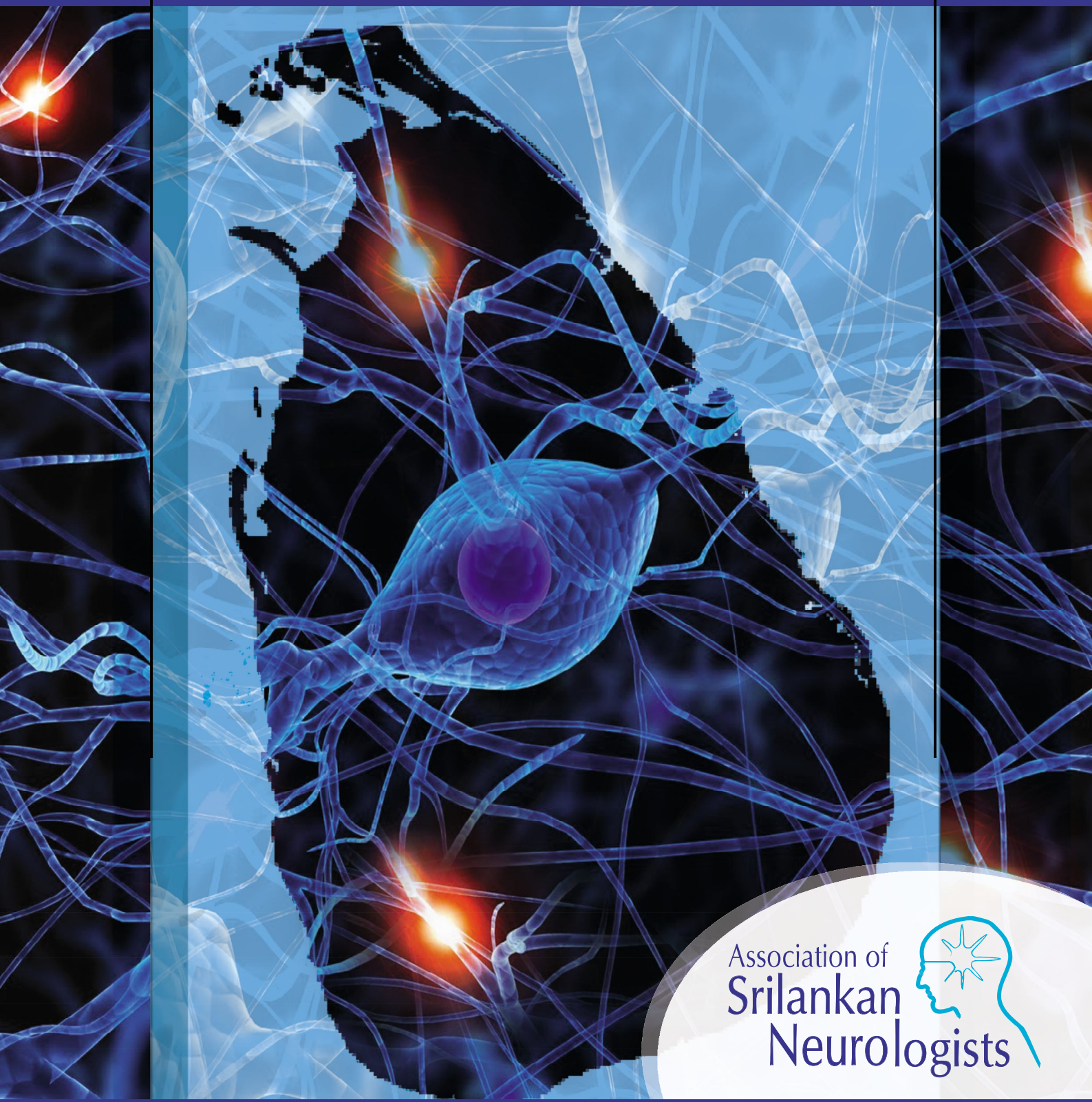
Sri Lanka Journal of Neurology

Official Journal of The Association of Srilankan Neurologists



Association of Srilankan Neurologists

SRI LANKA JOURNAL OF NEUROLOGY

AIMS AND SCOPE

The *Sri Lanka Journal of Neurology* (*SLJN*) is a forum for debate, education and entertainment for health professionals interested in Clinical Neurology, Neurosurgery and Neurosciences. The Journal is aimed at practicing Neurologists, Neurosurgeons and Neuroscientists with commitments in Sri Lanka and has relevance to all those working in the health sector. The Journal's prime responsibility is to the members of the Association of Sri Lankan Neurologists (ASN) and its objective is to promote good clinical practice and influence policy making across the medical world through publication of original research and peer reviewed articles on current issues and to foster responsible and balanced debate on issues that affect medicine and health care in Sri Lanka. Contributions to the *SLJN* reflect its national and multidisciplinary readership and include current thinking across a range of medical specialties and the Journal assists the ASN in its continuing medical education programme.

While members of the ASN receive the *SLJN* as one of the benefits of membership, it will be available to other health professionals on paying a subscription fee. The Journal has full editorial independence.

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Message from the President of ASN

Sri Lanka Journal of Neurology, 2012, **1**, 1

It is with great pleasure and a sense of pride that I am sending this short message today, the 17th of November 2012 on the occasion of the launch of the first dedicated journal of neurology in Sri Lanka. The ***Sri Lanka Journal of Neurology*** *(SLJN)* will be the official journal of the Association of Srilankan Neurologists (ASN). It is indeed a great honour to be the President of ASN at a time when such a historic event is taking place. I am also delighted to see a local journal that appeals to us neurologists providing an overview of the latest clinical and research findings. I am certain that it will recognize the complimentary elements of the discipline bringing together all the different multidisciplinary perspectives. While providing opportunities to all neurologists and trainees to publish their work I believe the *SLJN* can foster and propel progress and development of the specialty at a time when the world has moved in to an era of "Evidence-Based Practice" and accountability.

On a personal note I must thank Prof. Saman Gunatilake for readily accepting my invitation to be the first Editor-in-Chief of *SLJN*. Given his vast experience in editorial work in many medical journals we can be assured that *SLJN's* scholarly communications will uphold the highest professional standards. As the inaugural Editor-in-Chief he will help develop the vision and scope of the Journal. The small but high caliber Sri Lankan neurology community is certainly competent enough to produce, edit and publish quality scientific literature that is valid and reliable. In addition to the local editorial board the *SLJN* has appointed an international advisory panel comprising of world leaders in neurology. Their guidance and advice would further strengthen the Journal to be in line with international guidelines and publication ethics.

These are indeed exciting times for neurology in Sri Lanka. Today our services are expanding and are available in all nine provinces of the country. The ASN is going from strength to strength forging new links and crossing new boundaries. With the launch of the *SLJN* I believe we are turning a new page in the history of neurology in Sri Lanka. Also I sincerely hope that this will further strengthen our already strong professional skills and standards.

I wish the *SLJN* all success in the future.

Bimsara Senanayake
President,
ASN 2012

Editorial

The beginning

Sri Lanka Journal of Neurology, 2012, **1**, 2

The formation of the Association of Srilankan Neurologists in 2007 is still fresh in our memories, though we have progressed rapidly. Our annual scientific sessions are of very high quality with many local and overseas participants and official delegations from the Association of British Neurologists every year. Our CME programmes are well attended and are popular with monthly lectures and case presentations. We conducted a MCQ course for trainees and it has received high praise. A journal of the Association is another milestone and this year we launch the *Sri Lanka Journal of Neurology,* the official publication of the Association. The idea was first mooted by Dr Bimsara Senanayake, the current President of the ASN, and he and the council have placed their confidence in me to carry out this special task as the Editor in Chief. The *Ceylon Medical Journal* (CMJ), the oldest and the most popular, regular journal in the country is published only quarterly. There are many other journals having started finding it difficult to publish regularly due to lack of proper research articles. In a survey of articles published in the *CMJ* and recently in an article in *Practical Neurology*, it was shown that neurology case reports lead the way in journals and in grand rounds. *Practical Neurology* article also showed that the number of Neurology text books is far ahead in number when compared to other specialties. This fascination for Neurology led to the coining of a new word “Neurophilia”.

The *Sri Lanka Journal of Neurology* (SLJN) is a forum for debate, education and entertainment for health professionals interested in Clinical Neurology, Neurosurgery and Neurosciences. The Journal is aimed at practicing Neurologists, Neurosurgeons and Neuroscientists with commitments in Sri Lanka and has relevance to all those working in the health sector. The Journal’s prime responsibility is to the members of the Association of Srilankan Neurologists (ASN) and its objective is to promote good clinical practice and influence policy making across the medical world through publication of original research and peer reviewed articles on current issues and to foster responsible and balanced debate on issues that affect medicine and health care in Sri Lanka. Contributions to the *SLJN* will reflect its national and multidisciplinary readership and will include current thinking across a range of medical specialties and the Journal will assist the ASN in its continuing medical education programme. The success of the Journal and its continuation will depend solely on the commitment of the ASN membership, and the performance in the past few years is good evidence how the Sri Lankan Neurologists though small in number can rally round to advance their field to the benefit of the specialty and their patients.

I wish the *SLJN* long life.

Saman B Gunatilake
Editor in Chief

Special article

Birth of the unique Institute of Neurology, Sri Lanka

J B Peiris[1]

Sri Lanka Journal of Neurology, 2012, **1**, 3-4

Neurology in Sri Lanka has progressed by leaps and bounds over the past four decades. When I became only the second neurologist in Sri Lanka (then Ceylon) in 1972, I was the only neurologist for a population of about 12 million. I remained the only neurologist for the next 10 years. However, the care of the neurology patient was relatively good in the hands of the General Physicians. All medical students of the 135 year old Colombo Medical School did a two week compulsory appointment in Neurology, while the trainee general physicians did a mandatory three month appointment. At that time, the general physician too had their postgraduate training and qualifications from the UK. Postgraduate training continued in the UK, till the Postgraduate Institute of Medicine (PGIM) of the University of Colombo was set up in 1980. From that time, PG training and examinations have been conducted by the PGIM, with a stint of training overseas, commonly in the UK.

Prior to seventies medical neurology was a neglected field in Sri Lanka, as indeed it was in many other countries. The WHO included neurosciences under mental health!

Institute of Neurology, Colombo, Sri Lanka.

Thus it was not surprising that in 1972, neurology and I received step motherly treatment from the Ministry of Health. The male patients were accommodated in 1/3 of a medical ward, with some of the patients accommodated in an air raid shelter, no more than eight feet high! The female patients were in three separate general medical wards. There was no intensive care unit and patients requiring ventilator assistance were managed in 'an iron lung'. (poliomyelitis was prevalent at that time as was Guillain Barre' syndrome). There was no dedicated ICU, EEG, EMG and physiotherapy and the medical Neurology 'unit' was dependent on a quota from the neurosurgical Unit (NSU) for angiography, myelography, air encephalography and ventriculography (there was no CT, MRI for many more years to come). The NSU was in a custom made plush new building with its own dedicated neuro-radiologist and pathologist, who fortunately were very helpful to the Medical Neurology unit. The favourite investigation for neuro-trauma was a direct puncture angiography.

It is not surprising that the young neurologist fresh from his training in Queen Square (London, Edinburgh and Glasgow) was disillusioned with the work environment but unlike some of his colleagues he did not consider migration an option. Instead he decided to build an all inclusive Institute which would be a pleasure to work in. This was no easy task.

Immediate requirements for such a gigantic venture were land within the hospital premises, funds, an architect and a cooperative builder who would take on a 'turn key job' – to build and adjust according to funds available, on a minimal profit basis. Friendly architects and engineers helped with plans and supervision of construction entirely free of charge. Finding a dedicated team was a challenge as the colleagues and even assistants (except a dynamic physiotherapist) did not give even an encouraging word. Finally it was a non medical, hospital welfare services committee of the All Ceylon Buddhist Congress which came to the rescue to collect funds. Sri Lanka being a predominant Buddhist country, is amenable to donations especially for health and education (Sri Lanka accounts for more than 90% of cornea donated worldwide).

Even so, obtaining donations (finally totalling about one million UK pounds in the early 1980s) was no easy task. Fortunately, there was a gracious lady who gave the funds required for the ground floor. This was in memory of her departed husband and his photograph adorns the ground floor of the Institute together with the photo of the neurologist responsible for building it.

The modus operandi adopted was to obtain donations dedicated for a specific purpose. We encouraged donors by specifying amounts which would entitle us to buy individual items like beds and lockers, as well as larger

[1]*Senior Consultant Neurologist and the Founder Patron of the Association of Srilankan Neurologists.*

amounts which would entitle the donor to have a unit of 4-6 beds, a ward, or a floor. Donations to the 'Neuro Hospital Fund' were acknowledged in the daily press. Larger donations for units and wards carried the benefactor's name. Even so, funds were hard to come by initially but later it became almost a prestige to give a donation. Philanthropists, politicians, public figures, patients and relatives, all chipped in with donations – big and small. Many were the donations in kind like tiling a floor or providing beds and equipment. A generous donor even gave us a 25 acre coconut estate which we gave the public trustee to auction. With difficulty we convinced the Lotteries Board to allow us to hold a Neuro Hospital Lottery – we ended with a profit only because some of the prize winners did not collect their winnings!

- The fund raising committee had weekly meeting on Sundays for three years and the technical committee also met once a week. I, the sole neurologist headed both committees.
- The 4 floor INSTITUTE OF NEUROLOGY was built in 3 years entirely from public donations. It was an enjoyable struggle and was well worth it. I made several good friends and also a few enemies, who did not like the project or a change in their slumberous life.
- It was, indeed, a dream come true and perhaps I can proudly say 'I did it my way'.

While waiting for my grandiose idea to materialize, I did not go into limbo but tried to improve the available set up. I was able to establish a small neurology intensive care unit of four beds with two simple Blease ventilators – indeed the priority need of the day.

The Institute of Neurology, complete with medical, surgical, paediatric wards, intensive care unit with ventilators and piped oxygen, lecture rooms, outpatient clinics with its own pharmacy, physiotherapy, electro-physiology, operating theatre and a private wing, encouraged postgraduates to take up neurology as a career. From the single neurologist for the whole country we now have an Association of Sri Lankan Neurologists (ASN) with over 30 neurologists distributed throughout the country, including paediatric neurologists and neurophysiologists. As the Founder Patron of the ASN I am certain that the new Institute of Neurology and the dedicated teaching helped in no small manner to popularize neurology as a specialty. It is a rare success story in the public sector harnessing the support from a grateful public.

Dr. J. B. Peiris with his successful gigantic venture.

Paper

Pattern of incidence in Guillain-Barre syndrome admitted to Teaching Hospital, Galle, Sri Lanka from 1995 to 2000

K D Pathirana[1], **C Hewage**[2]

Sri Lanka Journal of Neurology, 2012, **1**, 5-9

Abstract

Guillain-Barre syndrome (GBS) is the commonest cause of acute flaccid paralysis in Sri Lanka. Annual incidence of GBS in Sri Lanka is not known. The aim of this study was to find out the incidence of GBS in administrative district of Galle, Sri Lanka based on hospital records.

Method: We conducted a retrospective analytical study to find out the incidence and epidemiological patterns of GBS in patients admitted to Teaching Hospital Galle (THG). We scrutinized the case notes of all the patients categorized G 61.0 of 10th Edition of International Classification of Diseases Classification, from 1995 through 2000. The cases fulfilling NINCDS criteria for GBS were included in the study. We excluded the patients referred from other districts for calculation of the incidence of GBS in Galle. Official population statistics and the regional rainfall recorded in the meteorological department were used for analysis.

Results: There were 114 patients fulfilling the inclusion criteria over the study period. Seventy-six patients were from Galle District and 54% were males. The age distribution showed a bimodal pattern with peak incidence in 10-19 age group and a smaller peak in 30-39 age group. Number of cases from Galle District reported in years 1995 to 2000 was 8, 16, 15, 18, 8 and 11 respectively. This is equivalent to a crude incidence of 0.8, 1.6, 1.5, 1.8, 0.8 and 1.1 per /100,000 population for each year respectively considering the mean population of 1.04 million. Mean crude incidence for the study period was 1.26 per 100000.

Seasonal variation with clustering following high rainfall was seen in years 1996, 1997 and 1998. Identified preceding illnesses recorded in the notes were upper respiratory tract infection in 22.7%, diarrhoea in 14%, varicella in 8% and non-specific viral infection in 14%.

Conclusion: The mean incidence of GBS in Galle District is 1.26 per 100,000 population with a range of 0.8 to 1.8 over the study period. The age distribution and seasonal variation are different from those reported from many other countries. The clinical features and preceding illness were similar to those described in other series.

Index words: Guillain-Barre syndrome, Epidemiology, Sri Lanka

Introduction

Following the near eradication of poliomyelitis, GBS has become the commonest cause of acute flaccid paralysis in many countries. The incidence of Guillain Barre Syndrome varies from country to country with a wide range in incidence worldwide. In a recent meta-analysis of community based studies, Sejver et al has found that the incidence varies from 0.62/100,000 population to 2.66/100,000 in western European and North American countries[1]. Global annual incidence varies from 0.4 to 4.0/100,000 with a median of 1.3.[2,3] Developing countries have reported a higher incidence than that of the developed world. Incidence of GBS in Sri Lanka and many south Asian countries is not known.

A seasonal variation in incidence had been reported in some studies from Sao Paulo (Brazil),[4] Taiwan[5] and Iran[6]. Although a seasonal pattern had been observed by some clinicians in Sri Lanka there are no publications in the literature. With the known pathogenesis of immune mediated mechanisms augmented by infections it is likely that the seasonal pattern seen in Sri Lanka is related to epidemics of diarrhoea and upper respiratory tract infections. Therefore this may in turn be related to the patterns of rainfall and floods.

The aims of this study were to find out the incidence of GBS during 1995 to 2000 from the hospital records, to see whether the there is a seasonal pattern of cases and if so whether the seasonal pattern is related to those of diarrhoea, upper respiratory tract infection, or other possible precipitating factors like vaccination. Although a community based prospective study is ideal for estimating the true incidence, the information obtained from this study too would be useful for planning the management strategies and identifying the causative factors in our region. During the study period THG was the only tertiary care centre in Southern Sri Lanka. Although there were patients transferred to THG from other districts patients with acute illness like GBS going to centres outside THG was unusual. Those who are transferred out of THG were initially registered in THG. Cross boarder references bypassing THG was not

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practiced by doctors in primary or secondary care centres. Hence it was assumed the patients who were residents in Galle District admitting to THG will reflect the incidence of GBS in the district of Galle.

Methods

Case notes of patients diagnosed as GBS were obtained from the record rooms of Teaching Hospital Galle (THG), from 01st January 1995 to 31st December 2000. During this period THG was the only tertiary care hospital in the district with facilities to manage patients with any paralytic illness like GBS. Patients fulfilling NINCDS diagnostic criteria were included in the study. Age, gender, date of onset, locality of the patient and preceding events like diarrhoea, upper respiratory infection, other viral infections, lymphoma and other malignancies, vaccination prior to the diagnosis of GBS were recorded. The number of cases of diarrhoeal illnesses reported to hospital was obtained from hospital statistics. Official population statistics were obtained from the District Secretariat in Galle and official rainfall figures for the corresponding period was obtained from the meteorological department. For calculation of the incidence only the residents in Galle District were considered.

The incidence of GBS for each year is calculated using official statistics of the population in the Galle District obtained from the Department of Census and Statistics. The incidence of each category is grouped according to the likely date of onset and the locality. The patients coming from other areas than Galle District were excluded from the calculations of the incidence. The pattern of the incidence was plotted with incidence of diarrhoea and monthly rainfall of the area obtained from the Department of Meteorology for the corresponding period.

Results

There were 114 patients fulfilling above criteria over the study period. Seventy six patients were from Galle District. The age distribution (Figure 1) shows a bimodal pattern with peak incidence in 10-19 age group and in 30-39 age group. There were 41 (53%) males and 35 females. Age specific incidence varied from 0.74 to 1.71 per 100,000 population. The incidence for the age group below15 years was 1.11 per 100,000 population (Table 1).

