in the first assessment of the patients compared to the controls. There was no significant impairment when scores in the second assessment was compared with the controls (23).

Discussion

Small magnitude adverse difference of SNCV, MNCV, amplitude and area of CMAP on distal stimulation and F-wave occurrence in acute OP poisoned patients compared to the controls was observed. Although it is a small magnitude, the difference is clinically significant as any damage to be evident by electro physiologically nearly 50% of the fibers need to be damaged as the remaining unaffected fibers compensate the affected ones. Therefore, the absolute values are greatly underestimated.

The results of autonomic function tests showed significant impairment of heart rate variation during deep breathing and the patients had four fold residual urine in their bladder compared to the healthy subjects.

There was no detectable NMJ dysfunction assessed with exercise modified slow RNS or significant difference in the inter peak latencies of BAER after clinical recovery of acute OP poisoning.

Although there was a slight transient cognitive impairment detected with the screening tests following acute OP exposure, no long term cognitive defects was detected by MMSE in clinical settings.

Diabetes is well known to cause neuropathy. Therefore we excluded patients with diabetes from the study. Occupation matched controls were recruited since there is evidence that occupational exposure to pesticides can cause neuropathies. Very few studies were found in the literature which focused on SNCS / MNCS following acute ingestion of OP. There have been no studies which have looked at the effects of acute OP exposure on peripheral nerve function compared to matched controls. Most large studies have examined nerve function in farm workers who had chronic, probably low level exposure to pesticides.

Table 3: Decrement response, post exercise facilitation and post exercise exhaustion of the patients and the controls

Parameter	Controls		Patients		Controls vs 1 st assessment		Controls vs 2 nd assessment		1 st assessment vs 2 nd assessment	
	Mean % (SE)	1 st assessment Mean % (SE)	2 nd assessment Mean % (SE)	Mean difference (controls – patients)	95% CI	Mean difference (controls – patients)	95% CI	Mean difference (1 st – 2 nd assessment)	95% CI	
										Mean % (SE)
Decrement at rest (A ₂)	-0.5 (0.3)	-1.4 (0.5)	-0.9 (0.3)	0.9	1.9 to -0.2	0.4	1.2 to -0.5	-0.7	-1.8 to 0.3	
Decrement at rest (A ₄)	-0.6 (0.4)	-1.5 (0.5)	0.8 (0.5)	0.9	2 to -0.4	-1.5	-0.2 to -2.7	-2.3	-4 to -0.5	
Decrement at rest (A ₅)	-0.5 (0.5)	-1.0 (0.5)	0.8 (0.5)	0.6	2 to -0.9	-1.3	0.05 to -2.7	-1.9	-3.9 to -0.1	
Decrement at immediately after maximal isometric exercise (B ₂)	-0.9 (0.5)	-1.2 (0.5)	-0.3 (0.2)	0.3	1.6 to -1	-0.6	0.6 to -1.8	-1.2	-2.4 to 0.05	
Decrement at immediately after maximal isometric exercise (B ₄)	-0.5 (0.5)	-0.2 (0.5)	0.4 (0.5)	-0.3	1.2 to -1.7	-0.9	0.5 to -2.3	-0.7	-2.6 to 1.2	
Decrement at immediately after maximal isometric exercise (B ₅)	-0.8 (0.5)	-0.2 (0.5)	0.6 (0.6)	-0.7	0.9 to -2	-1.5	0.2 to -3	-0.8	-2.9 to 1.3	
Decrement 2 min after maximal isometric exercise (C ₂)	-1.6 (0.4)	-1.6 (0.4)	-1.2 (0.7)	0.03	1.2 to -1	-0.4	1.1 to -1.9	-0.5	-2.3 to 1.3	
Decrement 2 min after maximal isometric exercise (C ₄)	-1.3 (0.5)	-1.2 (0.4)	1.6 (1.0)	-0.2	1 to -1.4	-2.9	-0.8 to -5	-3.0	-5 to -0.8	
Decrement 2 min after maximal isometric exercise (C ₅)	-1.6 (0.5)	-0.8 (0.5)	1.5 (1.0)	-0.7	0.8 to -2	-3.1	-1 to -5	-2.4	-5 to 0.3	
Post exercise facilitation (B _{1/A1})	1.05 (0.04)	0.9 (0.03)	1.0 (0.03)	0.06	0.2 to -0.06	0.03	0.1 to -0.08	0.02	-0.09 to 0.1	
Post exercise exhaustion (C _{1/A1})	1.01 (0.04)	1.0 (0.05)	1.0 (0.04)	0.02	0.1 to -0.1	0.04	0.2 to -0.08	0.02	-0.1 to 0.2	

Table 4: The mean latency difference of BAER in the patients and the controls

	Control group		Test group		Mean differences				95% CI	
	1 st assessment N=70	2 nd assessment N=53	1 st assessment N=70	2 nd assessment N=53	Controls vs 1 st assessment	Controls vs 2 nd assessment	1 st assessment vs 2 nd assessment	Controls vs 1 st assessment	Controls vs 2 nd assessment	1 st assessment vs 2 nd assessment
<i>Right side</i>										
1-111	2.2 ± 0.6	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.07	0.11	0.04	-0.04 to 0.1	-0.1 to 0.05	-0.08 to 0.07
111-V	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.5	0.02	0.08	0.05	-0.04 to 0.09	-0.08 to 0.06	-0.09 to 0.05
1-V	4.0 ± 0.3	4.0 ± 0.2	4.0 ± 0.2	3.9 ± 0.2	0.01	0.03	0.04	-0.03 to 0.1	-0.1 to 0.06	-0.1 to 0.07
<i>Left side</i>										
1-111	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.03	0.03	0.005	-0.2 to 0.07	-0.05 to 0.2	-0.2 to 0.1
111-V	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.03	0.007	0.02	-0.09 to 0.1	-0.2 to 0.05	-0.07 to 0.1
1-V	3.9 ± 0.2	3.7 ± 0.2	3.7 ± 0.2	3.9 ± 0.2	0.06	0.03	0.03	-0.09 to 0.1	-0.08 to 0.1	-0.15 to 0.07

Table 5: Score of individual domains in the MMSE

MMSE / Domain	Controls (n = 61)	1 st assessment (n = 60)	2 nd assessment (n = 42)	Mean difference		95 % CI	
				Controls - 1 st assessment	Controls - 2 nd assessment	Controls vs 1 st assessment	Controls - 2 nd assessment vs 1 st assessment
MMSE total score	25.1 (3.3)	26.5 (2.8)	26.6 (3.3)	-1.4	-0.05	-1 to 1	-2.4 to -0.4
Orientation	9.4 (0.9)	8.8 (1.4)	9.8 (0.5)	0.6	-0.4	-1 to -0.2	-1.5 to -0.6
Registration	2.9 (0.2)	2.9 (0.3)	2.6 (0.6)	0	0.3	-0.07 to 0.07	-0.6 to -0.3
Attention and calculation	3.2 (1.8)	2.8 (1.8)	3.0 (2.0)	0.4	0.1	-1 to 0.3	-0.9 to 0.6
Recall	2.4 (0.8)	2.6 (0.8)	2.6 (0.6)	-0.1	-0.1	-0.2 to 0.4	-0.3 to 0.2
Language	8.5 (0.8)	8.0 (1.4)	8.2 (1.3)	0.5	0.4	-0.9 to -0.1	-0.8 to 0.04

Reduction of SNCV and MNCV of the patients in our study indicate that there may be demyelination following acute OP exposure. Since we did not follow up the patients beyond six weeks of exposure we do not know whether the changes were reversed or worsened with time.

Reduced amplitude and/or area of CMAP on distal stimulation were observed in several comparisons. These indicate that there may be an axonal damage since amplitude and area under negative curve of CMAP are directly proportional to the number of functioning axons (10). If the whole length of the nerve is affected, F-wave latency should be prolonged. Reduced nerve conduction velocity only in the distal segment may be an evidence of distal demyelination with sparing of proximal segment. Since we did not perform segmental nerve conduction studies focal damage cannot be excluded.

F-wave studies are also important for recognizing the proximal segment involvement since it is produced by antidromic activation of motor neurons. It is also important to identify marginal changes of standard MNCS since an impulse travels a long pathway to produce an F-wave, and additive effects are more obvious in F-wave latency measurement as it measures the delay in a much longer segment (10). The latency of and F-wave includes the time required for the evoked action potential to ascend antidromically to the anterior horn cells, the time between the beginning of antidromic activation and subsequent orthodromic discharge (the central "turnaround" time) and the time required for the resultant action potential to descend orthodromically from the anterior horn cells to the muscle fibers. F-wave abnormalities may be loss of response (reduction of occurrence) or prolonged latencies (10). F-waves do not occur with each stimulation. They depend on excitability of motor neurons. In normal individuals F-wave occurrence is more than 90% (10).

There was a statistically significant reduction of F-wave occurrence observed in the median and the ulnar nerves in the first assessment compared to the controls. Although there was prolongation of F-wave latency, it was not statistically significant.

Some nerves such as the ulnar and the common peroneal are highly vulnerable to external damage in the ulnar groove and behind the head of the fibula

respectively. Improper nursing care may be partially contributed to the nerve damage.

Although autonomic function in farm workers has been looked in to, there were no studies that looked at autonomic function following acute OP exposure. In the current study neurophysiological parameters of the exposed individuals were compared with the parameters of matched controls.

Variation of heart rate during rest, deep breathing and isometric muscle contraction were tested in flower bulb farmers who had chronic mixed pesticide exposure by Ruijten M.W.M.M *et al.* (1994). Significant autonomic dysfunction was shown in variation of heart rate during rest and deep breathing (24). We did not assess variation of heart rate during rest but results for heart rate variation during deep breathing were similar in both studies.