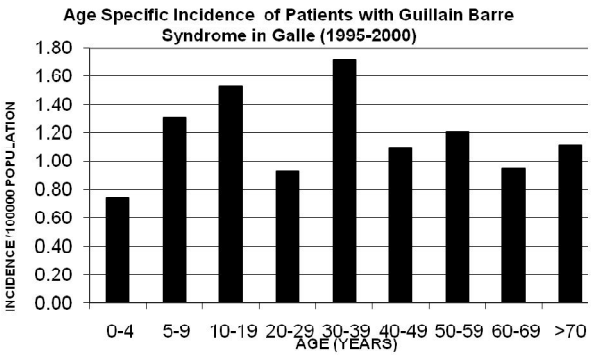

Figure 1.

Table1. Age specific incidence rate in different years per 1000000 population 1995-2000)

Age (years)	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*
<4	0	0	1.12	3.36	0	0
5-9	0.98	0.98	1.96	1.96	0.98	1.96
10-19	0.48	2.88	1.92	2.4	0.96	1.44
20-29	0.62	1.24	1.86	1.24	0	1.24
30-39	0.68	2.04	0.68	2.04	2.04	1.36
40-49	1.65	0.82	2.46	0.82	0	0.82
50-59	1.21	3.63	0	0	0	2.42
60-69	1.54	0	0	1.54	3.08	0
>70	0	0	4.48	4.48	2.24	0

The mean population of Galle District for the study period was 10.14 million. Numbers of cases reported in years 1995 to 2000 were 8, 16, 15, 18 and 8 and 11 respectively. This is equivalent to a crude incidence of 0.8, 1.6, 1.5, 1.8, 0.8 and 1.1 per /100,000 population for each year respectively. Mean incidence for the study period was 1.26 per 100,000.

Seasonal variation was noted with clustering of cases around months of December-January and May-June. There was no clear association with the incidence of diarrhoea or respiratory tract infections. The seasonal clustering occurred with or followed the high rainfall in years 1996, 1997 and 1998 and 2000 (Figure 2). Preceding events were recorded in 34 (44%) patients. Identified preceding illnesses were upper respiratory tract infection in 18 (22.7%), diarrhoea in 5 (14%), non-specific viral fever in 5 (14%) and varicella infection in 3 (8%). One patient had mumps and another viral hepatitis.

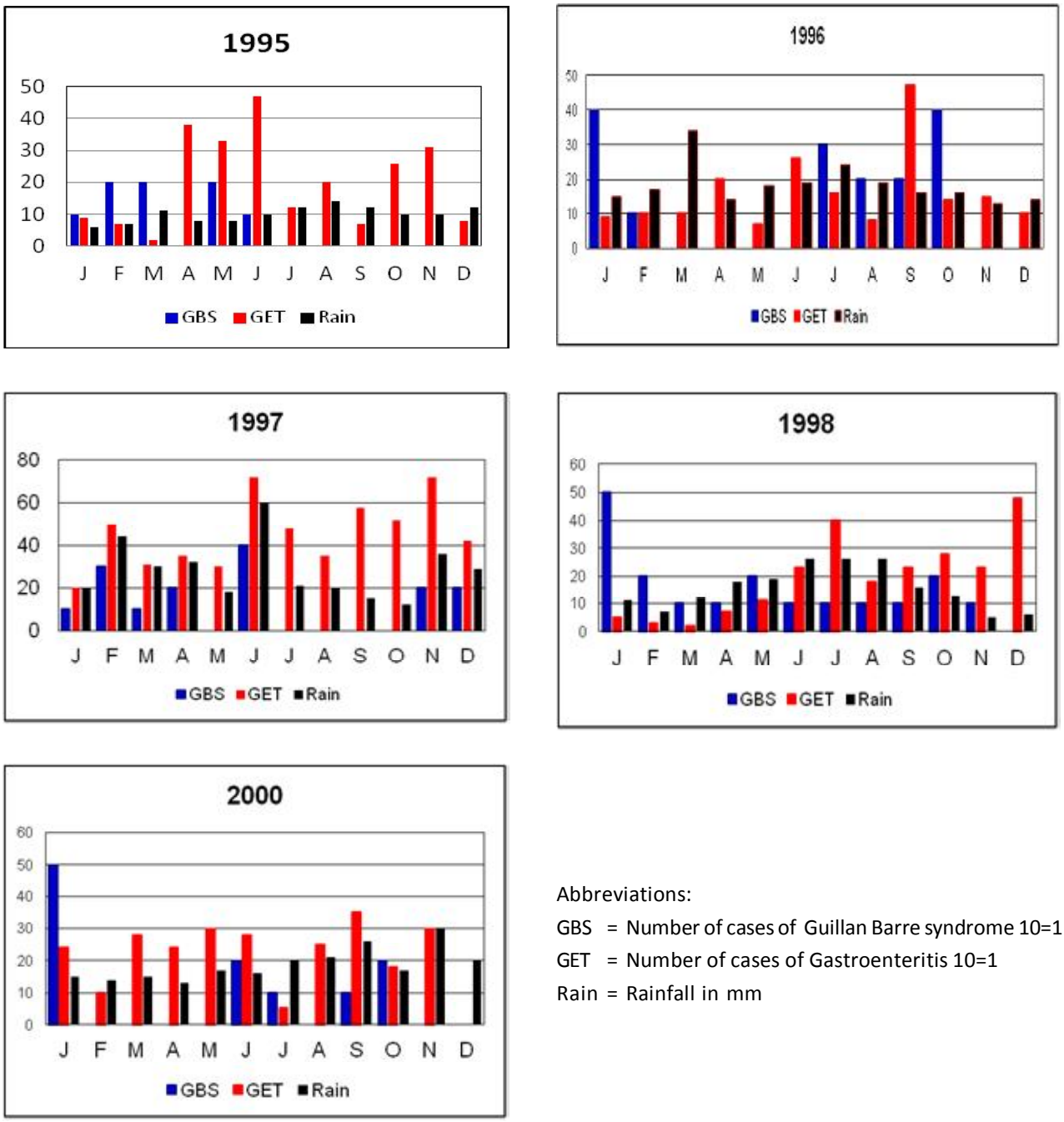

Figure 2. Relationship between Guillain Barre syndrome, gastroenteritis and regional rainfall in Galle 1995-2000.

Discussion

No proper incidence studies of GBS in Sri Lanka are available. THG is an ideal location to study the incidence of GBS. Nearly all patients with acute severe illnesses in Galle District are sent to THG for management. "Cross border" referrals of patients with GBS out of Galle without attending THG were very unusual during the study period. All the patients suspected to have GBS were referred to THG by the doctors in the peripheral hospitals (personal communications). Therefore the figure we found is very likely to reflect the true incidence of clinically significant GBS accurately. Very mild cases of GBS may not have been referred to THG or may not have been diagnosed as GBS and possibility of very mild cases being missed is still a possibility. A rare occurrence of wrong ICD classification is a potential cause for error.

We found that the incidence of GBS varied from 0.8 to 1.8 per 100,000 population over the study period with a mean incidence of 1.26 per 100,000. This value is between the reported incidence in most of developed and developing countries[1-9]. The age specific incidence in our series is different from that of the developed countries. In most of the other series the incidence is higher among elderly with the peak incidence in 5th or 6th decade of life[2,6,12,13] whereas it was the 2nd or 4th decade in our series. The higher incidence seems to follow or occur with the higher rainfall.

Seasonal variation in incidence is reported from some countries and not from others. For example, in Western Norway and Stockholm[11,12] a higher incidence had been reported in summer and winter, while in Taiwan and Southern Finland[14,15] it is during spring. In China and Paraguay, the higher incidence is during summer[16,17]. Studies in Western Australia and Spain has shown no seasonal variation[18,19]. In our study a higher incidence was seen during the months of December-January and May-June. Sri Lanka being a tropical country, no seasons are seen, but the months of December, January coincide with the winter and May, June with the summer season of the temperate countries.

The incidence in the age group below 15 years is 1.1 per 100,000 population which is higher than reported from developed countries[2] but lower than those reported from developing countries like Iran and Bangladesh[7,20]. This figure is of importance in planning acute flaccid paralysis surveillance in the polio eradication program.

Although *Campylobacter jejuni* infection is known as the commonest precipitating event, upper respiratory tract infections were the commonest in many retrospective studies. This is observed in our study too. Our study shows that GBS in Sri Lanka is very much similar in clinical epidemiology to that in other countries except for minor variations especially with respect to peak age incidence and preceding illnesses. Clustering of cases was seen during the rainy season.

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Paper

Guillain-Barre syndrome in Sri Lanka: subtypes and trends

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Sri Lanka Journal of Neurology, 2012, **1**, 10-13

Abstract

Objectives: To evaluate Guillain-Barre syndrome (GBS) subtypes in Sri Lanka.

Design setting: The patients satisfying established criteria for diagnosis of GBS were included. The cases were classified into GBS subtypes based on electrodiagnostic findings.

Patient intervention: None

Measurements: Clinical neurophysiological evaluations were done. The studies were repeated as appropriate.

Results: The evaluations were done between 2 and 143 days from onset (median = 7 days). There were 1153 patients (Male: Female = 1.4 :1) with age 1 to 86 years (mean = 43.7). Of them 191 (16.6%) were below 13 years (Male: Female = 1.2:1). GBS subtypes were demyelinating type 577 (50%), axonal forms 475 (41.2%), Miller-Fisher syndrome 5 (0.4%) and unclassifiable 96 (8.3%). Among the children there were 99 (51.8%) with demyelinating type, 82 (42.9%) with axonal forms, 10 (5.2%) with unclassifiable findings and none with MFS. There was some clustering of both demyelinating and axonal cases in the early and late months of the year whereas in children there is excessive occurrence of GBS cases of both types in the first 5 months of the year. There is a second peak of axonal GBS later in the year. Overall tendency of reduction in the number of cases, especially axonal forms, is noticeable over the years.

Interpretation: The age and sex distribution of the cases is similar to that of other countries. The occurrence of axonal subtypes is prominent. The proportions of GBS subtypes and case clustering in children may be related to the preceding infection.

Index words: acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, Axonal Guillain-Barre syndrome, seasonal variations, Miller-Fisher syndrome

Introduction

Guillain-Barre syndrome (GBS) was considered primarily an acute demyelinating neuropathy and was named acute inflammatory demyelinating polyradiculoneuropathy (AIDP)[1,2]. The concept of axonal GBS was first brought forward by Feasby et al[3]. Subsequently GBS due to acute primary axonal neuropathy got firmly established, especially after the studies in northern China. These cases of acute motor axonal neuropathy (AMAN) reported from China showed a distinct seasonal variation and age preponderance, occurring more frequently in summer months among children and young adults[4,5]. When sensory nerve fibres are also affected, in addition to motor involvement, in axonal GBS, this subtype is called acute motor and sensory axonal neuropathy (AMSAN)[3,6]. Other recognized subtypes include Miller-Fisher syndrome (MFS) and several minor variants[6,7]. The demyelinating and axonal subtypes of GBS can often be distinguished by electrodiagnostic studies whereas MFS is largely a clinical diagnosis[7].

In North America and Europe, patients with GBS usually have AIDP and only a minority (5%) has axonal subtypes[8]. Reports from other regions such as northern China, Japan and Central and South America have shown that axonal subtypes constitute a relatively higher proportion (30-47%) of GBS cases[4,5,9,10]. In India, axonal forms of GBS have been detected in 11% of all cases of GBS and a higher proportion (44%) has occurred in a younger group of patients aged 1 to 18 years[11,12].

Though a case of primary axonal GBS has been reported from Sri Lanka[13], large scale data is lacking. We have studied the cases of GBS over several years to determine the proportions of different subtypes and identify any trends in incidence.

Methods

Data were obtained by reviewing the database of consecutive cases that fulfilled established diagnostic criteria for GBS[14] and presented for neurophysiological assessment. Study involved patients seen over a period of 9 years between 1 October 2003 and 30 September 2012. The selected cases were previously healthy and those with diabetes, uraemia, and any other condition which had the potential to affect the peripheral nervous system were excluded. The demographic data recorded

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included age, gender, date of symptom onset, duration of symptoms, clinical history and neurological findings. The subjects underwent sensory nerve conduction studies (NCS) in sural, ulnar, median and superficial radial nerves, motor NCS in peroneal, tibial, ulnar and median nerves. Orthodromic method was used for median and ulnar sensory studies whereas antidromic method was used for sural and superficial radial nerve studies. F wave study was carried out in tibial and ulnar nerves. Surface stimulation and recording techniques were used according to established methods[15,16].

The cases were classified into AIDP, AMAN and AMSAN by applying previously used criteria[8,17] based on NCS findings. The subjects having pure motor conduction blocks (CB) with temporal dispersion of compound muscle action potentials or motor conduction slowing were classified as AIDP whereas those without such changes were classified as AMAN[17]. The subjects who were initially unclassifiable had repeat NCS and assigned to a GBS subtype according to the findings. Some cases could not be classified to a subtype even after repeating the NCS and were categorised as unclassifiable. Those having ophthalmoplegia, areflexia and ataxia without overlap clinical features were classified as Miller-Fisher syndrome irrespective of NCS findings. Those with above triad with additional clinical features were classified according to NCS findings as described above.

All the tests were performed on Neuropack® MEB 9200 K (Nihon Kohden, Tokyo, Japan) nerve conduction/ electromyography/evoked potential testing equipment.

Results

Patients

A total of 1153 patients were included in the study. Of them 673 were males and 480 were females (Male: Female = 1.4:1). The age range was 1 to 86 years (mean = 43.7). There were 191 (16.6%) patients below 13 years of age, of whom 103 were males and 88 were females (Male: Female = 1.2:1). The clinical neurophysiological evaluations were done between 2 and 143 days from the onset. A vast majority was assessed within the first week (median = 7 days).

Subtypes

There were altogether 577 (50%) with demyelinating type GBS (AIDP), 475 (41.2%) with axonal type (AMAN and AMSAN), 5 (0.4%) with MFS and 96 (8.3%) with unclassifiable electrodiagnostic findings. Among the children below 13 years of age, there were 99 (51.8%) with demyelinating type, 82 (42.9%) with axonal forms, 10 (5.2%) with unclassifiable findings and none with MFS.

Unclassifiable cases had miscellaneous nerve conduction abnormalities in the electrodiagnostic assessment. Commonest observation among them was F wave abnormality (40% of cases).

Trends

When the cases were studied according to the month of onset, only a mild fluctuation of total number of cases with slightly greater numbers of cases observed to occur in early and late months of the year (Figure 1). Both AIDP and axonal forms display the same trend. In children below 13 years of age, there is excessive occurrence of GBS cases of both types in the first 5 months of the year (Figure 2). There is a second peak later in the year in the months of September, October and November. This second peak is peculiar because it consists of greater numbers of axonal forms than AIDP in all 3 months.

There is an overall tendency of reduction in the total number of cases over the years (Figure 3). This reduction is especially contributed to by a reduction of axonal forms.

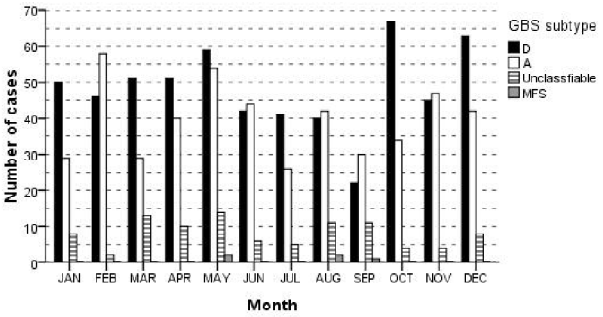

Figure 1. Monthly variation of Guillain-Barre syndrome subtypes over the period of study in all the cases. D = Acute inflammatory demyelinating polyradicul-neuropathy; A = axonal forms; MFS = Miller-Fisher syndrome; Unclassifiable = cases unclassifiable to other subtypes.

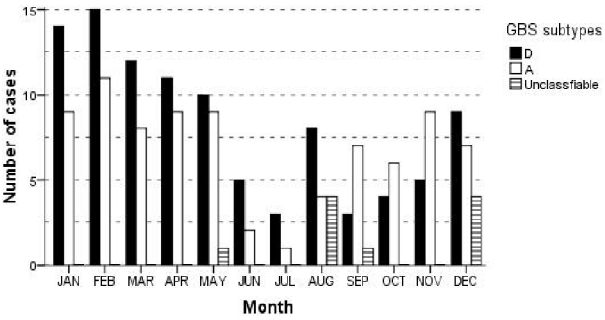

Figure 2. Monthly variation of Guillain-Barre syndrome subtypes over the period of study in children below 13 years of age. D = acute inflammatory demyelinating polyradiculneuropathy; A = axonal forms; Unclassifiable = cases unclassifiable to other subtypes (there were no cases of Miller-Fisher syndrome is this group).

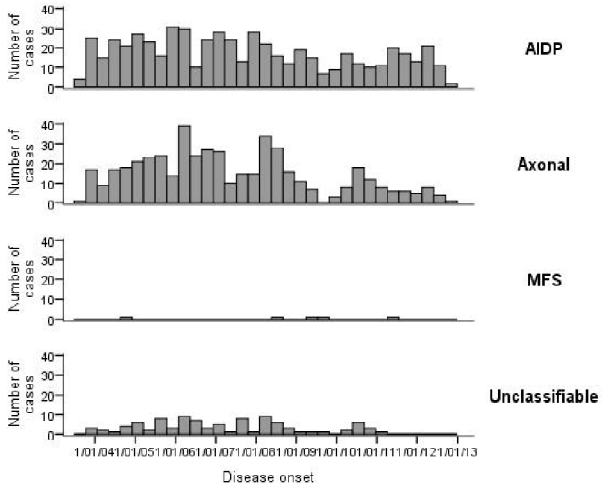

Figure 3. Annual variation of Guillain-Barre syndrome subtypes over the period of study in all the cases. AIDP = Acute inflammatory demyelinating polyradiculneuropathy; Axonal = axonal forms; MFS = Miller-Fisher syndrome; Unclassifiable = cases unclassifiable to other subtypes.

Discussion

The age distribution and male preponderance observed in patients with GBS in Sri Lanka are similar to those of other countries[4,5,8-12]. Majority of cases are of demyelinating type GBS (AIDP) while the axonal type (AMAN and AMSAN) also contributes to over 40%. Similar distribution of subtypes is observed among the children less than 13 years of age. These figures are closer to those of other Asian and South American countries and are markedly different from North America and Europe where axonal forms are rare. These differences of occurence of pathological subtypes may be related to the type of organism responsible for the preceding infection which occurs in about two-thirds of all the cases of GBS[18,19]. Axonal GBS is known to have a particular association with *Campylobacter jejuni* infection[9,10,20] and it could be a potential causative agent in Sri Lanka as well. This is a largely unexplored area in this country so far. Very low numbers of MFS cases observed is not unusual. However there could be under-detection because some typical cases may not have presented for neurophysiological studies because clinical diagnosis is obvious.

Observation of case clustering particularly in children could be related to outbreaks of infections for which weather and environment changes may play a role. Since there are no clearly demarcated climatic seasons and the weather patterns widely vary in different localities even within a climatic zone, analysis of the relationship between the weather patterns and GBS is complex.

Overall reduction in number of cases over the years might reflect a trend of diminishing incidence of infections by potential causative agents for GBS. On the other hand this may reflect a reduction in the number of referrals to our centre due to availability of better neurological services with appointment of more neurologists to other centers in the country.

The present study reflects the profile of GBS subtypes in Sri Lanka. Further studies into infective aetiologies and their prevention may be based on these findings.

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Paper

Demographic patterns of Sri Lankan patients with multiple sclerosis – and a regional comparison

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Abstract

Retrospective data from a series of Sri Lankan patients (n=35) with multiple sclerosis (MS) is described. This is believed to be the largest such case series with a descriptive analysis of data regarding the demographic patterns of MS in the country. Subsequently the Sri Lankan data are compared with similar series from India and Pakistan. The clinical spectrum of MS in Sri Lanka seems to be similar to that of the region with regards to age at onset, gender, dominant clinical presentations, and progression and disability patterns. Pyramidal, sensory and optic nerve involvement dominated the initial presentation while optico-spinal Devic's type being rare. Majority of the cases were of relapsing and remitting type. A significant proportion of patients had high EDSS scores with considerable disability. Usage of disease modifying agents (DMAs) was low across the region. In conclusion western type of MS seems to be the common form of the disease in Sri Lanka and in the region.

Index words: multiple sclerosis, optico spinal MS, Sri Lanka

Introduction

Multiple sclerosis is uncommon yet increasingly seen in Sri Lanka. The first cases were reported over a decade ago[1]. The apparent increase in the incidence could be the result of a combination of factors such as expansion of neurological services with more neurologists, availability of MRI facilities and greater awareness. However, accurate epidemiological data are not yet available. In this study the clinical characteristics, investigation findings, treatment methods and progression of the disease in 35 Sri Lankan patients with clinically definite MS (CDMS) is retrospectively analyzed. All 35 patients were diagnosed by a board certified neurologist using the revised McDonald criteria of 2005[2]. This data are compared with the available similar regional studies from India[3] and Pakistan[4].

Objective

The objective of this descriptive analysis was to study the demographic patterns of Sri Lankan patients with CDMS and to compare this data with the regional and western disease patterns.

Methods and Results

All patients included in the analysis were diagnosed as CDMS by a board certified neurologist using the revised McDonald criteria of 2005[2]. No family history of a similar illness was recorded in any of the patients. A Caucasian ancestry was found in one. One patient lived in an MS prevalent country in her childhood. Average age of the patients at onset was 29.8 years with the youngest being 15 years and the oldest 45 years. Majority of them (87%) were females. Pyramidal and sensory involvement was seen in 73% of the patients. Optic nerve involvement was noted in 70% of the patients. Bladder involvement (51%) and cerebellar signs (53%) were noted in approximately half the cases. Respectively 36.6% and 26.6% patients reported significant fatigue and pain. Tremor and epilepsy was rare being seen in only 6.6% cases. Devic's type optico spinal cases were rare (3.3%). At the time of evaluation 51% were categorized as relapsing remitting MS (RRMS). The rest were secondary progressive (26.6%), primary progressive (20%) and progressive relapsing (3%).

All patients were subjected to a MRI scan of the brain. 33/35 (94%) patients satisfied Barkhof's MRI criteria for MS. Periventricular "Dawson's fingers" were seen in all such positive brain MRIs. Respectively 67.8%, 26.6%, 40%, 36.6% had corpus callosal, cerebellar, brain stem lesions and T1 "black holes". GAD enhancement was performed in only 23/35 patients and half of them had enhancing lesions. Lumbar puncture was done in only 23 (65.7%) patients. Oligoclonal bands were seen only in 5/23 (21%). In two patients with significant spinal cord lesions NMO-IgG antibody was tested. It came positive in one.

High dose IV methyl prednisolone was used in 32 patients to treat the 'acute attack'. Disease modifying treatment (DMT) with interferon was initiated in five cases. However, only around 50% patients qualified for this treatment (RRMS). Only 50% of the patients were

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Table 1.

Clinical distribution	*Sri Lanka (N=35)*	*NW India (N= 100)*	*Pakistan (N= 142)*
1. Pyramidal	73.3%	87%	70%
2. Sensory	73.3%	65%	45%
3. Optic N	70%	57%	
4. Bladder/ sphincter	50%	46%	
5. Cerebellar	53.3%	44.3%	
6. Devic's type	3.3%	7%	3%
Age at onset	29.86Y	29.49Y	27Y
Sex ratio M:F	1:4	1.45	1:1.45
Disability	Only 50% fully independent - high rate of disability In 26.6% EDSS was 7.5-8 and in 23.3% EDSS was 6-7.		31% severely and 45% moderately disabled. Average EDSS 3.68 +/- 3

Table 2.

Type of MS	*SL*	*NW India*	*Pakistan*
RRMS	50%	65%	81%
SPMS	26.6%	25%	45%
PPMS	20%	5%	21%
PRMS	3.3%	5%	0%

fully independent at the time of the evaluation. Eight patients with an EDSS of 6-7 were walking with constant unilateral or bilateral support using sticks or walkers while nine were confined to a wheel chair with an EDSS of 7.5-8. Hence this series showed a high disability rate.

Regional comparison

These data were compared with two similar descriptive analysis coming from North West India and Pakistan Tables 1 and 2.

Discussion

The clinical profiles of MS patients throughout the region seem to be similar with almost identical age at onset and a female preponderance[3,4]. The initial clinical presentation was dominated by pyramidal, sensory and optic nerve symptoms in all three series. Relapsing and remitting type of MS form the bulk of the cases. Contrary to the earlier belief optico-spinal or Devic type presentation seem to be less common than earlier thought. Most Sri Lankan patients did not have a Caucasian ancestry, a family history or a history of time spent in a MS prevalent region of the world in childhood. Hence the cases were indigenous. MRI patterns and lesion distribution in our patients were very similar to the pattern seen in the western countries. The low yield of OCB positive cases (21%) could be a regional phenomenon but the improper detection techniques used throughout the region is the easier explanation for very low OCB positivity. MS in south Asia progresses in a similar fashion to that of western countries with significant levels of disability especially with long-standing disease. Disease modifying agents (DMAs) such as beta interferon is used only in a very few eligible patients largely due to cost issues. In Sri Lanka only 1/3

of the patients with RRMS who qualified for such treatment actually got treated. Limited access to DMTs and delayed initiation of such treatment in some could lead to more disability. An Indian study shows that after starting β-interferon all patients who could tolerate the drug had a significant reduction in the relapse rate[12]. Most patients had no relapse at all during follow-up for a mean period of 2.25 years. In India prospective studies backed by MRI data have shown no distinct differences between MS seen in the west and India. Neuroepidemiological studies done in the southern parts of India have failed to capture MS cases in the community. In Pakistan retrospective data from the largest series of patients (n=142) with MS show predominant RRMS of western type with significant disability levels[4].

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Paper

Response to treatment with methylprednisolone pulses in children with electrical status epilepticus in sleep (ESES)

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Sri Lanka Journal of Neurology, 2012, **1**, 17-23

Introduction

Encephalopathy with status epilepticus in sleep (ESES) is a partly reversible, age-related childhood epileptic encephalopathy with heterogenous manifestations affecting cognition, motor abilities, behaviour and speech occurring in association with variable types of seizures. Continuous spike wave in slow wave sleep (CSWS), Landau Kleffner syndrome (LKS), atypical benign rolandic epilepsy (BRE) are different manifestations within this broad spectrum of epileptic encephalopathy due to continued spike wave activity in slow wave sleep. The term ESES for this EEG phenomenon was first introduced by Tassinari et al in 1977 and subsequently converted to status epilepticus in sleep (SES)[1,2]. There is now agreement that CSWS and LKS are within the same spectrum of epilepsy syndromes sharing common characteristics. In CSWS, there is cognitive and/ or behavioral impairment acquired during childhood, associated with strong activation of the interictal epileptiform discharges during non-rapid eye movement (NREM) sleep that is unrelated to any other factor. The syndrome of LKS is considered as a type of CSWS/ESES but with a particular clinical presentation where acquired aphasia is the core symptom.

Although it is considered a self limiting epileptic syndrome, literature on the outcome is sparse; outcome related to therapy is hardly or minimally described. There is no single therapy that is most effective for treatment of seizures in ESES, and most therapies are based on expert consensus guidelines. Some studies describe benefit and improved neuropsychological outcome following long term high dose Benzodiazepines[3], leveteracetam[4], sulthiame and ACTH therapies. Current consensus is that corticosteroids remain the preferred treatment method, however the type of steroids or dose remains to be studied[5,6]. The response to regular administration of methyl prednisolone is not reported or limited to occasional case history[7]. This paper describes the clinical outcome in 10 children following treatment with high dose methyl prednisolone pulses.

Method

This descriptive study was performed at the University Unit of the Lady Ridgeway Children's Hospital, Colombo, Sri Lanka. Children diagnosed as having CSWS over a two year period (2008-2010) were included in this analysis. The diagnosis of CSWS was made following clinical diagnosis based on history of epilepsy associated with evidence of epilepsy occurring with an encephalopathic state having discriminatory electro-encephalopgraphic findings. The encephalopathic state was defined as neuropsychiatric regression occurring since onset of epilepsy and the characteristic EEG findings as presence of significant activation of spike wave activity in slow wave sleep with spike wave index of at least 50%. These children were prospectively followed up from the time of confirming diagnosis of until completion of the treatment schedule.

All of them were treated with cycles of high dose methyl prednisolone (30mg/kg/day) given for 3 consecutive days. This is followed by a slow taper off with oral prednisolone over the next 4 weeks (oral prednisolone 2mg/kg for 2 weeks followed by 1mg/kg for two weeks). All anticonvulsants that were being used by the patients at the time of diagnosis were continued. The second cycle was repeated after a 4-6 week interval at the same dose. The balance cycles (at same dose) were spaced out (6-12 weeks) according to the degree of reappearance of symptoms.

The therapeutic response was assessed using a modified 40 item epilepsy outcome rating scale developed to assess the impact of the child's epilepsy on the parents (Annex 1). This covered 5 broad areas of dysfunction secondary to the epileptic encephalopathy, i.e. impact due to poor seizure control, impact on independent mobility, impact on communication, impact on cognition and behaviour, impact on overall general wellbeing. These were assessed against a 5-point marking scheme which indicated following scales. 1 = never a problem, 2 = rarely a problem, 3 = sometimes a problem, 4 = frequently a problem and 5 = almost always a problem. This was assessed at the time of the diagnosis when treatment was commenced and repeated after completion of 6th treatment cycle.

Results

There were 10 children who were prospectively followed up for this study. Mean age at diagnosis was 7.12 $\pm$ 2.5 years. Male: female ratio was 1:1. Nine of them had symptomatic (MRI proven) aetiology for their epilepsy. Eight children were clearly in stage two of the illness at time of diagnosis but the two older (>11 years) children were most likely reaching end of their second stages at the time of establishment of the diagnosis of

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their epilepsy. Mean duration of follow up for their epilepsy (before and after diagnosis) was 24.6 ± 6.5 months (second stage is when the CSWS is identified on EEG).

Onset of epilepsy

Mean age of first seizure was 30.6 ± 14.5 months (range 9-57 months) and were focal seizures with mainly motor manifestations in all. Three of them experienced their first ever seizure as a status epilepticus (30%). Mean age to onset of second stage was 50.6+16.1 months. Average time gap between onset and second stage was 20 ± 10.19 months.

Neuropsychiatric regression

The most prominent feature of encephalopathy in this group of was loss of cognitive skills which was noted in all children , acquired hemiplegia in two, complete loss of ambulation in five, severe ataxia in seven, partial regression or complete loss of speech in six, oro-facial manifestations as part of epileptic opercular syndrome in four.

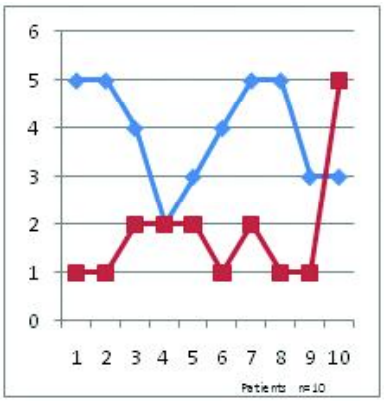
Summary of important findings in each of these ten children is outlined in Table 1.

Table 1. Clinical profiles in the 10 children diagnosed with ESES

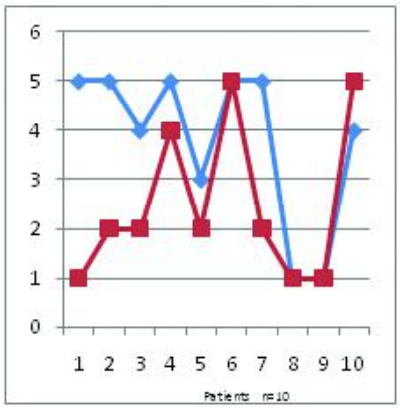
Patient	*Current age*	*Aetiology*	*Pre-morbid development*	*Onset of first stage*	*Onset seizure type*	*Onset age of second state*	*Other seizure types*	*Neuro-dysfunctions*	*Age of onset of pulse therapy*
1	6.5 years	Nil	Nil concerns	24 months	Simple focal motor (versive)	30 months	Focal oro-motor seizures, atonic astatic seizures	Ataxia, epileptic opercular syndrome, Cognitive regression	60 months
2	7 years	Ex-Preterm Agenesis of corpus callosum	Normal	36 months	Prolonged focal motor (mouth)	48 months	Hemi-facial, hemiconvulsive, generalised clonic seizures Epileptic oper-cular syndrome Cognitive dysfunction	Ataxia with later loss of ambulation, loss of speech	64 months
3	6.6. years	Right congenital arterial ischaemic stroke	Delayed	26 months	Left sided focal motor (clonic)	48 months	Hemiclonic seizures, atonic astatic seizures, negative myoclonus	Worsening of left hemiplegia, motor dyspraxia, cognitive dysfunction	60 months
4	7 years	Right sided polymic-rogyria	Delayed months	32 motor	Focal months	56 motor	Nocturnal focal seizures, atypical absences, Generalised tonic clonic seizures	Significantly delayed hence acquired dysfunction not reported	72 months
5	7 years and 10 months	Hypoxic ischaemic encephalo-pathy	Delayed	57 months	Focal status (versive and clonic)	72 months	Hemifacial, hemiconvulsive Nocturnal convulsive seizures	Acquired hemiplegia, dysarthria	78 months
6	6 years nine months	Hypoxic ischaemic encephalo-pathy	Delayed	42 months	Focal motor (clonic)	75 months	Tonic nocturnal seizures, atypical absences	Significantly delayed hence only loss of acquired speech noted	75 months

(Continued)

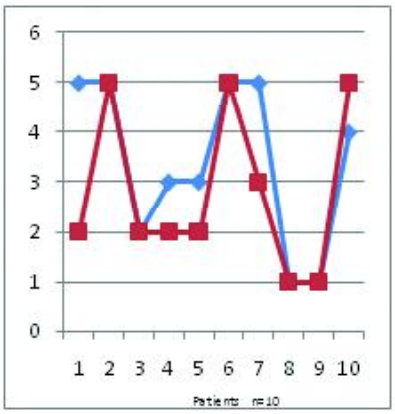
Patient	*Current age*	*Aetiology*	*Pre-morbid development*	*Onset of first stage*	*Onset seizure type*	*Onset age of second state*	*Other seizure types*	*Neuro-dysfunctions*	*Age of onset of pulse therapy*
7	5.5 years	Focal cortical dysplasia	Mild delay	18 months	Bilateral convulsive seizures	48 months	Hemifacial, hemiconvulsive, generalised tonic clonic, nocturnal convulsive seizures	Loss of ambulation, loss of speech, epileptic opercular syndrome, poor cognition	50 months
8	12 years	Right sided cortical atrophy	Delayed	13 months	Tonic (nocturnal)	24 months	Generalized tonic, drop attacks	Fine motor regression	144 months
9	12.4 years	Cortical dysplasia of R/ occipital region	Mild delay	9 months	Focal status	21 months	Generalized tonic clonic, status	Language regression, cognitive regression	138 months
10	6.4 years	R/ hippo-campal sclerosis	Normal	36 months	Focal status	60 months	Focal, absence, drop attacks	Arrest in motor development, ataxia, Speech regression	58 months



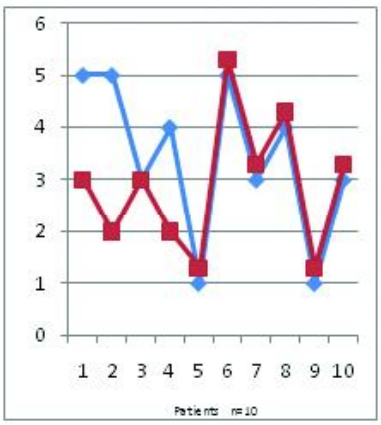
Improvement in seizure control



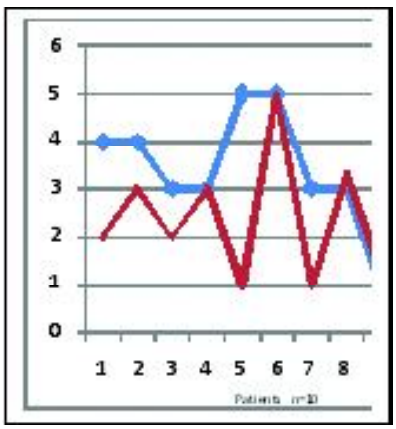
Improvement in independent ambulation



Improvement in speech and communication



Improvement in cognitive functions



Improvement of general well being

Figure 1. Therapeutic outcome – parental assessment before and after 6 cycles of therapy

1 = never a problem, 2 = rarely a problem, 3 = sometimes a problem, 4 = frequently a problem and 5 = almost always a problem

Therapeutic outcome

All patients were offered methyl prednisolone when diagnosis of ESES was established. Regular anticonvulsants taken at time of establishing the diagnosis were continued. All except one child completed all 6 pulses of methyl prednisolone therapy.

In the nine children who completed treatment a satisfactory therapeutic outcome was seen in the 5 domains assessed. This is illustrated in Figure 1. The best response was noted for improvement in the seizure frequency. There were three who completely stopped having the habitual seizures which were experienced before the therapy. In others the seizure control can be classified as Modified Engel classification class 2, 3 and 4. In those with complete loss of ambulation or severe incapacitating ataxia affecting independent ambulation (n=8) ability to ambulate with no or some support was noted in five. Mild to moderate improvement in the frequency of oro-facial manifestations was noted in three. Improvement of speech was noted only in three. One patient developed significant deterioration in her gait, speech with significant oral dysfunction (drooling) following administration of first dose of methyl prednisolone. Similar deterioration was noted after large dose of oral steroid therapy (prednisolone) was offered as an alternative.

Though the response to pulse therapy was good it was transient in all due to recurrence of symptoms such as ataxia, drooling and difficulty in ambulation. Duration to commencement of deterioration range between 5-12 weeks after the first three cycles of therapy. Most sustained impact was on control of seizures. Only one child developed a serious adverse reaction (SAR) as a severe pneumonia. At least one or more of the following were experienced by all children: increase in weight, appearance of cushingoid features, hirsuitism, increased appetite, frequent corizal symptoms, and striae.

Discussion

ESES though resolves in an age limited manner, it leaves catastrophic neuropsychological deficits in the affected children. The pathophysiology of the neuropsychological regression associated with ESES is related to the disturbances caused by continuous spike wave activity during slow wave sleep. It can be considered as a model of clinical effects of a localized disruption of EEG activity during sleep caused by long-lasting sleep-related focal epileptic activity. Depending on area of most spike wave activity variable degrees of impact on learning, cognition, behaviour and motor functions manifest. This highlights the crucial role of slow wave sleep in the neuroplasticity that govern normal neuropsychological development[8]. Positron Emission Tomography studies using 18 F-fluorodeoxyglucose has demonstrated hypermetabolism in the region of focal continued spike wave activity, in children having normal MRI. This finding emphases the role played by frequent spike wave activity[9].

Response to therapy in ESES is difficult to describe due to its prolonged course of illness associated with fluctuation of severity of symptoms. However, apart from the two older children, all others in our group experienced the onset of second stage between 30-75 months making comparison of the response to therapy acceptable. Considering the younger age in this group of 8 children, this response is unlikely to be related to spontaneous resolution of the epileptic encephalopathy as well. Both these features are supportive of a true therapeutic response to the methyl prednisolone therapy rather than random association.

Resolution of ESES had been achieved with high dose corticosteroids or adrenocorticotropic hormone (ACTH) therapy, albeit with transient results in many patients[10,12]. In one of the largest series of 44 children, positive response (clinical or neuropsychological improvement in conjunction with improvement in the EEG tracing gradient) within three months was described in 77% of patients, with normalisation of EEG in 21 patients[5]. The main form of steroid therapy administered to this cohort was hydrocortisone. The children were maintained on high dose steroids over 9 month duration and a sustained response was experienced in only 45% of all children. Forty one percent of those with initial response subsequently relapsed on discontinuation of therapy.

Conclusion

Based on the response seen we conclude that high dose methyl prednisolone may play a role in control of symptoms (seizures) and haltering the accompanied regression in children with ESES. Although the described response is based on short duration of follow up, repeated pulses at longer intervals may help maintain the children with minimal symptoms and better neuropsychiatric and motor functions. Large scale studies are needed to establish this further.

Disclosure

The authors of this paper declare no conflicts of interest.