In the tests reflecting parasympathetic damage (heart rate response to Valsalva manoeuvre, heart rate variation during deep breathing and immediate heart rate response to standing) a positive result was shown only with heart rate response to deep breathing. It is well known that the response of the heart rate can be abolished by atropine (7). The first assessment of the patients was conducted within the mean of three (IQR 1 - 4) days after the cessation of atropine therapy. The effects of atropine may not have disappeared completely even 6 weeks after exposure. On the other hand, only 48/66 patients were able to do the Valsalva manoeuvre. The sample size may not have been adequate to draw a conclusion. Or else the autonomic function of exposed individuals may not have been affected.

Change of diastolic BP 3min after standing was significantly low in the patients, but recovered completely at six weeks after exposure. Blood pressure response to standing reflects sympathetic function. But it begins to show abnormal results with more severe sympathetic nerve damage (7). Sympathetic damage in our patients may not have been severe enough to give abnormal results in the blood pressure response to standing.

Reduction of amplitude and prolongation of latency in SSR are in favor of sympathetic damage at one week after exposure. SSR represents the change in voltage measured at the skin surface following a single electrical stimulus. It depends on the electrical activity arising from sweat glands (10).

Latency of SSR is inversely proportional to the number of sweat glands innervated (10). Hence sympathetic innervations to sweat glands were less in the patients compared to the controls. In the second assessment both the latency and the amplitude of SSR were improved. We could not eliminate the effects of atropine on sweat glands and changes in the first assessment may have been due to effects of atropine. However patients did not show sympathetic dysfunction as reflected in SSR at six weeks after exposure.

It is well known that high residual urine volume is associated with increased risk of urinary tract infections. Since our results showed that residual urine volumes in patients were significantly higher than in the controls, it is very important to follow up such patients further.

One third of patients were admitted with co-ingestion of alcohol. Acute alcohol ingestion is unlikely to have had any effects on the parameters we assessed, since the assessments were carried out at one week after the exposure. It is well known that long term alcohol consumption is associated with neuropathies including autonomic neuropathy. Adjusted multiple linear regression did not show widespread effects of alcohol consumption on autonomic function.

The number of patients who could complete the test of blood pressure response to sustained hand grip was significantly lower than the number of controls who could complete the test. The difference may be due to muscle weakness following poisoning.

The gold standard electrophysiological tool to explore the neuromuscular junction function is single-fiber electro myography (SF-EMG) (15, 25, 26). We explored whether RNS with exercise might be a useful alternative method as SF-EMG is not available in most centers.

Few patients had RNS abnormalities in the first assessment and this was no different from the controls. Results of RNS six weeks after the exposure showed significant decrement response. However RNS does not appear to be a useful method to explore medium to long term NMJ function.

NMJ dysfunction has been demonstrated by fast repetitive nerve stimulation with OP poisoning before clinical recovery (27), but there is no evidence whether these changes persist over the long term.

A study done to see the effects of occupational exposure to OP on neuromuscular function did not show any detectable neuromuscular disturbances with RNS and with SF-EMG (28).

The frequency of neuromuscular transmission abnormalities detected by SF-EMG was significantly higher than those detected by RNS (28,29).

Decrement response is more obvious in fast repetitive stimulation than the slow repetitive stimulation. The current study concentrated only the slow repetitive stimulation with exercise modification to magnify the function of NMJ. However this may not be sensitive enough to detect subtle abnormalities (30).

The amplitude of compound muscle action potential may increase during high-frequency nerve stimulation or after voluntary activation of muscle (10). The measurement of CMAP amplitude in fast repetitive stimulation is not recommended by some since amplitude of the CMAP during high frequency stimulation may give variable and inconsistent results (15). Therefore we measured CMAP amplitude just after and two minutes after the isometric muscle exercise. Even with isometric muscle exercise the current study was not able to demonstrate significant decrement comparing to the controls. Previous studies on neuromuscular synapse function in organophosphate workers also did not show significant decrement response compared to the controls (13,14).

With each depolarization, Ca^{++} is release into the periterminal space. If another depolarization occurs, high Ca^{++} concentration leads to increase in acetylcholine quanta released. If neuromuscular transmission is impaired this greater acetylcholine release briefly improves synaptic transmission, producing facilitation (15). Marked facilitation is characteristic of presynaptic blockade. Although facilitation can also sometimes be positive with postsynaptic problems (15).

Although it was recommended to calculate the changes in CMAP size between the first and the fourth or the fifth response of a train of stimuli (15) we took the second response as well, since Maselli *et al* (2004) and Jayawardana *et al* (2008) observed the maximum decrement at the second stimulus (27,31). The data set of the current study showed

the maximum decrement either at the second or the third stimulus.

The majority of the cases of the current study showed increment pattern progressively over the train. For that reason the mean percentage decrements shown in the table 2 are negative values. This pattern is described as pseudo increment and is a normal variant (32).

Even though a decrement response (>8%) was observed in few occasions both in the patients and the controls, even these decrements were not confirmed. False positive results of repetitive nerve stimulation is possible since the studies are technically difficult; artifacts resulting from electrode placement, movements, changes of skin resistance and intramuscular temperature cannot be entirely controlled (25).

Very few human studies have examined ototoxic effects with pesticide exposure. No studies have assessed the ototoxic effects following acute exposure to OP.

BAER is a sensory evoked potential used to assess the integrity of the auditory pathway from the eighth nerve to the auditory cortex (16). The inter peak latencies (I - III, III - V and I - V) of BAER provide a straightforward method to roughly localize lesions in the auditory pathway (16).

Animal studies by Bielefeld E C *et al.* (2005) and Harris K C *et al.* (2006) showed shifting of evoked potential threshold and loss of inner and outer hair cells following application of 10mM, 5mM and 3mM of PQ to cochlea through a surgical incision (33,34). The current study did not look into the auditory threshold level.

Clerici W J (1996) demonstrated disruption of generation and transmission of afferent cochlear signals by generation of reactive oxygen species within the perilymphatic space with artificial perilymph and hydrogen peroxide (35). Even though OP produces reactive oxygen species after ingestion, the concentration of substances reaching the perilymphatic space may not be sufficient to damage the cochlea.

Kimura K *et al.* (2005) studied the effects of the event-related evoked potentials in tobacco farmers who were exposed to different pesticides including OP. They did not see any significant effects on the event-related evoked potentials (36).

Cognitive function was tested with the simple and quick assessment tool of MMSE. The MMSE provides a measure of cognition which covers a broad set of cognitive domains: orientation, registration, short term memory, attention, calculation, visuo-spatial skills and apraxia (18). The sensitivity and specificity of MMSE were 100% and 69% to the cut off level of less than 24 evaluated against the performances at CAMCOG (Cambridge Cognitive Score) (18).

Stephens R *et al* (1995) reported impaired cognitive function in sheep farmers who were exposed to OP through sheep dipping, which involves immersing each animal in a pesticide solution to control parasitic infections. Exposure to OP was appeared to be splashing on to the skin where protective cloths were seldom worn. The speed of performance of simple reaction time, symbol-digit substitution and syntactic reasoning were significantly slower in the farmers than the controls. No impairment was found in short term memory (by digit span test and visual spatial memory) and long term memory (by serial word learning, category search classification, category search recognitions) in the cases compared to the controls (1,37).

Steenland K *et al* (1994) investigated chronic sequel of acute occupational OP poisoning (38,39). They studied cognitive function via finger tapping (motor speed test), sustained visual attention, visuomotor accuracy, visuomotor speed, symbol digit, visual memory and serial digit learning tests. Significant impairment found in sustained visual attention and symbol digit tests in the cases compared to non-exposed reference (38,39).

A study done on volunteers with varying degrees of occupational exposure to OP showed significant impairment on the Bender Visual Motor Gestalt test (used to evaluate visual motor maturity) and part B of the Trail Making test (Trail Making test is neuropsychological test of visual attention (37).

The study done by Fiedler N *et al* (1997) recruiting tree fruit farmers who had occupational exposure to OP demonstrated significantly slow simple reaction time for the dominant and nondominant hands of the exposed than the controls. No significant impairment seen in the visuomotor coordination, verbal memory, verbal ability and expressive and receptive language (38,39).

The review article by Kamel F *et al.* (2004) looked into association of pesticide exposure with neurological dysfunction. They found inconsistencies among the studies. Most studies found deficits in one or more tests of cognitive function but different tests were affected in different studies (40).

The current study did not showed persistent impairment of cognitive function following acute OP exposure. The methods we used may not be sensitive enough to detect mild cognitive impairment. Further studies are required with more sophisticated neurobehavioural tests to assess cognitive function following acute OP poisoning.

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Self-limiting nephrotic range proteinuria associated with dengue haemorrhagic fever

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Introduction

Dengue fever (DF) is the most prevalent mosquito-borne viral disease in South and Southeast Asia (1). Association of gross nephrotic-range proteinuria with DF has not been reported in Sri Lanka. We report a female with dengue haemorrhagic fever (DHF) complicated with acute liver failure and self-limiting, nephrotic-range proteinuria

Case Report

A 33 year-old previously healthy female presented with fever, vomiting, arthralgia of three days. On admission, she had pulse rate of 92bpm and blood pressure of 100/70mmHg.

On the fourth day of fever, her blood pressure revealed a significant drop to 80/70mmHg. Her initial full blood count revealed a platelet count of $89 \times 10^9/L$ and clinical diagnosis of DHF was made and she was managed with intravenous fluids according to WHO guidelines. On admission urine ward test revealed no proteinuria. Initial serum alanine transaminase (ALT) and aspartate transaminase (AST) were 800 u/L and 3100 u/L. Repeat ALT, AST later rose up to 3900 u/L and 15000 u/L respectively (**Table 1**) with international normalized ratio (INR) of 1.79. Diagnosis of grade 2 hepatic encephalopathy was made and N-Acetyl Cysteine and liver failure regimen was commenced. On the fifth day, she became dyspnoeic with bilateral pleural effusions and ascites.