Annex – 1

Epilepsy outcome rating scale for Parent/ Carer

Scale definition: 1 = never a problem, 2 = rarely a problem, 3 = sometimes a problem, 4 = frequently a problem and 5 = almost always a problem

A In relation to your child's seizures how concerned are you about:	1	2	3	4	5
1. Having one seizure after another	○	○	○	○	○
2. Having seizures frequently	○	○	○	○	○
3. Having seizures during day time	○	○	○	○	○
4. Having seizures during night time	○	○	○	○	○
5. Having frequent drop attacks	○	○	○	○	○
6. Having twitching movements in the body	○	○	○	○	○
7. Developing prolonged seizures	○	○	○	○	○
8. Having long intervals before recovery	○	○	○	○	○
9. Seizures causing damage to the brain	○	○	○	○	○
10. Your child becoming injured due to seizures	○	○	○	○	○

B In relation to your child's mobility and hand functions how concerned are you about:	1	2	3	4	5
1. Having difficulty in sitting up supported	○	○	○	○	○
2. Having difficulty in standing unsupported	○	○	○	○	○
3. Having difficulty in walking unsupported	○	○	○	○	○
4. Having frequent falls	○	○	○	○	○
5. Your child injuring his/herself due to falls	○	○	○	○	○
6. Having difficulty in feeding self	○	○	○	○	○
7. Having difficulty in playing with toys	○	○	○	○	○
8. Having difficulty in using a pen	○	○	○	○	○
9. Your child having difficulty due to toileting	○	○	○	○	○
10. Having difficulty in dressing	○	○	○	○	○

(Continued)

C In relation to your child's speech and communication how concerned are you about the child:	1	2	3	4	5
1. Having difficulty in talking	○	○	○	○	○
2. Having difficulty in making any sound	○	○	○	○	○
3. Having difficulty in expressing needs	○	○	○	○	○
4. Having difficulty in pointing for his/her needs	○	○	○	○	○
5. Having speech that is difficult for you to understand	○	○	○	○	○
6. Having difficulty in talking at normal speed	○	○	○	○	○
7. Showing no interest in communication (verbal or gestural)	○	○	○	○	○
8. Having difficulty in understanding what you are saying	○	○	○	○	○

D In relation to your child's other disabilities how concerned are you about:	1	2	3	4	5
1. Having frequent drooling of saliva	○	○	○	○	○
2. Him/her being irritable	○	○	○	○	○
3. Having difficulty in understanding (cognition)	○	○	○	○	○
4. Having temper tantrums	○	○	○	○	○
5. Being hyperactive	○	○	○	○	○
6. Having difficulty in swallowing	○	○	○	○	○
7. Difficulty in taking out on a trip	○	○	○	○	○
8. Difficulty in taking him/her in a vehicle	○	○	○	○	○
9. You having difficulty in falling sleep due to worry	○	○	○	○	○
10. Taking your child meet relatives and friends	○	○	○	○	○
11. Difficulties in attending school	○	○	○	○	○
12. Impact of your child's illness on spouse and other children	○	○	○	○	○

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Paper

'Neurophobia' of medical undergraduates: does it affect exam performance? The Sri Lankan perspective

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Abstract

'Neurophobia' is the 'fear of neural sciences and clinical neurology held by medical students and doctors'. Neurophobia, results in doctors performing a poor neurological examination and referring patients indiscriminately to neurologist. It is said to originate in medical school. The extent of the problem in Sri Lanka is yet to be established. The present study aims to ascertain whether neurophobia actually affects the medical undergraduates' performance at the final year examination or is a simple 'perceived' phobia without an impact on students' performance.

Materials and methods: The marks of students' for the Structured Essay Questions (SEQs) were analyzed at three consecutive final year examinations (2008-2010). Data were analyzed using SPSS v14. A p-value ≤ 0.05 was considered statistically significant.

Results: Sample size for years 2008-2010 were 160, 151 and 155 respectively, while the average marks (±SD) for all SEQs were 58.1±7.7, 54.5±7.7 and 59.8±9.2 respectively. In the 2008 batch the marks in neurology (59.8±14.6) was significantly higher only from marks for pulmonology question (53.1±12.7). In 2009 the marks for the neurology question (69.4±15.0) was significantly higher than all other questions, while in 2010 the marks obtained for the neurology (54.6±23.4) was significantly lower than the marks for the cardiology (61.8±9.2), pulmonology (77.6±9.6) and nephrology (60.9±9.2). The students' overall average decreased significantly by exclusion of the neurology question in 2009 from 58.2±8.0 to 54.5±7.7 ($p<0.001$), but not in the other years studied. With the exclusion of the neurology question marks, the average of those having an overall average for all questions of <50 improved, but in the better students (overall average >50) the average remained unchanged.

Conclusion: The impact of neurophobia on the performance of medical undergraduates at SEQ examinations seems to be very minimal. However, further studies are needed in other areas to assess the impact of neurophobia, on clinical practice, on patient-based clinical examination and management.

Index words: neurology education, neurophobia, medical students, Sri Lanka

Introduction

The term 'neurophobia' is defined as the 'fear of neural sciences and clinical neurology held by medical students and doctors'[1]. Neurophobia is a common phenomenon, and medical students and doctors at all levels have difficulties in dealing with patients having neurological problems[2-4]. This results in doctors performing a poor neurological examination or indiscriminately referring patients with simple conditions to neurologists in order to avoid dealing with them[5]. Neurophobia is said to begin in medical school[6]. The reasons identified for this are poor undergraduate training of neurology, complexity of the neurological examination and difficulty in understanding basic neuroscience. However, the extent of the problem in Sri Lanka and how it affects the student's performance at examinations is not known.

At Faculty of Medical Sciences, University of Sri Jayewardenepura, medical undergraduates learn basic neuroanatomy and physiology as a part of the first two years teaching programme in basic sciences. In the 3rd and 4th years the students learn clinical skills in general medical wards and at a two week attachment to a neurology unit in a teaching hospital. In addition during the fourth and final year they are taught neurology topics at lectures, and tutorials and in the final year during a two month attachment to the Medicine Professorial Unit. However, recently the curriculum was changed and a specialized module on neurology was introduced during the 3rd and 4th years. This study includes batches prior to the curriculum change.

In the present study we tried to ascertain whether the knowledge of neurology or the lack of it actually affects the medical undergraduates' performance at the final year examination at Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.

Methods

This retrospective study was undertaken during September-October 2010. The marks obtained by the

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students for the Structured Essay Questions (SEQs) were analyzed. The results of the SEQs at three consecutive final year examinations (2008-2010) at Faculty of Medical Sciences, University of Sri Jayewardenepura were included in the study.

Structure of the SEQ question papers

The 2008 and 2009 papers carried four SEQs each, whereas the 2010 paper carried six questions. The sub-specialty areas of each year's questions are given below in the order they appeared on the question paper,

2008 – Cardiology, Neurology, Pulmonology, Short notes

2009 – Neurology, Nephrology, Cardiology, Short notes

2010 – Nephrology, Neurology, Pulmonology, Cardiology, Hepatobilliary, Metabolic

In 2008 the main themes of the questions were on heart failure, Guillain Barre syndrome and Tuberculosis, while the short notes were on diabetic nephropathy, rheumatoid arthritis and lung function tests respectively. In the 2009 SEQ paper the questions were on stroke, chronic renal failure and secondary hypertension, followed by short notes on oesophageal varices and hyperthyroidism. The 2010 question paper carried questions on nephrotic syndrome, lateral medullary syndrome, bronchial asthma, myocardial infarction, hepatitis and syndrome of inappropriate ADH secretion in the given order.

Data analysis

All data were double entered and cross checked for consistency. All marks are given out of a total of one hundred. Data were analyzed using SPSS version 14 (SPSS Inc., Chicago, IL, USA) statistical software package. The significance of the differences between means was tested using Student's t-test or ANOVA. A p-value ≤ 0.05 was considered statistically significant in all analysis.

Results

Sample size for years 2008-2010 were 160, 151 and 155 respectively. The mean marks (±SD) of students' for all SEQs for the years 2008-2010 were 58.1±7.7, 54.5±7.7 and 59.8±9.2 respectively. There was no significant difference between the marks of the 2008 and 2010 batches. However the overall marks between 2008 vs 2009 and 2009 vs 2010 batches were significantly different ($p<0.05$). The average and range of marks obtained for each SEQ by the respective batches of students are given in Table 1.

Table 1. Average marks of students for each SEQ

		Average±SD	*Range*	*Average all SEQs±SD*
2008 (n=160)	Neurology	59.8±14.6	12.5-90	
	Pulmonology	53.1±12.7*	15-83	
	Cardiology	60.2±8.8	33-83	58.1±7.7
	Short notes	59.5±7.0	40-78	
2009 (n=151)	Neurology	69.4±15.0	24.5-100	
	Nephrology	58.5±5.5*	36-71.5	54.5±7.7
	Cardiology	45.7±16.0*	0-85	
	Short notes	59.3±7.4*	36-74	
2010 (n=155)	Neurology	54.6±23.4	0-95	
	Nephrology	60.9±9.2*	30-82	
	Pulmonology	77.6±9.6*	40-95	
	Cardiology	61.8±9.2*	38-83	59.8±9.2
	Hepatobilliary	49.8±12.0*	10-80	
	Metabolic	54.0±18.8	0-93	

* Statistically significant difference ($p<0.001$) observed between neurology question and the respective SEQ

In post-hoc analysis of variance for the 2008 batch the marks obtained for neurology (59.8±14.6) significantly varied (higher) only from marks obtained for the pulmonology question (53.1±12.7). There were no significant difference observed between the neurology question and the two other SEQs in the 2008 batch. In the 2009 batch the marks obtained for the neurology question (69.4±15.0) was significantly higher than the marks obtained for all other individual questions (Table 1). In post-hoc analysis of variance for the 2010 batch the marks obtained for the neurology question (54.6±23.4) was significantly lower than the marks for the cardiology (61.8±9.2), pulmonology (77.6±9.6) and nephrology (60.9±9.2) questions, while being significantly higher than the question on hepatobiliary (49.8±12.0) system (Table 1).

When students marks for different SEQs were categorized into groups of <35, 35-50, 50-75 and >75 the marks obtained for the neurology questions in all batches demonstrated a wider dispersion than almost all other questions (Table 2). The students overall average was not significantly affected by exclusion of the neurology question in the 2008 and 2010 batches. However, the average significantly decreased when the neurology question was excluded from the 2009 batch from 58.2±8.0 to 54.5±7.7 ($p<0.001$) (Table 3). The effect of the neurology question on the overall average mark of students having an overall average of <35, 35-50, 50-75 and >75 was analyzed and are presented in Table 4. The average of students who were having an overall average for all questions of <35 or 35-50 improved with the exclusion of the neurology question and in the better students (overall average 50-75 or >75) the average reduced significantly when the neurology question marks were excluded (Table 4).

Table 2. Number of students (%) obtaining marks in different category of marks

		Number of students (%)					
Batch	*Marks*	*Neurology*	*Nephrology*	*Pulmonology*	*Cardiology*	*Hepatobiliary*	*Other*
	< 35	6 (3.8%)		11 (6.9%)	1 (0.6%)		0 (0%)
2008	35 - 49.9	23 (14.4%)		52 (32.5%)	13 (8.2%)		8 (5.0%)
	50 - 74.9	99 (61.9%)		92 (57.5)	138 (86.2%)		144 (90.0%)
	≥ 75	32 (20.0%)		5 (3.1%)	8 (5.0%)		8 (5.0%)
	< 35	2 (1.3%)	0 (0)		37 (24.5%)		0 (0%)
2009	35 - 49.9	18 (11.9%)	8 (5.3%)		54 (35.8%)		10 (6.6%)
	50 - 74.9	63 (41.2%)	143 (94.7%)		53 (35.1%)		141 (93.4%)
	≥ 75	68 (45.0%)	0 (0)		7 (4.6%)		0 (0%)
	< 35	33 (21.3%)	3 (1.9%)	0 (0)	0 (0)	13 (8.3%)	23 (14.8%)
2010	35 - 49.9	28 (14.4%)	11 (7.1%)	1 (0.6%)	15 (9.7%)	59 (38.1%)	40 (25.8%)
	50 - 74.9	59 (38.1%)	133 (85.8)	41 (26.4%)	127 (81.9%)	79 (51.0%)	71 (45.8%)
	≥ 75	35 (22.6%)	8 (5.2%)	113 (73.0%)	13 (8.4%)	4 (2.6%)	21 (13.6%)

Table 3. Students average with and without the neurology question

Batch	Mean (±SD)		
	All questions	Neurology excluded	p
2008 (n = 160)	58.1 ± 7.7	57.6 ± 7.2	0.511
2009 (n = 151)	58.2 ± 8.0	54.5 ± 7.7	<0.001
2010 (n = 155)	59.8 ± 9.2	60.8 ± 7.9	0.289

Table 4. Average marks with and without the neurology questions in students of different overall average

Batch	Average category (n)	Mean (±SD)		
		All questions	Neurology excluded	p
2008 (n= 160)	<35 (0)			
	35-50 (21)	44.7±3.9	46.5±4.1	<0.05
	50-75 (137)	59.9±5.7	59.1±5.8	NS
	>75 (2)	75.2±0.0	71.2+1.2	<0.05
2009 (n=151)	<35(0)			
	35-50 (36)	45.1±3.1	49.0±4.1	<0.05
	50-75 (115)	61.2±6.3	57.6±5.8	<0.05
	>75 (0)			
2010 (n=155)	<35(0)			
	35-50 (25)	45.6±3.5	49.8±4.5	<0.05
	50-75 (127)	62.2±6.7	62.6±6.0	NS
	>75 (3)	78.6±3.9	77.0±3.6	<0.05

Discussion

This is the first report on the effects of knowledge of neurology and neurophobia on medical students' examination performance in Sri Lanka. We report little or no significant difference in the students' marks for neurology SEQs and other SEQs for the 2008 batch, a significantly higher average for neurology in 2009 and a lower one in 2010. The average marks of students for neurology in 2010 could be lower in comparison to other essay questions probably due to the question being on lateral medullary syndrome an area that the students are exposed to less frequently in wards and during teaching activities, while in the same year the other SEQs being on nephrotic syndrome, bronchial asthma and myocardial infarction which are topics that are more commonly encountered and frequently taught. However, the exclusion of the neurology SEQ for the calculation of average did not significantly improve the average of the students in any of the years. In fact in 2010 a significant reduction in the average occurred when the neurology SEQ was excluded.

In students with an overall average below 50 the exclusion of neurology question significantly improved the overall average. In contrast the students with an

overall average above 50 the average either reduced or remain unchanged when the marks for the neurology question was excluded. This highlights the fact that better performing students tend to benefit more from neurology questions and that the students who were under performing in other subject areas were also weak in their neurology knowledge.

Although the impact of neurophobia on the performance of medical undergraduates at SEQ examinations seems to be very minimal, neurophobia has far reaching implications. The neurophobia begins at medical school and continues to clinical practice later in the career. In a recent survey among medical students, senior house officers and general practitioners in the UK basic neurosciences and clinical neurology were ranked highest in terms of difficulty in learning when compared to other organ systems[6]. It is indeed from this inability to apply basic sciences to clinical situations stems the root of the neurophobia[1]. Integrating clinical neurology with the basic neurosciences, improved teaching of clinical neurology and paring down the basic neuroscience syllabus to the essential are some of the means adopted by neurologists around the world to combat this problem[5-7].

In the Sri Lankan context at present there are no studies addressing this important aspect of medical education. The impact of neurophobia on the performance of medical undergraduates at SEQ examinations seems to be very minimal. However, further studies are needed in other areas of clinical practice, like on patient-based clinical examination and patient management to assess the true impact of neurophobia.

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Review

Stroke mimics in the era of thrombolysis

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Abstract

Stroke thrombolysis has emerged as a valuable treatment for acute ischaemic stroke in the first 4.5 hours after symptom onset. The need for rapid initiation of treatment and the small but inherent risk of life-threatening side effects requires a high degree of diagnostic accuracy with only limited time for investigation. It is widely recognized that a significant proportion of patients presenting with "stroke-like" symptoms will in fact have an alternative diagnosis – so called stroke mimics. There has been anxiety that wrongful treatment of stroke mimics could be harmful. This paper reviews the published data on the incidence of stroke mimics and the outcome of thrombolysis in these cases. We conclude that the risk of adverse outcomes from thrombolysis in these cases appears to be minimal on the available evidence and is certainly significantly less than the potential harm that could result from denial of, or delay in administration of thrombolytic therapy.

Index words: stroke mimics, thrombolysis

Introduction

A significant proportion of patients presenting with stroke like symptoms will be found to have an alternative diagnosis other than ischaemic stroke. These conditions are known as "stroke mimics". Stroke mimics can be difficult to distinguish from true ischaemic strokes acutely. With the advent of thrombolysis and other interventions for acute stroke, identifying stroke mimics has become a major diagnostic challenge. If thrombolysis is performed in a patient with a stroke mimic, however what is the risk of complications? Clinicians embarking on establishing a stroke thrombolysis service may have considerable anxiety that they are using a treatment that carries significant risk of life threatening side effects. This may lead to denial or deferral of treatment while further investigations are performed with the result that valuable time is lost and any benefit from thrombolysis is significantly reduced. The clinician in this dilemma might well ask, "Is this anxiety justified?" Published data now goes some considerable way to answering this question and enables increasingly safe, rational decisions to be made in the emergency room when time pressures are challenging.

Epidemiology of stroke mimics

Stroke mimics usually require extensive neuroimaging and laboratory work up to confirm the diagnosis. Studies in patients who were not thrombolysed show that the prevalence of stroke mimics varies from 1.3% to 25%[1,2]. Further studies suggest the rate of misdiagnosis of acute stroke by US emergency physicians ranges from 5% to 33%[3]. More recent studies have estimated that the prevalence of stroke mimics ranges from 3% to 13% in patients treated with tissue plasminogen activator [4,5,6,7,8,9]. The prevalence of stroke mimics varies greatly between the different studies reflecting the diagnostic criteria and imaging modality used. The lower prevalence of stroke mimics in recent studies may be due to better clinical and imaging criteria. Some of the earlier studies used clinical criteria and CT with only a few patients having a MRI[1,3] while in later studies[4,5,6,8,9,10] all patients were subject to a MRI scan. Efforts to increase the availability of acute treatment of stroke while concurrently reducing the time for thrombolysis increases the likelihood of stroke mimics receiving treatment. The prevalence of stroke mimics varies depending on the diagnostic criteria used. For example, patients considered to have acute cerebral ischaemia but with no supporting evidence for stroke on subsequent imaging have been classified as neuroimaging negative cerebral ischaemia and may account for more than one quarter of stroke presentations[6,10].

Differential diagnosis of stroke mimics

In clinical practice the commonest causes of a stroke mimic presentation are post-ictal paralysis, complex migraine and psychogenic conversion disorder. Other rarer causes include hypoglycaemia, cerebral tumour or abscess, sub-dural haematoma, metabolic encephalopathy, Uhtoff's phenomenon in multiple sclerosis and transient global amnesia[1,6,8, 9,10,11]. The relative frequency of these diagnoses varies between studies. Post-ictal paralysis accounts for between 19.6-38%, complex migraine between 19.6-37% and psychogenic weakness 21-26.8%[4,6].

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Clinical history and examination with appropriate investigations, particularly brain MRI with DWI will identify stroke mimics ultimately, but in the emergency room the clinician may have to depend on clinical assessment alone as tests are not possible within the thrombolysis time window. Certain clinical findings may be helpful, however. Hand et al[1] have demonstrated that cognitive impairment and abnormal signs in other systems suggested a stroke mimic. They also noted that the following suggested a stroke: an exact time of onset, definite focal symptoms, abnormal vascular findings, presence of neurological signs, being able to lateralize the signs to the left or right side of the brain, being able to determine a clinical stroke sub classification.

A more recent study[9] showed that aphasia and accompanying convulsions were commoner in mimics. Known cognitive impairment, aphasia and accompanying convulsions were independent predictors of stroke mimics.

Outcome of thrombolysis in stroke mimics

Several studies have looked at outcomes in patients presenting with a stroke mimic who receive thrombolysis [4,5,6,7,8,9,10].

One of the earliest of these looked at 151 patients of whom 6 had a final diagnosis other than stroke. If TIA was also included into the definition of stroke mimics the number increased to 10[7]. This group suffered no harm from thrombolysis and overall had less disability as measured by the modified Rankin Scale (mRS) at discharge.