Table 1: Laboratory investigations

Day of Fever	D3	D4	D5	D6	D7	D8	D9	D10	D11	D14
Plt ($\times 10^6/L$)	89	10	23	31	44	129	135	144	191	299
HCT (%)	37.5	49.9	39	42.5	39.1	37.6	33.2	34	33	33.5
WBC ($\times 10^6/L$)	3.06	4.3	9.9	10.3	7.4	7.3	8.1	7.6	7.1	7.8
Creatinine (mol/L)	-	103	110	133		73	-	-	-	76
ALT (U/L)	-	800	3900	2020	1010	148	-	-	-	68
AST (U/L)	-	3100	15000	8800	1580	139	-	-	-	70
Albumin (g/dL)	-	-	-	-	2.39	2.36	-	-	-	3.5
INR	1.0	-	1.79	1.55	1.0	-	-	-	-	-
UWT albumin	0	-	-	-	4+	4+	2+	1+	0	0
PCR	-	-	-	-	13.4	-	-	1.47	-	-
Ca ⁺² (mg/dL)	-	-	8.4	7.2	-	-	-	-	-	-
CRP (mg/dL)	19.8	-	-	-	-	-	47.1	-	-	-

D - Day of fever, WBC - white blood cells, HCT - Hematocrit, Plt - platelet count, Creatinine - serum creatinine, ALT - alanine transaminase, AS aspartate aminotransferase, INR - International normalization ratio, UWT alb - Urine ward test for albumin, PCR - protein/creatinine ratio

During the next 48 hours she improved with rising platelet counts and decreasing liver enzymes. IgM and IgG against dengue virus (DENV) were positive. Bilateral pleural effusions and ascites remained unresolved after recovering from critical phase. Serum albumin tested on the seventh day of illness was low (2.26g/dL). Urine ward test on the same day revealed gross (4+) proteinuria and the urine protein to creatinine ratio (PCR) was in the nephrotic range (13.44g protein/g creatinine (>3.5 nephrotic range)). Gross (4+) proteinuria persisted up to day ten and cleared gradually. On the fourteenth day, urine albumin was absent and repeat serum albumin was 3.5g/dL.

Hypoalbuminemia associated with gross proteinuria was treated with albumin infusions. After resolution of gross proteinuria, she was discharged on the fourteenth day. Urine analysis carried out two weeks later on the follow-up visit revealed normal PCR, AST, ALT and serum albumin levels.

Discussion

Plasma leakage leading to DHF is the most dreadful complication in DF. Proteinuria is sometimes observed in DF and DHF, typically without evidence of renal involvement.

Hanh *et al.* measured urine albumin to creatinine ratios (UACRs) daily in children with suspected DF in Vietnam and found that low-level albuminuria is common in relatively mild DF (2). They observed that peak values reach around the critical period for dengue-associated plasma leakage, but concluded it is unlikely to be useful for early diagnosis or risk prediction (2).

In contrary, Farhad *et al.* found that peak UACR could potentially predict DHF in patients with dengue requiring close monitoring (3). In their series, patients with uncomplicated DF did not develop significant proteinuria, while 96% of patients with DHF had significant proteinuria. They observed that maximum proteinuria coincides with defer vascence and reported a statistically significant association of higher degree of thrombocytopenia with significant proteinuria (3). In their series, proteinuria was self-limiting and resolved with recovery from fever.

Renal biopsies in patients with DHF have showed histology similar to IgA nephropathy (4). Identification of soluble immune complex in DHF specific for DENV in serum has been reported indicating that immune complexes get deposited in vascular and glomerular tissue leading to proteinuria (5).

Nephrotic range proteinuria is rarely been reported in patients with DHF (6,7). Our patient had no manifestations of renal damage, such as rising serum creatinine, haematuria or urinary casts but, only had transient gross nephrotic-range proteinuria and significant transient hypoalbuminemia. The half-life of serum albumin is around 21 days (8). Therefore infective or inflammatory disorders with liver involvement lasting for more than three weeks can lead to hypoalbuminemia. This patient had gross proteinuria associated with low serum albumin on the seventh day of fever, indicating urinary loss and plasma leakage of albumin as the most likely causes for low serum albumin level.

Delayed resolution of pleural effusions and ascites with rise in urine protein excretion prompted us to test for serum albumin and treatment with albumin infusions lead to rapid recovery of effusions and ascites. Hypoalbuminemia is a common feature in DHF but, we report this patient to highlight that nephrotic range proteinuria is a rare, self-limiting complication of DHF. It should be suspected when there is a delay in the resolution of ascites and pleural effusion. Albumin infusions given even after recovering from critical phase of DHF to treat ascites and pleural effusions associated with severe hypoalbuminemia can restore reduced plasma oncotic pressure secondary to transient urinary protein loss and expedite recovery.