Six further more recent studies have documented excellent functional outcomes in patients with stroke mimics who received thrombolysis with no cases of cerebral haemorrhage[4,5,6,8,9,10]. This is as expected, bearing in mind that the most common causes of stroke mimics are conversion disorders, migraine and seizures. Furthermore there were no cases of orolingual oedema and the overall outcomes were good in the stroke mimic group. The largest more recently available data come from the Helsinki Stroke Thrombolysis Registry, which looked at the outcomes of 985 consecutive ischaemic stroke patients from 1995 to 2008. This also addressed the issue of outcomes in neuro-imaging negative stroke patients who are given thrombolysis[10]. They identified 14 stroke mimics (1.4%), 275 neuro-imaging negative strokes (28.3%) and 694 neuro-imaging positive ischaemic strokes (71.5%). There were no significant differences between the patients with neuroimaging negative ischaemic strokes and stroke mimics with regard to medical history or clinical features except that stroke mimics were younger with a mean age of 55.5 years (45-59) vs70 years (59-77) in acute ischaemic strokes. Of the stroke mimics none had haemorrhagic complications, while 6 (2.2%) in the neuroimaging negative group had haemorrhagic complications. An excellent outcome was more common in stroke mimics and neuroimaging negative group at 3 months[10].

Overall the results of these studies are reassuring although it is acknowledged that the absolute numbers of stroke mimics is small and so the data should still be interpreted with caution. It is important also to note that all of the studies used recombinant tissue plasminogen activator as the thrombolytic agent and these results cannot be extrapolated to the use of other thrombolytic agents. Table 1 gives a summary of findings of these studies.

Table 1. Summary of the most recent studies on stroke mimics and thrombolysis

	Study details	*Stroke mimics (SM) identified*	*Characteristics and outcome of stroke mimics*
Guilan et al 2012	Total number 621 patients Stroke mimics 15 (2.4%) Based on CT and MRI Few had multimodal CT	Somatoform disorders Headache with neurological deficits and CSF lymphocytosis Herpes encephalitis Glial tumours Migraine with aura Focal seizures Cerebral venous thrombosis	SM were younger, had lower baseline deficit, fewer vascular risk factors and predominantly left hemispheric symptoms. Good outcome with no symptomatic ICH or disability (functional outcome at 3 months mRS >2) Use of intravenous thrombolysis appears to be safe in SM with favourable prognosis.

(Continued)

	Study details	*Stroke mimics (SM) identified*	*Characteristics and outcome of stroke mimics*
Forster et al 2012	Total number 648 patients Stroke mimics 42 (6.49%) Based on MRI	Seizures Conversion disorder Dementia Migraine Brain tumour	Cognitive impairment, aphasia and accompanying convulsions were independent predictors of stroke mimics. Orolingual angioedema occurred in one patient. None had intracerebral bleed or deteriorated clinically.
Artto et al 2012	Total number 985 patients Stroke mimics 14 (1.4%) Based on CT and MRI	Conversion disorder Encephalitis Epilepsy Demyelination Migraine	Stroke mimics were younger and had less severe symptoms at base line and better 3-month outcome. Stroke mimics were more likely to be females. None developed symptomatic ICH. No difference in medical history or clinical features.
Tsivgoulis et al 2011	Total number 539 patients Stroke mimics 56 (10.4%) Based on CT and MRI	Conversion disorder Complicated migraine Seizure	Stroke mimics were younger and had milder baseline stroke severity. No cases of symptomatic ICH. 96% of the stroke mimics were functionally independent at hospital discharge.
Chernysher et al 2011	Total number 512 patients Stroke mimics 69 (14%) Based on CT and Multimodal MRI	Seizure Complicated migraine Conversion disorder Aseptic meningitis Epidural spinal mass Heat stroke Syncope	Stroke mimics were younger and had a lower baseline deficit. Median discharge NIHSS was 0. Median length of stay in hospital was 3 days. None had symptomatic intracerebral haemorrhage. Overall outcome was good.
Winkler et al 2009	Total number 250 patients Stroke mimics 7 (2.8%) Based on CT and MRI	Seizures Conversion disorder Non convulsive status due to glioblastoma multiforme	Stoke mimics had a lower baseline disability. None of the mimics had orolingual oedema or intracerebral haemorrhage Stroke mimics had a favourable outcome.

Conclusion

The currently available data indicate that intravenous thrombolysis does not adversely affect the favourable natural history of stroke mimics. The benefit of treatment with tissue plasminogen activator for patients presenting with an acute stroke episode would not seem to be negated by the potential for harm to patients presenting with stroke mimics or imaging negative stroke. The available evidence (even allowing for the low incidence of stroke mimics) suggests there is no justification for withholding treatment in the patient presenting with a clinical picture of acute stroke whilst further investigations, such as DWI, MRI imaging, are obtained, if this would lead to a delay in treatment. Imaging prior to thrombolysis is only to exclude a haemorrhage, not to identify stroke mimics. The clinical features that might suggest a stroke mimic, as well as a younger age and female gender are not sufficiently robust to enable the clinician to make a safe decision on avoiding thrombolytic treatment in the emergency room.

The extremely low rates of adverse events and excellent functional outcomes in stroke mimics however, should reassure clinicians to give thrombolytic therapy for stroke and not withhold it based on the sole concern that the patient's neurological symptoms may be attributed to a stroke mimic.

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Review

Treatment of epilepsy in adults

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Case vignettes

1. *A 60-year old patient with long standing temporal lobe type epilepsy was taking carbamazepine 800 mg a day in divided doses of 200, 200 and 400 mg. He was tolerating the dose well, but his seizures were not controlled well. He had an exacerbation of seizures and saw a neurologist. He was advised to take an extra tablet of 200 mg of carbamazepine every time he had a seizure and over the next two weeks he ended up taking 400 mg three times a day. When he was seen at this stage he was very ataxic, had diplopia and was feeling very sleepy.*

2. *A 25-year old female was taking 600 mg of sodium valproate for juvenile myoclonic epilepsy. She was well controlled without any seizures. A physician who saw her changed her medication to carbamazepine as she was pregnant 18 weeks. She ended with relapse of her seizures and had to be put back on 400 mg valproate with good results.*

3. *A 13-year old boy was started on valproate by a neurologist after having two seizures during sleep. Despite increasing the dose to 800 mg daily he was getting seizures about once a month. EEG showed centro-temporal spikes and after changing over to oxcarbazepine 150 mg twice a day his seizures completely stopped.*

Above examples show practical problems in the management of epilepsies today. Some of us still base our treatment decisions on large scale studies done in the 1980s when seizures were lumped together and treatment was solely based on seizure type. New knowledge has shed light on basing treatment on the epileptic syndromes rather than seizure types for more effective and rational treatment. The Ceylon College of Physicians guidelines on epilepsy is very brief and is based on seizure types and makes naïve statements like "if under 25 years use valproate and if over 25 years use carbamazepine". A comprehensive update of these guidelines is needed. Even NICE UK guidelines are at times outdated when published and their undue emphasis on cost-effectiveness results in their recommendations at times being not the best for an individual patient. Most recent 2012 updated NICE guidelines are undecided on the value of levetiracetam because of its current cost. This review is an attempt to overcome these problems and to make some clinically useful recommendations based on current evidence and personal experience.

Global prevalence of epilepsy is about 3 to 9 per 1000 population[1]. Globally 10% of people will have at least one seizure and one third of them will develop epilepsy[2,3]. The prevalence of epilepsy in Sri Lanka is around 9 per 1000 population[4]. Epilepsy is one of the commonest neurological diseases in our country and patients are managed by both specialist neurologists as well as general physicians. Optimal management of epilepsy should encompass both optimal seizure control as well as minimal adverse effects. Antiepileptic drugs have many side effects but the availability of more than 20 antiepileptic drugs give the physician a wide array to choose from. Further it is also important to choose the most efficacious drug for the particular seizure type or the syndrome. In this review we would discuss the current evidence based treatment for epilepsy in adults addressing the indications for starting treatment, drug selection, epilepsy in pregnancy and in the elderly, failure of treatment, duration of treatment and the withdrawal of treatment.

Epilepsy is not a single disease entity but consists of many syndromes and diseases, which have a multitude of clinical manifestations and aetiology. Classification of epileptic seizures and syndromes are required for the appropriate management and prognosis. The short and long term management of epilepsy varies with the disorders manifesting with the seizures. This emphasizes the need for accurate diagnosis as the first step in the treatment of epilepsy.

Details of seizure types and classification are not discussed here but in brief there are three steps required in the process of diagnosis – **to confirm the paroxysmal event as a seizure, to identify the type of seizure and finally to find the cause and the epileptic syndrome or disease.** Once epilepsy is diagnosed and the type of seizure and aetiology is identified appropriate therapeutic interventions are required. Total seizure freedom without clinically significant adverse effects is the aim of therapy. Antiepileptic drugs form the mainstay of management while some now benefit from neurosurgical interventions, stimulation techniques and ketogenic diet.

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Should therapy be commenced after the first unprovoked seizure?

After confirming the event to be a seizure the next step is to decide when to commence antiepileptic therapy. The decision to treat is based on the balance between the likelihood of further seizures and the risk of adverse effects of treatment. Once therapy is commenced the goal is to maintain freedom from seizures with minimal drug related adverse effects and is usually achieved with a single appropriately selected anti-epileptic drug at target therapeutic dose. Poly therapy is best avoided and commenced only in those who fail to respond to several trials of single AED at therapeutic dose.

The usual practice is to commence antiepileptic therapy after the second unprovoked seizure. There is evidence from two large open labeled, randomized clinical trials - First Seizure Trial Group (FIRST) study[5] and the Multicentre Study of Early Epilepsy and Single Seizure (MESS) study[6] showing that immediate treatment after the first seizure reduced the recurrence rates of subsequent seizures, but the risk reduction at 2 years was 42% in the FIRST study and 18% in the MESS study. Reanalysis of the MESS study showed that the recurrence at 2 years varied from 30% in the low risk group to 73% in the high risk group.

Thus the decision to treat the first seizure should be based on the risk category including the severity of the seizure, time of occurrence and individual characteristics. A patient with a high risk of recurrence could be commenced on an appropriate antiepileptic after the first unprovoked seizure. One should also consider that the restrictions imposed by seizures on everyday activities are of greater relevance to an adult than to a child. More than 50% of patients will not have a recurrence after the first unprovoked seizure and, thus treatment can be differed except in patients with a high risk of recurrence, severe seizures and patients with seizures following a stroke or other identifiable lesions and in elderly patients.

In all other patients antiepileptics are commenced after the second unprovoked seizure, if the severity of the seizure is significant to the individual, if it occurs within 2 years of the first and if the patient wishes to take treatment.

Which antiepileptic drug should be commenced?

The choice of antiepileptic drug would be based on the efficacy of the drug for the seizure type and the tolerability based on the results of well conducted randomized controlled clinical trials. But unfortunately due to the availability of only very few well conducted trials[7] the current leading guidelines differ in their recommendations. Adverse effects including idiosyncratic reactions, teratogenicity, chronic side effects and enzyme inducing effects and potential for side effects influence the choice of antiepileptics in addition to efficacy and effectiveness. All current guidelines consider individual patient characteristics, seizure types and characteristics of special relevance such as child bearing potential, old age and co-morbidities when choosing the appropriate antiepileptic[8,9,10].

In general the older AEDs which have stood the test of time are generally preferred over the newer AEDs. The newer AEDs like gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin are recommended in patients who have not benefited from treatment with the older AEDs or for those in whom the older AEDs are unsuitable because of contraindications, drug interactions, and poor tolerance[9]. General recommendations are for monotherapy and if initial therapy is unsuccessful monotherapy with another drug is tried and combination therapies tried only when attempts at monotherapy have failed.

Seizures are broadly categorized into partial and generalized seizures. The commonly prescribed antiepileptics are sodium valproate and carbamazepine along with phenytoin. Carbamazepine is used as first line for partial seizures and is also used as second line for generalized tonic clonic seizures. Sodium valproate is used as first line AED in primary generalized seizures, absence and myoclonic seizures. Valproate may also be considered in atypical absence, atonic and tonic seizures. Phenytoin is efficacious for tonic clonic seizures, partial seizures and for prevention and treatment of seizures occurring during or following neurosurgery and severe head injury.

Phenobarbital is used for tonic clonic and partial seizures and sometimes in atypical absence, atonic and tonic seizures. Ethosuximide is primarily used in absence seizures but when absences coexist with other seizure types valproate is preferred. Clonazepam is efficacious in tonic clonic or partial seizures. Clobazam is used as an adjunctive therapy in partial seizures.

All AEDs have CNS side effects which are dose related and may be apparent at therapeutic doses. Of particular concern is the effect of AEDs on cognitive functions. AEDs may have subtle effects on mood, cognition and memory that is usually apparent only on formal testing. Carbamazepine, phenytoin and barbiturates are enzyme inducers while valproate is an enzyme inhibitor.

Of the newer antiepileptics, studies have shown that lamotrigine, oxcarbazepine and topiramate can be used as monotherapy, while these three along with levetiracetam and gabapentin are used in combination therapy. The newer drugs are attributed to have a more acceptable adverse-effect profile, less drug interactions and convenient dosing regimens. On the other hand there

is very limited data on the effects of these drugs on the fetus and thus they are not widely prescribed during pregnancy.

Lamotrigine is used as monotherapy in partial seizures as well as in primary and secondarily generalized tonic clonic seizures. It is also used for seizures in Lennox-Gastaut syndrome. Carbamazepine is best avoided in L-G syndrome as it can aggravate generalized seizures while controlling partial seizures.

Oxcarbazepine is a carbamazepine analogue which is used as monotherapy or combination therapy for partial seizures with or without secondary generalization. It has a lower potential for drug interactions compared to carbamazepine. **Both carbamazepine and oxcabazepine are ineffective against, and can exacerbate absence and myoclonic seizures and therefore are best avoided in primary generalized epilepsies.**

Topiramate is recommended as combination therapy for those who are inadequately controlled with the conventional anti epileptic drugs and who have partial seizures with or without secondary generalization, seizures associated with Lennox-Gastaut syndrome, or primary generalized tonic clonic seizures. It is also recommended as monotherapy for patients with newly diagnosed epilepsy who have generalized tonic clonic seizures or partial seizures with or without secondary generalization. Users of topiramate should be well aware of its side effect profile as it has many potentially serious side effects. Levetiracetam is approved for combination therapy of partial seizures with or without secondary generalization and is a drug that is well tolerated.

In summary when considering the current guidelines the AAN (American Academy of Neurology) recommends for partial seizures with or without generalization carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate and valproate. The NICE (UK National Institute for Health and Clinical Excellence) recommends carbamazepine, lamotrigine, oxcarbazepine, topiramate and valproate while the SIGN (Scottish Intercollegiate Guideline Network) recommends carbamazepine, lamotrigine, oxcarbazepine, phenytoin and valproate. The ILAE (The International League Against Epilepsy) recommends carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproate.

Carbamazepine, lamotrigine, oxcabazepine and valproate have been recommended by all four major guidelines while topiramate is recommended in 3 of the major guidelines as first line therapy for adults with partial seizures, with or without secondary generalization[11].

If therapeutic doses need to be reached rapidly drugs such as levetiracetam, valproate or phenytoin which can be started or rapidly titrated to the fully effective dose are recommended while lamotrigine or topiramate which require slow titration are generally avoided.

Treatment of idiopathic generalized epilepsies

Valproate has superior efficacy in all seizures and syndromes of IGEs but its use in women of childbearing age is highly problematic. The adverse effects of valproate and its lack of efficacy in 20% of patients have prompted the search for newer drugs. Lamotrigine, levetiracetam, topiramate and zonisamide appear to be effective. Levetiracetam, because of its efficacy in all types of seizures and safer adverse reaction profile, seems to be the best substitute for valproate.

Carbamazepine, oxcarbazepine and phenytoin too can be considered but exacerbate absences and myoclonic jerks. Vigabatrin exacerbate absences. Gabapentin is ineffective in all types of idiopathic generalized epileptic seizures. Clonazepam is effective for myoclonic jerks, but is ineffective for GTCS. Lamotrigine is effective in primarily GTCS and absences, but may exacerbate myoclonic jerks.

Juvenile myoclonic epilepsy

Valproate has been recognized as the most effective drug with full control of seizures in about 80% of patients with JME. The effective dose may vary from 600 to 3000 mg a day. Phenobarbitone is extensively used in Europe for treatment of JME. It is effective in controlling GTCS and myoclonic jerks, but may exacerbate absences. Phenobarbitone 60-90 mg daily is sufficient. When myoclonic jerks persist clonazepam can be added to valproate and when only myoclonic jerks are the presentation, clonazepam can be the initial therapy. Lamotrigine is not suitable as it can exacerbate myoclonic jerks in JME though it would control generalized seizures and absences. **Levetiracetam is probably the best new AED in the treatment of JME.** The results of treatment of JME with levetiracetam are very impressive. In three independent studies 62%, 67%, and 63% of patients with JME became seizure free with levetiracetam monotherapy or polytherapy.

Antiepileptics and pregnancy

Several observational studies as well as a population based study report increased risk of congenital malformations such as spina bifida, atrial septal defects, cleft palate and craniosynostosis with valproate compared with other AEDs such as carbamazepine and lamotrigine[12,13,14]. Studies also show that valproate affects cognitive development[15]. The teratogenic effects of valproate are dose dependent especially at higher daily doses of 1000 mg or more.

For focal seizures carbamazepine is used as a first line drug. The choice of drugs for primary generalized seizures is more difficult with lamotrigine being the first choice with levetiracetam and topiramate being the possible alternatives to valproate.

Lamotrigine is less efficacious than valproate especially in syndromes associated with myoclonic seizures and absence seizures. Further the pharmacokinetics of lamotrigine requires frequent dose adjustments during pregnancy.

Data on levetiracetam and topiramate with regard to teratogenicity is insufficient and the adverse effects of topiramate on cognition raise concern[16, 17].

Antiepileptics in the elderly

Choice of an appropriate antiepileptic in the elderly is challenging, as they are more prone to adverse effects. Carbamazepine, an enzyme inducer is not recommended in the elderly as it is likely to cause drug interactions as well as impaired bone health, cause endocrine dysfunctions and changes in serum cholesterol levels as well as markers of cardiovascular risk factors[18].

Carbamazepine remains the drug of choice in focal seizures but lamotrigine and levetiracetam are preferred in patients on other medications where drug interactions and enzyme induction may cause problems as well as in patients in whom bone health is a concern.

In a retrospective review carried out comparing the effectiveness of 10 antiepileptics in elderly adults with epilepsy, lamotrigine was the most effective with levetiracetam being the next most effective[19].

Selection of formulation of AED

Currently with the introduction of sustained release preparations only carbamazepine sustained release preparation when given twice daily has shown to be superior with regard to tolerability compared to immediate release formulations[20]. Evidence is not strong for the other AEDs.

Optimal dosage

The lowest dose that provides seizure freedom should be used in order to increase tolerability and minimize the adverse effects. Evidence suggests that newly diagnosed patients respond to relatively low doses of AED. Optimal starting doses being 400 mg per day for carbamazepine, 1000 mg per day for levetiracetam, 100 to 200 mg per day for lamotrigine and 600 to 1000 mg per day for valproate[21,22]. Sometimes a starting dose of carbamazepine 200 mg in the morning may be difficult to tolerate and then the morning dose may have to be titrated from 100 mg up or use the controlled release formulations. Our personal experience is levetiracetam 500 mg daily is effective as adjuvant therapy in most cases. Factors such as age, comorbidities, attitudes towards potential side effects and risk of seizure recurrence should be taken into account when deciding the optimal dosage. Further gradual dose titrations increases tolerability and reduce idiosyncratic adverse reactions. Thus starting with a low dose and titrating to optimal dose is recommended unless an immediate anti seizure effect is required. The optimal duration of titration period depends on the type of AED, maintenance dose and individual response.

If seizures recur when the patient is stabilized on the selected initial maintenance dose, the dose is increased depending on the clinical response.

Current recommendations promote the identification of a serum concentration with the best response to an individual and its use as a reference to adjust dosage with anticipated pharmacokinetic changes such as in pregnancy or when a potentially interacting drug is added or removed or to assess unexpected changes in clinical response[23].

Failure of initial monotherapy

Failure of initial monotherapy could be either due to lack of efficacy or due to adverse effects. If the AED was discontinued due to idiosyncratic reactions, another AED has to be tried avoiding the use of drugs which have cross reactivity.

If the failure is due to lack of efficacy after titrations to the highest tolerated dose, non compliance, incorrect diagnosis and inappropriateness of the AED needs to be considered. If AED needs to be changed, it should be switched gradually to monotherapy with an alternative drug[24,25]. Some trials advocate monotherapy with an alternative drug before adjuvant therapy while others suggest combination therapy specially if the first AED was partially effective and tolerated[26].

Duration of treatment

Duration of treatment depends on prognostic factors, adverse effects of medication, patient's lifestyle and attitude towards continuation of medication and the possibility of relapse. The risk of relapse is greater in adults and so is the impact of a relapse with regard to driving and certain occupations. Further the psychosocial issues associated with long term medication may be significant.

Adolescent onset of seizures, focal seizures, underlying neurological illness and abnormal EEG when withdrawing the drugs predict a higher risk of recurrence while childhood epilepsy, idiopathic generalized epilepsy and normal EEG are associated with a lower risk of recurrence[27]. Discontinuation may be considered after 2 to 4 years of seizure freedom after discussing the potential risk and benefits with the patient. Symptomatic epilepsy, focal epilepsy and cognitive deficits are associated with poor outcome after a recurrence.

Evidence recommends that discontinuation should be individualized and gradual over a 3 month period and preferably over 6 months when withdrawing barbiturates and benzodiazepines.

Conclusion

Epilepsy is one of the most common neurological disorders and causes significant morbidity and mortality especially amongst the adult population who make up the working population of our society and is a cause of physical and social burden. Appropriate pharmacological treatment will be of immense benefit to the patient and one should keep in mind to prescribe an appropriate antiepileptic, which is also available and affordable to the patient.

Search strategy

References for this Review were identified through searches of PubMed until January 2012 with the search items “epilepsy”, “treatment”, “antiepileptic drugs”. References were also identified from relevant review articles. Only articles published in English were reviewed.

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Point of view

Redefining transient ischaemic attack

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Sri Lanka Journal of Neurology, 2012, **1**, 39-40

Index words: transient ischaemic attack (TIA), stroke, ABCD^2 score

Around 23% of patients with ischaemic stroke give a history of preceding transient ischaemic attack (TIA)[1,2] whilst TIAs occurred most often in the 48 hours to 2 weeks prior to the presenting stroke[2]. TIA is associated with high risk of early recurrent stroke[3] with stroke rates as high as 35% in some subgroups by 7 days[4]. The window between TIA and stroke is often hours to days and preventive interventions initiated urgently after TIA can substantially reduce the risk of stroke. Antiplatelet agents[5,6], antihypertensive drugs[7], statins[8], anticoagulation (in atrial fibrillation or intracardiac thrombi)[9] and carotid endarterectomy (for symptomatic carotid stenosis)[10] have shown to prevent stroke after a TIA. The ABCD^2 score [age (≥60 years = 1 point); blood pressure elevation when first assessed after TIA (systolic ≥140 mmHg or diastolic ≥90 mmHg = 1 point); clinical features (unilateral weakness = 2 points; isolated speech disturbance = 1 point; other = 0 points); duration of TIA symptoms (≥60 minutes = 2 points; 10 to 59 minutes = 1 point; <10 minutes = 0 points); and diabetes (present = 1 point)] is widely used to stratify the early stroke risk after TIA[4].

TIA has been traditionally defined as an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply. The 24-hour threshold used to distinguish TIA from stroke is arbitrary and arose in the mid-1960s[11]. At that time, it was assumed that transient symptoms disappeared completely because no permanent brain injury had occurred. However, with the advent of advanced imaging techniques such as diffusion-weighted MRI studies, it has been demonstrated that up to a third of ischaemic episodes with symptoms lasting only 24 hours or less were also associated with brain infarction[12]. This has led to the proposal of a revised definition of TIA as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction[13]. This is a tissue-based definition that relies on excluding end-organ damage (ie, infarction) rather than the arbitrary time limit specified in the original definition. The new definition takes into account that infarction can occur irrespective of the duration of the transient neurological symptom. Although the clinical symptoms of TIA typically last less than one hour, a systematic analysis has shown that symptom duration is not a reliable predictor for the presence of infarction[14]. The new definition entails the need for brain imaging (ideally, diffusion-weighted magnetic resonance imaging – DWI) in the acute phase.

Should the time-based clinical definition of TIA be replaced by the new tissue-based definition that incorporates brain imaging?

Several studies have shown that the presence of infarction, particularly on DWI, is associated with a higher risk of stroke in patients clinically presenting with a time-defined TIA[12,15,16]. The 7-day stroke risk among patients with acute infarction on DWI (7.1%) was 18-fold higher than those without acute infarction (0.4%). Furthermore, it has been shown that incorporation of brain infarction into the ABCD^2 score (ABCD^2-I) improves the prediction of stroke after TIA[12,15,16].

Although the presence of infarction is the major determinant of early stroke, the ABCD^2 score has predictive value in the acute phase in both tissue-positive and tissue-negative patients, identifying individuals at higher and lower risk within both these groups[15]. A high ABCD^2 score in patients presenting with a time-defined TIA, irrespective of whether tissue-positive or -negative, warrants early intervention to prevent stroke. Moreover, unstable vascular disease factors known to be associated with a high risk of stroke after TIA such as carotid stenosis and atrial fibrillation require early intervention in all patients presenting with a time-defined TIA. The advantage of the ABCD^2 system is that it has been designed as an initial assessment tool in a primary care / emergency setting based purely on clinical parameters. The identification of a brain infarct only refines the risk prediction of recurrent stroke.

The time-based definition of TIA, although arbitrary, has served the clinician well in recognising a neurovascular syndrome that provides an opportunity to prevent stroke. The ABCD^2 score augments this definition by providing a reliable clinical prediction tool to guide the clinician in prognostication and treatment of individual patients. In comparison, the recently proposed tissue-based definition of TIA utilises DWI in identifying a subcategory of time-defined TIA as true TIA with a relatively lower risk of stroke on the basis of absent brain infarction. However, the tissue-based definition has the

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disadvantage of requiring advanced imaging facilities in an acute setting.

It is therefore sensible to retain the time-based definition of TIA. It is simple and reliable. Where brain imaging facilities are available, time-defined TIA can be categorized as *with-infarction* and *without-infarction* to provide prognostic information. This classification recognizes that the clinical syndrome of TIA lasting less than 24 hours can occur with or without brain infarction, and that the latter carries a higher risk of early recurrent stoke. The $ABCD^2$ score should be used to refine the risk of stroke in both tissue-positive and -negative TIA, and to predict the risk of stroke after TIA when brain imaging is unavailable.

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Case report

Dopa-responsive dystonia – diagnosed 50 years after onset of symptoms

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Sri Lanka Journal of Neurology, 2012, **1**, 41-42

Introduction

Dopa-responsive dystonia (DRD) is a rare hereditary hyperkinetic movement disorder usually seen in childhood which responds dramatically to treatment with levodopa. Its features may mimic other neurological illnesses and is thus under-diagnosed. I report a patient with DRD, whose illness evaded diagnosis for over 50 years. Its treatment has brought excellent results even at this late stage of the disease. This case also gives an idea of the natural course of the illness, if untreated.

Case report

A 58-year old female presented with progressive gait difficulty since childhood. She was born to non-consanguineous parents, after a normal vaginal delivery. Her perinatal history was uneventful. At around 6 years of age, her gait was noticed to be slightly abnormal at times. While schooling, she recalls having difficulty walking even short distances, as her legs felt stiff and heavy. This would clear up after a good night sleep. Mornings were better and sometimes she felt almost normal. Symptoms progressed during the course of the day. Gradually the stiffness involved her hands. She found difficulty playing the piano and was reported to be clumsy by her teachers. She was seen by many doctors over the years but of no avail, and had then accepted to live with her disability.

In her late twenties, she had to walk holding onto furniture and walls. She could only stand with support towards the evenings. She had several falls due to loss of balance. She could not leave the house alone and preferred to stay at home. Her disability continued to progress even after 50 years of age. She could not get up from bed unassisted. She needed two persons to lift her up from a chair. Her hands had also further slowed down. Speech and swallowing, and higher functions were not affected. She had an elder brother who was well. There was no family history of any similar illness. Her situation had become desperate and she once again decided to seek medical advice.

She was brought in a wheelchair and needed two people to help her get onto the examination bed. She had marked increase in tone in both lower limbs with dystonic posturing of her feet. Power, deep tendon reflexes and plantar reflexes were normal. There was bradykinesia of the hands but no tremor. No sensory deficits were detected. General examination did not reveal any Kayser-Fleischer rings.

Investigations showed normal blood counts, liver and renal function tests. Serum caeruloplasmin level was normal. MRI brain did not reveal any abnormality.

She was diagnosed to have a childhood onset progressive dystonia with diurnal variation. A trial with levodopa 125 mg twice per day was commenced. The next morning, she was able to get out of bed without help and walk without any assistance. Over the next few days, all her disabilities with which she lived for over 50 years disappeared. She now goes for daily 4 km walks and is catching up with things she never could do previously. Three years since the diagnosis, she is on levodopa 125 mg three times a day. She is now totally independent in all activities of daily living and her neurological examination is normal.

Discussion

DRD was described by Segawa as a new entity in the 1971 and is also known as Segawa disease[1]. It is a genetically inherited disorder, and accounts for about 10% of the childhood onset dystonias. It typically presents around 6-16 years of age and is about 3 times more common in girls.

The classical presentation is an abnormal gait due to a foot dystonia. There is plantar flexion and inversion (equinovarus posture) of the foot causing the child to walk on toes. Patients have as a result undergone unnecessary corrective surgery for equinovarus deformity. The dystonia can slowly extend to the arms and trunk. Some have Parkinsonism features in addition like tremor and bradykinesia, and may be mistaken for Juvenile Parkinsonism. The presence of a “striatal toe” (dystonic extension of the big toe) may mimic Babinski sign and along with hyperreflexia, DRD may be mistaken for cerebral palsy or hereditary spastic paraparesis[2]. Patients with DRD do not demonstrate intellectual, cerebellar or sensory disturbances.

Another classical feature of DRD is diurnal fluctuation, where patients are relatively symptom free

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in the morning and become progressively disabled as the day progresses. Patients also show improvement after sleep.

DRD is commonly due to an autosomal dominantly inherited mutations of the gene Guanosine triphosphate (GTP) cyclohydrolase 1[3]. The gene regulates the production of an enzyme involved in activation of tyrosine hydroxylase involved in the production of dopamine. However, only 30-40% genetically affected persons manifest symptoms due to reduced penetrance and variable expressivity. Therefore a family history is important, though may not be found as in this patient. About 40% of patients with DRD do not carry this mutation and DRD results from other recessively inherited metabolic disorders.

A diagnostic feature in DRD is the dramatic improvement seen with low doses of levodopa resulting in a near complete resolution of symptoms[4]. All suspected patients need to be given an adequate trial with levodopa for at least 3 weeks. Motor benefit often begins almost immediately on starting levodopa and full benefit may be seen within days to a few months. The response to the therapy is sustained throughout their lives, without any of the long term complications like dyskinesia and wearing off as seen in Parkinson disease. A therapeutic trial with levodopa remains the most practical way in making the diagnosis. In the majority, a restoration of complete physical function can be achieved even after many years without treatment, like in this case.

Clinicians should be alert in suspecting DRD in all children with dystonia and those labeled cerebral palsy with an unclear history. This case highlights the need to maintain such alertness even in adults whose diagnosis may have been unfortunately missed for many years. Diagnosing DRD is one of the most rewarding experiences in the practice of neurology as the response to treatment is often dramatic and miraculous.

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Case report

Resolution of clinical and MRI abnormalities in osmotic demyelination syndrome – do corticosteroids have a potentially beneficial therapeutic effect?

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Sri Lanka Journal of Neurology, 2012, **1**, 43-44

Index words: osmotic demyelination, central nervous system, central pontine myelinolysis

Introduction

Central pontine myelinolysis (CPM) is a rare neurological disorder defined by osmotic demyelination of the central base of the pons and extra pontine areas of the central nervous system (CNS). The most common underlying causes are chronic alcoholism and rapid correction of hyponatremia[1]. CPM has a poor prognosis and there is no specific therapy of choice. We report here a patient with CPM who improved rapidly and showed complete resolution of MRI changes following corticosteroid therapy.

Case Report

A 42-year old, previously healthy male was admitted with a history of being found collapsed at home. He was living alone and had a history of chronic alcohol use. He was drowsy, confused and disoriented on admission. There were no focal neurological signs. He subsequently developed 2 episodes of witnessed generalised tonic-clonic seizures. Seizures were controlled with phenytoin therapy with no further recurrences. However, he continued to remain drowsy.

Initial laboratory investigations revealed a hyponatraemia due to SIADH (serum sodium 124 mmol/l, serum osmolality 236 mosm/l and urine osmolality 424 mosm/l). Blood counts, C-reactive protein, renal and thyroid functions and chest radiograph were normal. Serum transaminases and ammonia levels were normal. Computed Tomography (CT) scan of the brain showed effacement of sulci suggestive of cerebral oedema. Electroencephalograph revealed polyrhythmic generalised theta wave activity. He was treated with IV Ceftriaxone, IV Acyclovir and IV Dexamethazone on the suspicion of a possible underlying meningo-encephalitis. Hyponatraemia was managed with fluid restriction and oral salt and he also received IV Thiamine. CSF analysis showed normal protein, glucose and cytology. The PCR tests in the CSF for HSV and TB were negative. The antimicrobial therapy was stopped subsequent to the CSF results, but dexamethazone continued.

Slow improvement of the level of consciousness was noted from the 2nd day since admission which was assumed to be in keeping with the correction of serum sodium level. However, the patient was found to have spastic quadriparesis and a postural tremor of upper limbs with cog-wheeling. Magnetic resonance Imaging (MRI) of the brain showed symmetrical hyperintensity on T2-weighted and FLAIR images in the caudate and putamen and, in the central pons (Figure 1). He was continued on IV Dexamethazone therapy and started on oral Levodopa + Carbidopa and Benzhexol. The pyramidal and extrapyramidal symptoms showed gradual improvement together with level of consciousness over a two week period. The steroid therapy was then tapered off and stopped at the end of 3 weeks.

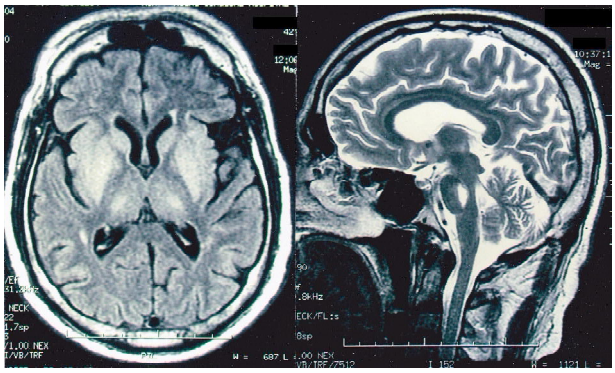

Figure 1. Axial FLAIR and sagital T_2-weighted MR images of the brain showing symmetrical hyperintense lesions in the basal ganglia, thalami and base of the pons in the acute stage.

The patient had a normal level of consciousness at 4 weeks and was mobilizing independently. There were mild extra-pyramidal symptoms and Levodopa was continued. A follow up MRI scan of the brain done at 8 weeks after admission showed resolution of the abnormalities (Figure 2).

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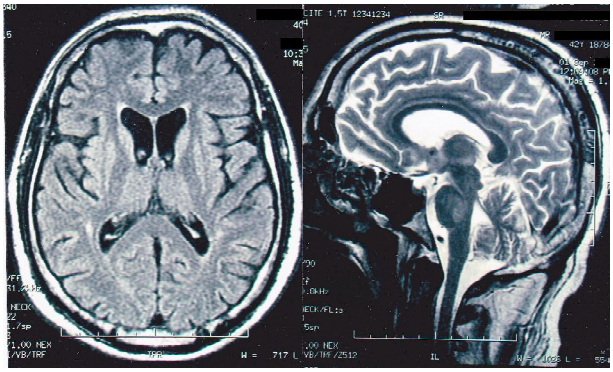

Figure 2. Follow up MRI at 8 weeks showing resolution of the abnormalities seen in Figure 1.

Discussion

The exact etiology and pathogenesis of CPM remain unclear. However, aggressive osmolar correction and in particular rapid correction of hyponatremia leading to disruption of the blood-brain barrier (BBB) caused by vascular endothelial damage is considered to play a critical role in the pathogenesis of osmotic demyelination[2]. Vasogenic oedema, release of myelinotoxic substances and damage to oligodendrocytes all contribute to the pathogenesis.

There are several publications concerning the successful use of plasmapharesis and imunoglobulin therapy in CPM suggesting a possible immune pathogenesis[3,4,5]. Bibl et al. successfully treated three young female patients with extensive therapeutic plasmapheresis soon after the diagnostic confirmation of CPM by MRI[5]. All patients had undergone correction of severe hyponatremia three to five days before the onset of neurological symptoms comprising of a rapidly evolving flaccid quadriplegia with dysphagia and dysarthria. Significant clinical improvement was obtained one month after plasmapheresis and neurological examination one year later disclosed partial recovery with total recovery in one patient. However, the pontine lesions remained unchanged in all patients even at 6 months after treatment. Grimaldi et al too report a case of CPM with clinical improvement following plasmapharesis, but persistence of MRI lesions[4].

Experience with corticosteroids in CPM is limited to the demonstration of its preventive effect on the development of the disease in animal experiments and two isolated case reports. Murase et al demonstrated severe neurological deficits with disruption of the blood brain barrier following rapid correction of induced hyponatreamia in rats, which was prevented by treatment with dexamethazone[6,7]. Hagiwara et al reported a case of CPM and extensive extra-pontine myelinolysis treated with pulsed IV methyl prednisolone resulting not only in complete recovery, but also resolution of extra-pontine MRI lesions on serial MRI[9]. Sajith et al described a patient with Addison's disease and CPM treated with hydrocortisone leading to clinical recovery and resolution of MRI lesions[10]. This patient had a similar presentation to our patient with extrapyramidal symptoms. The clinical recovery in our patient following dexamethazone therapy appear equivalent to the patients treated with steroids or plasmapharesis above. However, the unique feature following corticosteroid therapy appears to be the rapid resolution of MRI lesions in addition.

MRI appearances in the acute stage of CPM are largely due to the tissue water proton content, whereas the persistent lesions are likely due to fibrillary gliosis[11]. The resolution of MRI lesions with clinical improvement in patients treated with corticosteroids possibly indicates a potential therapeutic benefit in the acute treatment and prevention of long term severe neurological sequalae (recognized with chronic MRI lesions) in CPM.

Because of the severity of the neurological deficits, especially in the acute phase, and the possibility of a poor prognosis, treatment with corticosteroids should be further studied in CPM and extra-pontine myelinolysis. Controlled trials are needed to further assess this and other forms of immunotherapy for this condition.

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Case report

Leigh syndrome responsive to vitamin therapy

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Abstract

We report a case of Leigh syndrome in a girl aged four years and eight months who presented to us with progressive ptosis and worsening ataxia with frequent falls on a background of development delay. The clinical profile, bio-chemical analysis and MRI findings were consistent with a diagnosis of Leigh syndrome. Her clinical course was that of infantile onset, mild, slowly progressive form. She was given multivitamin supplement aiming to provide high dose thiamine and showed a remarkable response with disappearance of ptosis and marked improvement in function in the speech domain and motor skills.