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Congenital dyserythropoietic anaemia type II

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Introduction

Congenital Dyserythropoietic Anaemias (CDA) are a group of rare congenital anaemias characterized by ineffective erythropoiesis. CDA type II is also known by the acronym HEMPAS denoting Hereditary Erythroblastic Multinuclearity with Positive Acidified Serum lysis test. Nearly 450 cases have been reported worldwide (1). We report a case of CDA type II in a young male.

Case Report

A 24 year-old previously well male was admitted with fatigue and faintishness associated with a febrile illness for two weeks. He was found to have pancytopenia and was managed symptomatically. Two months later he presented with fatigue and yellowish sclera for one week duration. He is a product of non-consanguineous healthy parents with no significant family history.

On examination he was moderately pale and icteric with bilateral anterior cervical and axillary lymphadenopathy and mild hepatosplenomegaly. Rest of the physical examination was normal.

His initial full blood count revealed haemoglobin 4.5g/dl, white cells 3,300/mm³ and platelet 100,000/mm³ showing pancytopenia with evidence of a viral infection. In his second admission full blood count revealed haemoglobin 8.7g/dl, white cells 5,800/mm³, platelet 219,000/mm³ and blood picture appeared to have normochromic normocytic red cells with increased polychromatic cells, moderate anisopoikilocytosis and irregularly contracted cells, normal white cells and platelet. Reticulocyte count was 1.4% and reticulocyte index was 1.01%. Serum bilirubin was 184µmol/L, Direct Coombs test was negative.

Bone marrow examination revealed marked hypercellularity with massive erythroid hyperplasia showing predominantly dyserythropoietic maturation including binucleated late erythroblasts comprising 25% of the late erythroblasts and a few multinucleated erythroblasts. Granulopoiesis and megakaryopoiesis were normal. Bone marrow iron stores were 3+ according to 0 - 6 scale (2).

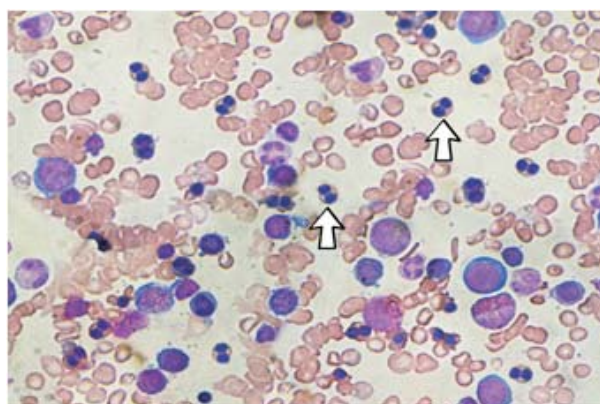


Figure: Bone marrow aspiration showing binucleated late erythroblasts (arrows)

Provisional diagnosis of CDA II was made and HAM test (3) with several donor sera was performed. It was positive showing lysis of patient's red cells with 6 out of 10 donor sera and absent lysis with his own serum.

His serum ferritin was 722ng/mL, ALT - 74U/L, AST - 89U/L, serum creatinine - 113mol/L. Abdominal ultrasound scan revealed mild hepatomegaly, moderate splenomegaly and multiple gallbladder calculi. Skeletal survey, 2D echocardiogram and lymph node biopsy were normal.

Based on clinical and haematological data CDA type II was diagnosed.

He was treated symptomatically and discharged on folic acid therapy after appropriate counselling. He's being followed up at our haematology clinic till date.

Discussion

CDA II is the commonest form of CDA with an autosomal recessive inheritance. The most frequently affected gene is SEC23B (CDAN2) in chromosome 20p 11.23 leading to defective glycosylation of red cell membrane constituents (band 3, band 4.5, glycophorin, glycolipids). Abnormal band 3 proteins is hydrophobic which tends to cluster at the cell surface leading to increased binding of IgG to the red cell surface and increased phagocytosis by macrophages. Defects in glycophorin A which has complement regulating activity, make the CDA II red cells more liable to lysis in acidified heterologous sera by naturally occurring complement fixing IgM anti HEMPAS antibodies (1,4,5).

It presents with anaemia of variable severity, jaundice and hepatosplenomegaly. In our patient, the diagnosis of CDA type II was made with typical bone marrow morphology and positive acid lysis with several donor sera.

Novel diagnostic tests are red cell membrane protein electrophoresis demonstrating abnormal band 3 protein and peripheral double membrane appearance in red cells on electron microscopy.

Our patient had been apparently well until his first hospital admission. He has not had any episodes of fatigue or icterus in his childhood. Even though the typical presentation of CDA II occurs during childhood, here it was delayed. His initial presentation was a transient pancytopenia which had recovered within two weeks and most probably due to a viral infection causing transient bone marrow aplasia. Since there was no significant icterus and the absence of markers of haemolysis in the initial presentation, CDA was not considered as a differential diagnosis. Yet it's extremely important to look for a congenital haemolytic anaemia in any young patient presenting with a pancytopenia. Presence of a considerable bone marrow reserve, degree of function of the reticuloendothelial system,

the type of genetic mutation and absence of cardiac comorbidities are the possible factors which had affected on his delayed presentation.

Secondary haemachromatosis, cholelithiasis and paravertebral extramedullary haemopoietic pseudotumours are known late complications (1,6).

Diagnosis of CDA II can easily be missed by routine full blood counts since it is a normochromic normocytic anaemia and blood picture and reticulocyte index provide important diagnostic clues of dyserythropoiesis. Therefore CDA has to be considered in the differential diagnosis of any young patient presenting with anaemia and hepatosplenomegaly.

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A case of scrub typhus meningoencephalitis in Southern Province, Sri Lanka

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Introduction

The incidence of rickettsial infections has increased worldwide recently. Sri Lanka also experiences a similar trend. Scrub typhus is the main rickettsiosis reported in Southern province Sri Lanka (1) and it is commonly present as PUO (pyrexia of unknown origin) (2). CNS manifestations are well known complications of scrub typhus. However, due to difficulty in diagnosis at an early stage of the disease, CNS complications are often missed (3). Thus, scrub typhus complicated with meningoencephalitis has not been documented yet from Southern Sri Lanka. Therefore a case of scrub typhus complicated with meningoencephalitis is presented here. Transmission of scrub typhus requires the presence of trombiculid mites and rodents and it is caused by a gram negative intracellular pathogen *orientia tsutsugamushi*.

Case report

A 29 year-old previously healthy lady from Ahangama had intermittent high fever with chills, arthralgia, myalgia, headache, irritability, drowsiness and vomiting for 10 days. On admission she recorded high fever (101°F). Thorough examination revealed an eschar over left breast closer to areolar (*figure 1*). There was marked neck rigidity. No neurological deficit was identified. Optic fundi were normal and she was haemodynamically stable.

Investigations showed a total white cell count of 10,000/mm³ with neutrophilia (80%), normal Hb (13.2 g/dL), and marginal thrombocytopenia (100,000/mm³). Blood picture was bacterial in

nature. Serum creatinine was 0.8 mg/dL. Total bilirubin was 0.8 mg/dL and direct 0.4 mg/dL, with albumin 3.5 gm/dL and total protein 6.4 gm/dL. SGOT and SGPT were elevated (160 and 180 U/L, respectively) and serum ALP was 90 U/L. Serum electrolytes and urine routine were normal and the imaging (chest X-ray / NCCT brain) and ECG were negative. CSF analysis on day 10 revealed lymphocytic pleocytosis (28 cells), high protein (85 mg), and normal glucose (60 mg/dl). There were red blood cells (240 cells/mm³) may be due to a collection error. Culture, gram stain and cytology of CSF were negative. Weil felix of day 12 revealed positive OX K antibody titer (1 : 320) while OX 19 and 2 were reported negative. Immunofluorescence Assay for IgG & IgM was carried out at University of Peradeniya revealed negative results for *Orientia tsutsugamushi* and *Rickettsia conorii*. Positive IgM and weekly positive IgG for *Orientia tsutsugamushi* were reported after an ELISA carried out at MRI Colombo.



Figure : Eschar on areolar of left breast

Figure 2 summarizes the drug therapy and disease repose to it. Doxycycline 100mg bd was started on admission but omitted as there was no improvement in 48 hours and IV chloramphenicol was started on day 12 of illness. Fever settled within 48 hours after starting IV chloramphenicol and complete, uneventful recovery was seen by 14 days of IV antibiotics.

Patient was followed up at 2 weeks, 1 month intervals after discharge. On each clinical assessment no complications were identified.

Based on the clinical picture of meningitis with eschar, dramatic response to chloramphenicol treatment, positive Weil Felix test, ELISA and CSF report, a final diagnosis of scrub typhus meningoencephalitis was made.