Introduction

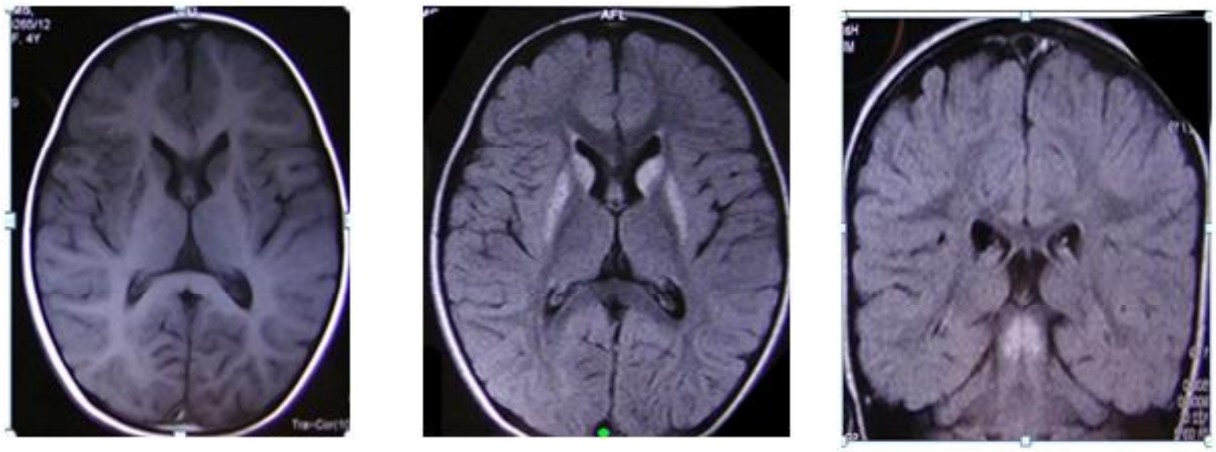
Leigh syndrome also known as sub acute necrotising encephalomyelopathy, is a rare neurodegenerative condition with a widely variable presentation. Some patients respond to vitamin supplementation. Due to the many underlying enzymatic defects giving rise to similar clinical profiles, it is difficult to clinically predict response to vitamin treatment.

Case report

The second born girl of parents who were distantly related was referred with a progressive ptosis of two months duration to the Neurology Unit at Lady Ridgeway Hospital for Children. Mother also complained of unsteadiness and frequent falls noted from around two years of age. There was also mild development delay noted mainly in gross motor and speech domains. The antenatal and perinatal period had been normal. There was no suggestive family history and her elder sister was in good health.

The clinical examination revealed a well nourished girl with bilateral partial ptosis with sparing of pupils. There was no ophthalmoplegia and the optic fundus was normal. Lower limb reflexes were symmetrically exaggerated with positive Babinski response. Gait ataxia was also seen. No other physical signs were present.

MRI showed bilateral symmetrical signal intensity changes in both heads of caudate nucleus and putamen as well as the brain stem. These were of low intensity in T1 and of high signal intensity in T2 and Flair. The mammillary bodies were spared (Figure). Laboratory evaluations showed an elevated CSF lactate (35.18 mg/dl; reference: 10-25 mg/dl).



A1 A2 B

Figure. MRI changes involving caudate and putamen symmetriclly A1) T1 hypo intensity, A2) FLAIR hyper intensity. B) brain stem: peri aqueductal FLAIR hyper intense symmetric lesion.

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An EEG done showed nonspecific changes with asynchronous and long sleep spindles. ECG as well as visual and auditory evoked potentials were normal. Urine amino acid chromatography was also normal. Investigations for Wilson disease and repetitive nerve stimulation and nerve conduction tests done previously had been negative.

The child was commenced on vitamin supplementation aiming to supply high dose of thiamine. After one month on treatment she showed a remarkable response with complete resolution of ptosis. There was also a marked improvement in the ataxia with no further falls. Mother also noted a significant gain in speech abilities.

Discussion

Leigh was the first to describe this rare disorder in a seven month old infant who had a rapid onset and a fatal outcome[1]. Subsequent work described this disorder to have a wide variability in its age of onset, clinical presentation and progression[2].

A number of enzyme defects at many different sites in the respiratory pathway are recognised to give rise to the neuropathological findings grouped together as Leigh syndrome. The related genetic defect is seen in nuclear DNA in majority though mitochondrial genes are involved in 20 to 25%. However, a genetic cause for a number of cases of Leigh syndrome continue to remain unknown[3]. The mode of inheritance of nuclear DNA defect is autosomal recessive in majority with X linked recessive pattern seen in few.

The age of disease onset is usually during the first two years of life though juvenile or adult onset may be seen occasionally. The initial findings may be non specific with slow growth, feeding difficulty, vomiting and development delay. More characteristic features such as ptosis, ophthalmoplegia, visual loss, pigmentary retinopathy, ataxia and basal ganglia syndromes would eventually appear[4]. The clinical course may be rapidly fulminant or protracted for years.

Our patient did not have clinical features of severe involvement such as dysphagia, muscle and movement problems and respiratory insufficiency. Her clinical features suggest a mild form with slow disease progression.

The biochemical evidence of elevated lactate in CSF is found in most cases as in our patient and adds weight to the diagnosis. Lactate to pyruvate quotient in blood and CSF aids refinement of the diagnosis[6]. Gold standard for diagnosis is identification of mutations in mitochondrial DNA and biochemical investigations of muscle biopsies[3,7]. These are currently not available in Sri Lanka. Combination of typical clinical features and characteristic imaging together with elevated lactate level is considered sufficient for diagnosis in the absence of specific investigations.

The MRI features found in our patient was characteristic with symmetrical caudate and putaminal lesions as well as brain stem peri aqueductal lesions. The other common sites of involvement include thalami, cerebellum and even cerebral white matter[9,10,11]. The putamen involvement is seen in almost all patients.

Thiamine is the most commonly used agent to treat this disorder. However, its effect is variable and seen only in some. Thiamine responsive patients usually have pyruvate dehydrogenase deficiency[13]. Symptomatic treatment of abnormal movements can contribute to enhance the quality of life.

Other available treatment options such as riboflavin, carnitine, biotin and ketogenic diet have been demonstrated to be useful in the presence of different enzymatic defects[14,15,16,17]. Most however progress and the commonest cause of death is respiratory insufficiency[18].

Conclusion

Leigh syndrome is a rare disorder with many aetiologies. Our patient probably had the form of disease with infantile onset and slow progression though the age at diagnosis was close to 5 years. She showed a remarkable response to thiamine suggesting pyruvate dehydrogenase deficiency. Improved availability of investigations and better awareness will help to enable early diagnosis, genetic counselling and directed treatment.

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Case report

Multi focal motor neuropathy presenting as acute quadriparesis – acute multifocal motor neuropathy (AMMN)

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Sri Lanka Journal of Neurology, 2012, **1**, 48-49

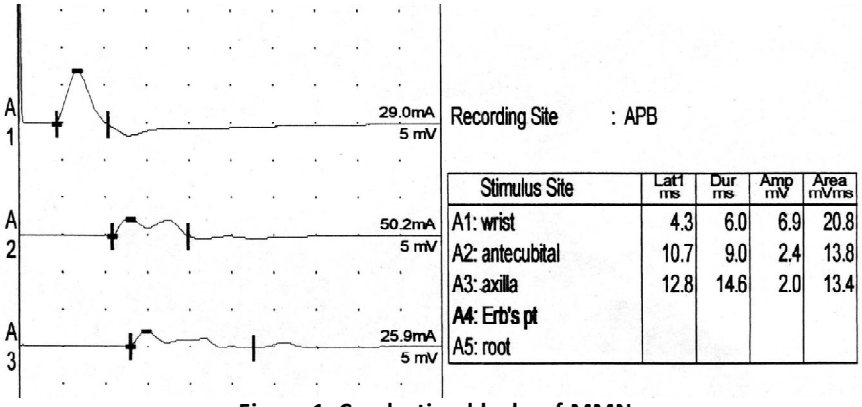
Index words: multifocal motor neuropathy, Motor neurone disease

Introduction

Multifocal motor neuropathy (MMN) is an acquired immune-mediated condition[1]. It usually progresses insidiously in a stepwise fashion with lower motor neuron type weakness, cramps, fasciculations, myokimia and later atrophy. Sensory symptoms are generally not present. Sometimes MMN is mistakenly diagnosed as motor neuron disease (MND). In most cases it is asymmetric and is strikingly multifocal and begins in one or both arms[2]. Rarely MMN can present as acute quadriparesis. Only a few cases of this rare atypical presentation are reported in world literature[3,4]. This variant known as acute-onset MMN (AMMN) should be differentiated from other immune-mediated neuropathies such as acute inflammatory demyelinating (AIDP) or axonal (AMAN) polyneuropathy, acute motor conduction block neuropathy (AMCBN), acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP). Persistent motor conduction blocks (CBs) at sites not exposed to compression or entrapment, absence of sensory symptoms, normal CSF protein and IgM reactivity against ganglioside GM1 favors AMMN over the other conditions. We report such a case of AMMN in a Sri Lankan patient and this is probably the first such report from Asia.

Case report

A 39-year old female presented with difficulty in walking of one day's duration. She was unable to stand, walk or sit within the next few days. Weakness was present in all four limbs but was more apparent in the upper limbs. Reflexes were diminished and there were no fasciculations. On direct questioning she reported some weakness in her hands over the preceding few months which progressed slowly to involve proximal upper limb muscles. Examination revealed predominantly distal bilateral asymmetric weakness in all 4 limbs. Reflexes were markedly diminished. There was no wasting or fasciculations. She did not have any sensory symptoms or signs. Rest of the examination was unremarkable. Serial EMGs done showed features of predominant motor neuropathy with persistent conduction blocks (CBs). Sensory involvement was demonstrable only in median nerve (probably a co existing CTS). CBs continued to appear in the subsequent studies making conditions such as AMAN / AIDP rather unlikely (Usually CBs disappear within weeks in these conditions). CSF analysis (done after day 10) was normal. CSF protein level was only 20 mg/dl and there was no increase in cells. This was further evidence against AIDP, AMAN or acutely presenting CIDP. Renal function tests, electrolytes, liver function tests, full blood count and inflammatory markers were normal. A diagnosis of acute onset multi focal motor neuropathy (AMMN) presenting with quadriparesis and persistent CBs was made. She was treated with a course of intravenous immunoglobulin (IVIg) for 5 days (0.4g/kg/day × 5 days) to which she responded dramatically. She was treated with a second cycle within a few weeks after which she regained normal power.



Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms
A1: wrist	4.3	6.0	6.9	20.8
A2: antecubital	10.7	9.0	2.4	13.8
A3: axilla	12.8	14.6	2.0	13.4
A4: Erb's pt				
A5: root				

Figure 1. Conduction blocks of MMN.

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Practice Points

- MMN is a rare but treatable motor neuropathy with an excellent prognosis
- Early accurate diagnosis demands a high degree of clinical suspicion
- MMN can be misdiagnosed as MND, hence important to exclude in all cases of MND
- In suspected but unconfirmed cases of MMN masquerading as MND a good response to a course of IVIG helps to differentiate the two
- Very rarely MMN can present as acute quadriparesis (AMMN) as described here
- Persistent CBs, normal CSF, asymmetrical weakness, ant GM1 antibodies helps differentiating AMMN from AIDP, AMAN, CIDP
- Magnetic resonance imaging shows gadolinium enhancement and/or hypertrophy of the brachial plexuses
- Unlike in CIDP treatment with steroids or plasma exchange can be harmful in MMN

Discussion

Multifocal motor neuropathy (MMN) usually is an indolent chronic distal multifocal disease which progresses slowly with lower motor neuron-type weakness, without sensory symptoms[1]. Diagnostic criteria include motor conduction block (CBs) at sites not exposed to compression or entrapment[2]. CBs may persist or reverse irrespective of clinical outcome. However CBs can persist for longer periods in MMN as opposed to AMAN and AIDP. It is a treatable condition with a good prognosis which is sometimes mistakenly diagnosed as Motor Neurone Disease (MND) which has a very poor prognosis. MMN is a very rare condition, affecting only about 1 per 100,000 people in the population. Men are about three times as likely to be affected as women. Most patients are between the ages of 30 and 50 years when symptoms are noted, with the average age of onset being 40 years. The diagnosis rests on identifying the typical clinical and electro-physiological features. Electro diagnostic studies reveal conduction block outside of common sites of entrapment in motor but not sensory nerves[1].

Acute-onset MMN (AMMN) as in this case should be differentiated from other immune-mediated neuropathies such as AMAN, AIDP, AMCBN and CIDP. Asymmetry, persistent CBs, normal CSF and predominate upper limb weakness is in favor of AMMN. CIDP is less likely in this case due to asymmetrical, predominantly distal weakness and normal CSF protein level. MMN show an excellent treatment response to repeated cycles of IVIg. We found only nine previously reported cases of AMMN in world literature[3,4]. We believe that ours is the first such case from Asia. The cases described so far are very similar to ours with the key features being the acute quadriparesis with areflexia, persistent CBs on EMG, normal CSF protein and an excellent response to treatment with IVIg.

In MMN cerebrospinal fluid examination may be normal, but a mild elevation of protein is not uncommon[5]. Elevated anti ganglioside antibodies, including GM1 IgM antibodies though likely to be helpful in confirming the diagnosis of MMN their absence does not exclude it[4]. Furthermore, elevated GM1 IgM can be found in patients with other neuropathies, motor neuron disease, or even normal individuals[5]. IVIg is the mainstay of treatment. Many other immunosuppressant medications have been tried in MMN. Of these, only cyclophosphamide has been shown to be of any significant, reproducible benefit. MMN does not usually respond to steroids or plasma exchange, and these treatments may worsen it[6,7,8].

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Case report

Rapidly progressive multifocal motor neuropathy with a dramatic response to therapy

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Sri Lanka Journal of Neurology, 2012, **1**, 50-53

Abstract

We report a young female with multifocal motor neuropathy (MMN) who had unusually rapid progression involving both distal and proximal weakness, which responded dramatically to treatment, without any relapses up to now.

Introduction

Multifocal motor neuropathy with conduction blocks is an acquired immune-mediated demyelinating neuropathy with slowly progressive weakness, fasciculations, and cramping, without significant sensory involvement. MMN is generally a slowly progressive illness with predominant distal paresis.

Clinically, it may resemble chronic inflammatory demyelinating polyneuropathy (CIDP) and in advanced cases, motor neuron disease (MND) with predominant lower motor neuron involvement.

The course and the management of MMN are different from those of CIDP and MND. Therefore, early and correct diagnosis is important to prevent disability.

A typical case of MMN was first documented in Sri Lanka in 1998[1].

Case report

A 25-year old female, diagnosed to have diabetes mellitus eight months back was admitted to Teaching Hospital Karapitiya, with progressive weakness and paresthesia of hands for six months. At the onset, she had weakness in fingers of the left hand followed by weakness and numbness in both hands over five months. Her day-to-day activities were severely compromised due to the illness. There was no proximal muscle weakness in the upper limbs, muscle cramps, or muscle twitching.

Two months after the onset of the disease, she had noticed difficulty in getting up from squatting position and climbing stairs, with more marked weakness on left lower limb. There was no history suggestive of cranial nerves or bulbar involvement. She denied any history of preceding febrile illness, diarrhoea, or exposure to toxic substances including heavy metals. She had no family history of similar disease.

On examination, she was not pale and had an average built. Cranial nerves and optic fundi were normal. Examination of the upper limbs revealed bilateral wrist drop (Figure 1) with no evidence of muscle wasting or fasciculations. There was reduced muscle power in all the small muscles of the hands. She had muscle power of grade 2 on the left hand and grade 3 on the right. Proximal muscle power of the upper limbs was normal. Deep tendon reflexes in upper limbs were diminished with no objective sensory loss.

Figure 1. Bilateral wrist drop.

In the lower limbs, proximal muscle power was grade 2 on the left side and grade 3 on the right. Power of the distal muscles of the lower limbs was normal. She had diminished deep tendon reflexes in lower limbs with flexor plantar response and normal sensation. The rest of the neurological examination was normal. Cardiovascular, respiratory, and abdominal examination were unremarkable.

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Table 1. Nerve conduction study

Motor nerve conduction study

Site	*Latency (ms)*	*Amplitude*	*Area*	*Segment*	*Distance (ms)*	*Interval (ms)*	*NCV (m/s)*	*NCV N.D.*
Median, R								
Wrist	3.96ms	6.00mV	15.11mVms	Wrist		3.96ms		
Elbow	10.05ms	342.00uV	956.40uVms	Wrist – Elbow	190mm	6.09ms	31.2m/s	
Ulnar, R								
Wrist	2.76ms	8.74mV	18.88mVms	Wrist – Midforearm		2.76ms		
Elbow	5.58ms	3.29mV	7.55mVms	Midforearm – below elbow	90mm	2.82ms	31.9m/s	
Axilla	8.7ms	1.80mV	5.42mVms	Below elbow – Above elbow	115mm	3.12ms	36.9m/s	
Site 4	9.72ms	1.70mV	5.43Vms	Axilla	60mm	1.02ms	58.8m/s	

F–wave study

Nerve	*Stim.site*	*F-Lat*	*F-Lat. N.D.*	*M.Lat.*	*F-M Lat*	*F-occur.*	*Distance*	*FWCV*	*N.D.*
Median R	Wrist					0/16.0%			
Ulnar R	Wrist	2.75ms				0/16.0%			

Sensory nerve conduction study

Site	*Latency*	*Amplitude*	*Area*	*Segment*	*Distance (mm)*	*Interval (ms)*	*NCV (m/s)*	*NCV N.D*
Ulnar, R								
Wrist	3.16ms	18.40uV	0.00uVms	Wrist	125mm	3.16ms	39.6m/s	
Median, L								
Wrist	2.76ms	25.20uV	0.00uVms	Wrist	135mm	2.76ms	48.9m/s	
Median, R								
Wrist	0ms							

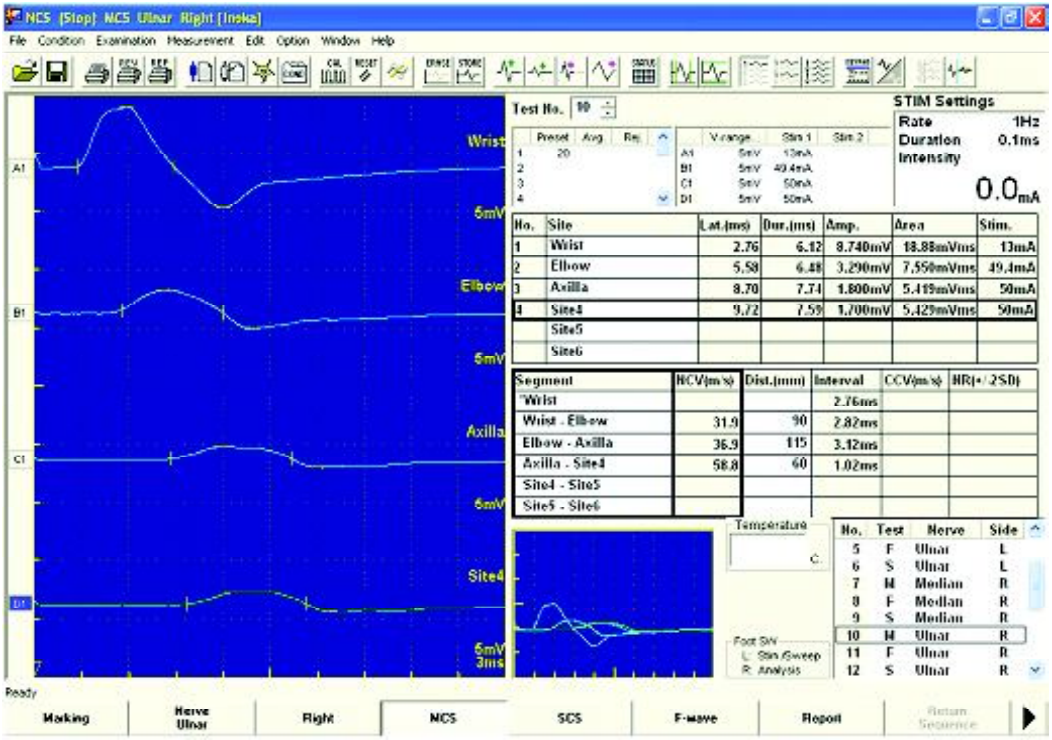

Figure 2. Ulnar motor studies.

Nerve conduction study showed evidence of segmental demyelination at multiple sites with delayed distal motor latencies, reduced motor nerve conduction velocities and multiple motor conduction blocks, i.e. the amplitude of the compound muscle action potential is significantly lower on stimulation of the proximal segments than that from the distal segment (Figure 2 and Table 1). Conduction blocks were noted at the sites other than the entrapment sites. F waves were absent. Sensory nerve conduction studies were normal.

Cerebrospinal fluid analysis was normal. Her FBS was 79mg/dl and HbA1c was 6.2%. Rest of the biochemical and haematological tests were normal. The diagnosis of MMN was made on clinical and neurophysiological grounds. She was given high doses (2g/kg) of intravenous immunoglobulin for three days and physiotherapy was continued. She made a rapid recovery with almost normal functional state within two weeks. Repeat nerve conduction study revealed improved conduction blocks.