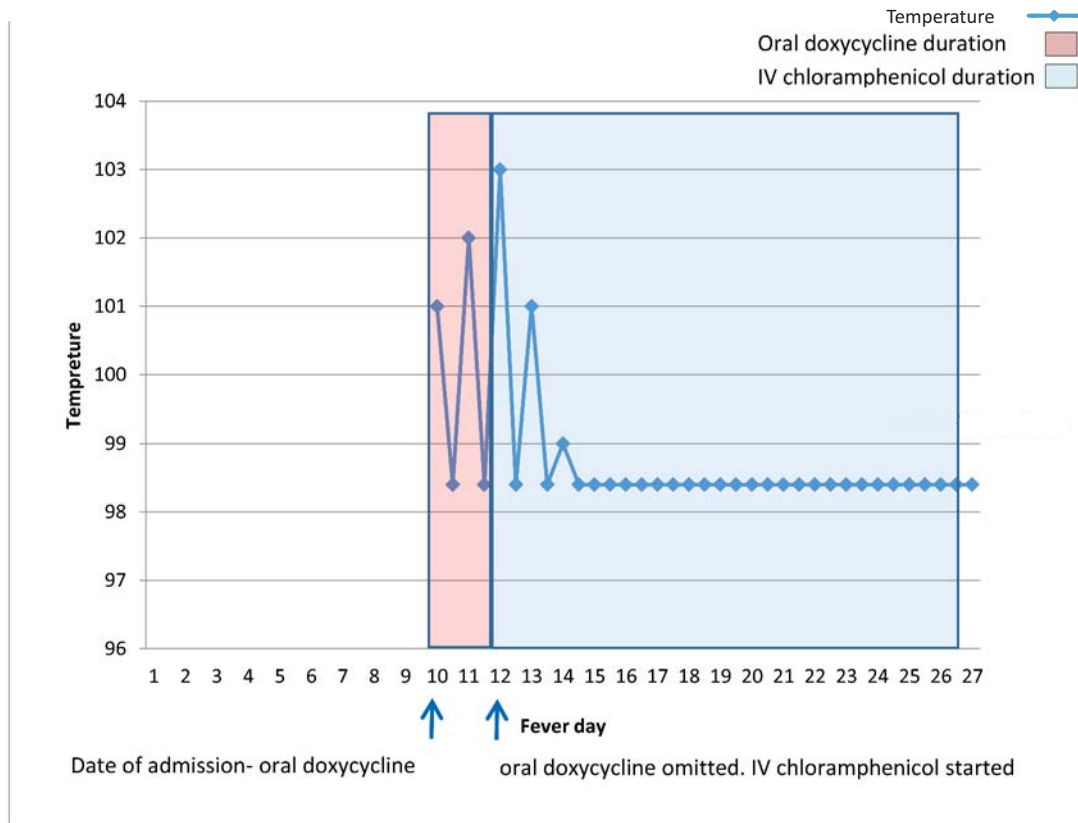


Figure 2: Temperature chart with antibiotics given on each day

Discussion

Recently a case series reported by Kularathne *et al.*, described 17 cases of neurological manifestations of spotted fever group Rickettsiosis in Central Province, Sri Lanka (2). Premarathne *et al.*, reported a case of hearing loss and a case with Parkinson disease due to scrub typhus in Western Province, Sri Lanka, (4,5). However, this is the first documented scrub typhus meningoencephalitis case from Southern Province of Sri Lanka. It may be due to inadequate reporting, misdiagnosis, non-specific nature of the disease or due to common use of

antibiotics such as doxycycline or azithromycin by physicians to treat acute febrile illnesses empirically at early stage, preventing such late complications.

The greatest degree of CNS involvement in rickettsiosis occurs in spotted fever and epidemic typhus, followed by scrub typhus (5). Although the clinical picture in this case was limited to meningoencephalitis, CNS manifestations can range from headache, seizures, delirium, hearing loss, focal CNS damage, cerebral hemorrhage, Parkinsonism and Guillain-barré Syndrome (4).

The pathognomonic eschar is present in nearly 60% of patients with scrub typhus. It's the most useful diagnostic clue in patients with acute febrile illness in areas endemic for scrub typhus and therefore should be thoroughly examined for its often inconspicuous presence in unexposed areas of the body (5).

IFA (indirect florescent anti-body assay) is considered the gold standard. Yet it is neither the most specific nor the most sensitive diagnostic test available. The most sensitive and specific diagnostic test is in vitro isolation in cell culture, which is not available in Sri Lanka. The Weil–Felix test is commercially available. 1 : 80 titer or a fourfold rise over previous levels is significant. Weil-Felix test OXK has a specificity of 97% but less sensitive. ELISA test has more sensitivity and specificity than IFA. In this case Weil-Felix and ELISA IgM showed positive results for scrub typhus. In scrub typhus meningitis, RBC are often found in the CSF and cellular reaction is usually lymphocytic predominant with approximately 20/mm³, CSF protein is usually about 60mg/L, and glucose concentration is normal (3). In this case the cell counts, protein and sugar were compatible with CSF reports available in literature of scrub typhus meningitis.

Oral doxycycline 200mg oral daily for 7 days is the treatment of choice. Chloramphenicol 500mg 6 hourly and rifampicin, 900mg per day for a week, are alternative 2nd line treatment. Rapid defervescence after antibiotics is so characteristic that it is used as a diagnostic test for scrub typhus (5). In this case IV chloramphenicol 500mg 6 hourly was used as its CSF penetration is superior to that of doxycycline (5).

In conclusion, we describe the first reported case of scrub typhus meningoencephalitis from Southern Province, Sri Lanka. The recent increase in scrub typhus causes a proportionate increase in the neurological complications. In order to allow early diagnosis and treatment in suspected cases and reduce morbidity and mortality, a high degree of clinical suspicion and familiarity with various clinical manifestations is vital. Therefore, we hope this report will encourage physicians to promptly diagnose, treat and further research on typhus meningoencephalitis.

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