Discussion

MMN is a rare disease with an estimated prevalence of 1-2/100,000 individuals[3]. It is more frequent in men than women with an approximate ratio of 3:1[2]. The mean age at disease onset is 40 years. Clinically MMN is characterized by slowly progressive or stepwise progressive, asymmetrical, and more distal paresis. The upper limbs are usually affected earlier and more severe than the lower limbs[2,3,5]. The most common initial symptom is wrist drop or finger drop and impaired grip strength. Cranial nerve involvement is uncommon. Most patients develop a slowly progressive disease course over several years. Beside, relapsing forms of MMN showing acute deterioration, stepwise progression, as well as spontaneous remission have occasionally been described[3,5]. After extensive literature search, we were unable to find a case of MMN with fairly rapid disease progression over few months leading to severe disability. The most prominent electrophysiological feature in MMN is multifocal persistent partial conduction blocks, i.e. the failure of a nerve impulse to propagate through a structurally intact axon present in motor but not sensory nerve fibers and located outside the common entrapment sites[3]. Approximately 40-50% of patients have IgM serum antibodies directed against GM1 ganglioside[3].

By contrast, with CIDP, treatment with plasma exchange and prednisolone is generally not effective in MMN and even associated with worsening of the disability in some patients[2,5]. Many clinical trials have shown that treatment with high dose intravenous immunoglobulin leads to improvement of muscle power in patients with MMN[3]. It is important to recognize this condition early considering the differences in the management and outcome from other demyelinating neuropathies.

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Case report

Two patients with neuromyelitis optica but contrasting clinical courses

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Sri Lanka Journal of Neurology, 2012, **1**, 54-56

Abstract

Neuromyelitis optica (NMO) is an idiopathic, relapsing, demyelinating disease of the central nervous system that preferentially affects the optic nerve and spinal cord. Diagnostic criteria for definite NMO require optic neuritis, myelitis, and at least two of three supportive criteria: onset brain MRI non-diagnostic of MS; spinal cord lesion extending over 3 or more vertebral segments; or seropositive for NMO-IgG. We report two Sri Lankan patients who fulfil the above diagnostic criteria but have contrasting clinical courses over a 4-year follow-up period. The NMO-IgG seropositive patient demonstrated a more severe, relapsing disease course whilst the seronegative patient did not relapse despite not being on long-term immunosuppressive therapy. Given that para-infectious NMO is often monophasic and seronegative, discerning guidelines in recommending maintenance immunosuppression in NMO is required particularly in settings where incriminatory infections are prevalent.

Index words: neuromyelitis optica (NMO), multiple sclerosis (MS), optic neuritis (ON), transverse myelitis, NMO-IgG

Introduction

Neuromyelitis optica (NMO), also known as Devic disease, is an idiopathic, severe, relapsing, demyelinating disease of the central nervous system that preferentially affects the optic nerve and spinal cord leading to cumulative disability. Although previously thought to be a variant of multiple sclerosis (MS), the recent discovery of antibodies to the aquaporin-4 channel (NMO-IgG) in the serum has led to the redefining of NMO as a distinct clinical and pathological entity[1]. Accordingly, the revised diagnostic criteria for definite NMO require optic neuritis, myelitis, and at least two of three supportive criteria: onset brain MRI non-diagnostic of MS; spinal cord lesion extending over 3 or more vertebral segments; or seropositive for NMO-IgG[2].

We describe two patients with NMO with contrasting clinical courses and discuss the need for discerning guidelines in prescribing maintenance immunosuppressive therapy.

Patient A

A 35-year old housewife presented in January 2008 with paraparesis. She has had two episodes of optic neuritis, first in the right eye in 2005 that completely recovered following treatment with intravenous methylprednisolone and the second in the left eye in 2006 that did not recover. She had not sought treatment for the second episode since she had been pregnant at that time. Apart for hypothyroidism for which she was on replacement therapy, her past medical history was unremarkable.

On examination, she had bilateral optic disc pallor L > R. Visual acuity was 6/18 on the right whilst she could only perceive finger movements with the left eye. Other cranial nerves and upper limbs were normal. She had spastic paraparesis (power 4/5) with a sensory level of D5 and bladder incontinence.

MRI of the brain was normal but the MRI of the cord showed a contrast-enhancing inflammatory lesion extending > 3 vertebral segments in the thoracic cord (Figure 1). CSF showed a mild lymphocytic pleocytosis with 18 lymphocytes and 42 mg/dl of protein. Routine haematological and biochemical investigations including inflammatory markers were normal whilst the vasculitic and viral screens were negative. Aquaporin-4 antibodies were detected in serum.

A diagnosis of NMO was made. She was treated with intravenous methyl prednisolone pulses followed by a combination of oral prednisolone and azathioprine. Her symptoms gradually improved apart for residual spastic weakness in her lower limbs. She subsequently defaulted treatment and relapsed in February 2009 with a longitudinally extensive transverse myelitis around D8 that improved with intravenous steroid pulses. She has since been on oral prednisolone and azathioprine and has not had any relapses as of May 2012.

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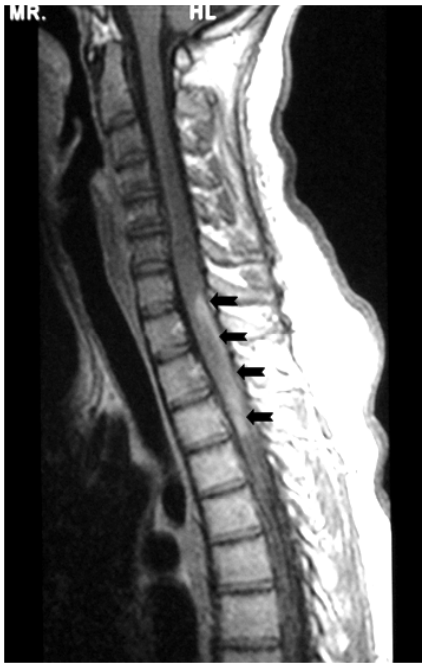

Figure 1. Satgital T1-weighted MR image of the spine shows a longitudinally-extensive, expansile lesion in the upper thoracic cord with enhancement following intravenous gadolinium administration (arrows).

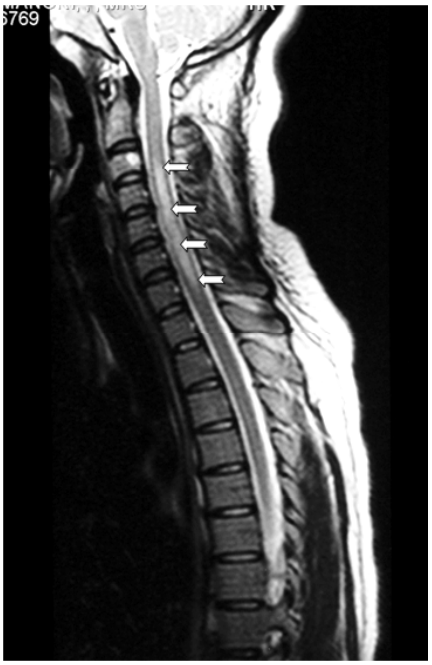

Figure 2. Satgital T2-weighted MR image of the spine shows a longitudinally-extensive, centrally located lesion in the cervical cord (arrows).

Patient B

A 28-year old housewife presented in January 2008 with paraparesis. Five weeks earlier, she has had retrobulbar neuritis in the right eye that completely resolved within 3 weeks following treatment with intravenous methylprednisolone. Her past medical history was unremarkable.

Examination revealed right-sided optic disc pallor. Visual acuity was 6/18 on right and 6/6 on left. She had spastic paraparesis (power 4/5) with a sensory level at D2 and sphincter involvement. Rest of the neurological examination was normal.

MRI of the brain was normal but the MRI of the cord showed a contrast-enhancing inflammatory lesion extending > 3 vertebral segments in the cervical cord (Figure 2). Visual evoked potential showed a delay in P100 in the right eye. CSF showed 5 PNL, 54 lymphocytes and 53 mg/dl of protein. Routine haematological and biochemical investigations including inflammatory markers were normal whilst the vasculitic and viral screens were negative. Aquaporin-4 antibodies were not detectable in her serum.

She was treated with intravenous methylprednisolone pulses followed by a two-week taper of oral prednisolone. She was not prescribed long term immunosuppressive therapy. She made a complete recovery and has not had any recurrences up to May 2012.

Discussion

Eighty- to ninety-percent of patients with NMO have relapsing episodes of optic neuritis (ON) and myelitis, rather than a monophasic course[3]. Frequent and severe relapses lead to incremental disability with more than 50% of patients becoming blind in one or both eyes or dependent for ambulation within 5 years of disease onset[3]. This is in contrast to MS in which relapses recover almost completely and patients accrue disability only during the later, secondary progressive phase of MS. Furthermore, NMO do not benefit with immunomodulatory therapies effective for MS (eg, interferon beta, glatiramer acetate)[4], but long-term immunosuppression has shown to reduce relapses. Hence, establishing a diagnosis of NMO has both therapeutic and prognostic implications.

According to the revised criteria, the presence of NMO-IgG is not essential for the diagnosis of NMO. Both patients in this report fulfill the criteria for diagnosis although NMO-IgG was negative in patient B. Interestingly, in the four-year follow-up period, patient B did not have any relapses despite not being on long-term immunosuppressive therapy whilst patient A followed the typical course described for NMO. Patients with nearly simultaneous ON and myelitis as in patient B are less likely to relapse than patients who have index events that are several months apart[5]. Nonetheless, it must be noted that ON and or longitudinally-extensive myelitis can occur secondary to infections such as varicella, EBV,

CMV, dengue, mycoplasma, *Treponema pallidum* and tuberculosis[6]. These 'para-infectious NMO syndromes' are often monophasic and negative for aquaporin-4 antibodies[6].

Observational studies suggest that maintenance immunosuppression is associated with reduced relapses and better clinical outcomes. Given that para-infectious, monophasic-NMO syndromes are likely to be common in regions where infections are prevalent, whether all patients diagnosed with NMO should be prescribed long-term immunosuppression at first presentation needs consideration. Patient B did not experience any relapses. However, relapses in NMO can happen decades after the index case[5] and a benign form of NMO cannot be clearly defined. Seropositivity of NMO-IgG is a useful marker to predict a higher risk of relapse[5,7] and to commence maintenance immunosuppression, but there are reports of relapsing seronegative-NMO. Currently maintenance immunosuppression is recommended when a diagnosis of NMO is established. Further studies on clinical, neuroimaging and serological predictors of outcome and randomized trials of long-term immunosuppression are required to develop discerning guidelines for long-term immunosuppression in NMO. Patient B understandably refuses long-term immunosuppression unless a relapse occurs given her good health since the presenting episode.

Acknowledgement

Professor Angela Vincent, Neurosciences Group, University of Oxford, United Kingdom for kindly performing the NMO-IgG assays.

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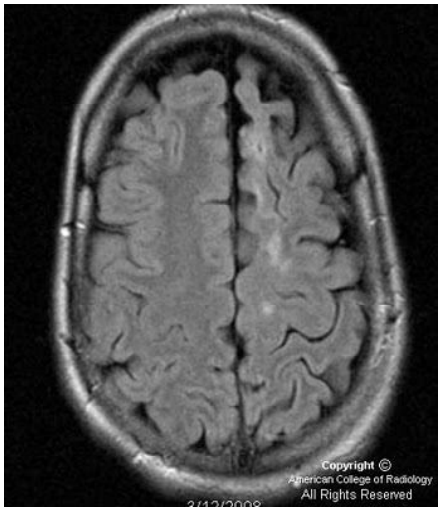
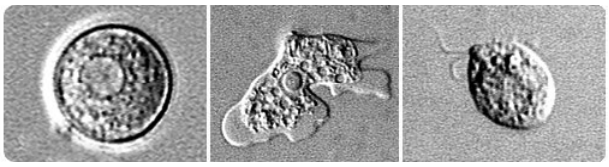
Epilepsy

Sri Lanka Journal of Neurology, 2012, **1**, 57

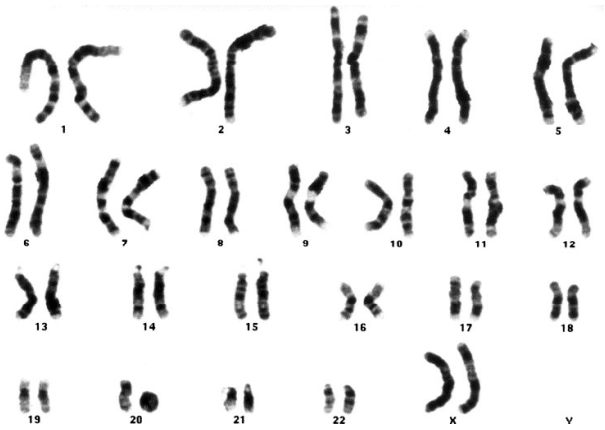
1. This 5-year old girl has epilepsy and learning disability. What is the diagnosis?



3. This 12-year old boy has intractable epilepsy and a hemiparesis. What is the diagnosis?



2. This organism is a cause of seizures and encephalitis and death seen in Pakistan and India. What is the organism?



4. This chromosome study is from a child who has epilepsy and minor learning disability. What is the diagnosis?

(Answers on page 61)

Guidelines to authors

Sri Lanka Journal of Neurology, 2012, **1**, 58-60

The *Sri Lanka Journal of Neurology* is published half yearly (June and December) by the Association of Sri Lankan Neurologists. Material received for publication in the *SLJN* must not be submitted for publication elsewhere without the editors' permission (see below under Previous Publication and under Cover Letter).

Contents

The *SLJN* publishes original papers and commentaries which have relevance to Neurology and allied sciences.

Papers

Original work concerning the causes, mechanisms, diagnosis, management and prevention of disease belong in this category. So do articles on health systems research, health economics and management, and medical ethics. They should have less than 2000 words, 5 tables and illustrations, and 20 references.

Case reports/Brief reports

This category includes case reports of drug adverse effects, of a single event that could lead to a new piece of knowledge, preliminary reports of drug trials, new patient management methods, and reports of new techniques and devices. They should not exceed 1000 words, and contain more than 3 tables or illustrations, and more than 10 references.

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Leading articles are solicited by the editors, and are expert opinions on current topics or commentaries on other papers published in the *SLJN*. They do not usually exceed 1500 words or have more than 20 references. Tables and illustrations are usually not included in leading articles.

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The *SLJN* also welcomes essays expressing opinions, presenting hypotheses, broaching controversial issues, clarifying recent advances in the basic sciences, and essays pertaining to medical education, history of medicine, biographical sketches, health politics and patients' rights in relation to neurosciences. They should not have more than 2000 words, 5 tables and illustrations, or 20 references.

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The *SLJN* will also consider for publication letters (less than 400 words of text, 3 authors, and 5 references), obituaries (less than 400 words), and contributions to the picture-story series (not more than 250 words of text, 3 authors, 3 references and 2 clear black and white or colour photographs).

Submitting Manuscripts

Cover letter

Manuscripts should be submitted with a letter stating (1) that the contents have not been published elsewhere; (2) that the paper is not being submitted elsewhere (or provide information on previous publication); and (3) that the authors agree to transfer copyright to the *SLJN* if the article is selected for publication. The letter should acknowledge any potential conflict of interest (see Ethical Responsibilities below) and call the editors' attention to any possible overlap with prior publications. The name, full mailing address, and telephone number of the author responsible for correspondence about the paper should also be included. E-mail addresses are mandatory.

Submit an original copy and 3 copies (photocopies are acceptable) of all parts of the manuscript, 3 original glossy prints of all figures. All submissions must be accom-panied by an electronic copy of the manuscript and illustrations emailed to the editor.

The manuscript should be mailed, with adequate protection for figures, to Prof Saman Gunatilake, the Editor, *SLJN*, Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda. SRI LANKA. Email: saman.gunatilake@hotmail.com

Ethical responsibilities

Criteria for authorship

Only persons who contributed to the intellectual content of the paper should be listed as authors. Authors should meet all of the following criteria, and be able to take public responsibility for the content of the paper.

1. Conceived and planned the work that led to the paper, or interpreted the evidence it presents, or both.
2. Wrote the paper or reviewed successive versions, and took part in revising them.
3. Approved the final version.
4. Each author should have contributed sufficiently to the work to take public responsibility for the content.

Collecting and assembling data reported in a paper and performing routine investigations are not, by themselves, criteria for authorship.

Conflict of interest

Financial support for the work, including equipment and drugs, should be listed on the title page. Authors should describe in the cover letter any financial interests, direct or indirect, that might affect the conduct or reporting of the work they have submitted. Information about potential conflict of interest may be made available to referees and will be published with the manuscript, at the discretion of the editors.

Previous publication

In the cover letter give full details on any possible previous publication of any content of the paper. eg.

1. Reworked data already reported.

2. Patients in a study already described and published.
3. Content already published or to be published in another format.

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The authors must ensure that informed consent forms have been obtained. Authors should state in the methods section, when appropriate, the ethical guidelines followed. If patients are recognisable in illustrations, signed consent by the patients (or guardians) must be submitted with the paper.

Selection for publication

All articles received will be acknowledged to the corresponding author. Each manuscript will be read by the members of the editorial board to decide whether it should be further reviewed. Those selected for review may be sent anonymously to referees.

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Referees are asked to treat papers as confidential communications and not to share their content with anyone except colleagues they have asked to assist them in reviewing, or not to use content for their own purposes. They are asked to declare any conflict of interest (such as personal ties to authors), and not to copy manuscripts.

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All articles are submitted anonymously to the Editorial Board which meets regularly. Members of the board assess articles on the basis of importance of the research problem, scientific strength, clarity of presentation and appropriateness for readers of the *SLJN*.

Editors reserve the right to modify style, shorten articles, make editorial corrections where necessary, and to determine priority and time of publication.

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The *SLJN* will consider all manuscripts prepared in accordance with the uniform requirements for manuscripts submitted to biomedical journals developed by the International Committee of Medical Journal Editors [1]. A summary of these and the requirements of the *SLJN* are given below.

Manuscript typing

All parts of manuscript, including tables and figure legends, must be typed with double-spacing. References must also be double spaced. Manuscripts should be typed in capital and lower case letters, on white paper, 216 × 279 mm (8 × 11 in), or A4 (212 × 297 mm). Arrange components in the following order: title page, abstract, text, references, tables in numerical sequence, and figure legends. Begin each component on a separate page. Number all pages consecutively, starting with the title page.

Title page

The title page should contain the following:

1. Main title, subtitle (if any) and a maximum of 5 index words (or phrases).
2. Authors listed in the form and order in which they are to appear in the published article.
3. Institutional affiliation for each author, in a footnote on the title page of the article. The institutions listed should reflect the affiliations of the authors at the time of the study, not their present affiliations, if they differ.
4. Financial support information. Include the grant number, if any, and the granting agency. Other financial support, such as that for equipment and drugs, should also be listed.
5. Name, address, e-mail and telephone number of author responsible for correspondence.
6. The number of words in the manuscript, exclusive of the abstract, references, tables, figures, and figure legends.

Abstract

Abstracts for articles are limited to 250 words; those for Brief Reports, to 150 words. Authors of original research articles are asked to submit a structured abstract organised into the following categories (where relevant):

Objective(s)

Design setting

Patients Intervention (if any)

Measurements

Results

Interpretation

Authors are asked to see papers in any recent issue of the *British Medical Journal or Annals of Internal Medicine* for guidance on structuring the abstract.

Headings in text

Use only three levels of headings in the text. Clearly indicate the levels of headings by using different typographic conventions (such as all capital letters or bold type) or by positioning (flush to margin, indented). Keep headings short (three or four words).

Style

The *British Medical Journal, Lancet* and *Annals of Internal Medicine* are recommended to authors as guides to style, clarity of presentation and conciseness.

Units

Use SI units throughout [2], except for systemic arterial blood pressure and haemoglobin content. Other units may be given in parentheses. Use only arabic numbers.

Name of drugs and instruments

Generic names must be used for all drugs. Include the proprietary name only if it is needed for a specific purpose. Instruments may be referred to by proprietary

name, giving the name and location of the manufacturer in the text in parentheses.

References

Number references in the order in which they are first cited in the text. Use superscripted arabic numerals in the text.. Note that the *SLJN* requires the COMPLETE name of journal (and not its abbreviation), year, volume and first and last page numbers.

The reference list should not include unpublished material. Symposium papers may be cited from published proceedings; oral presentation of a paper at a meeting does not constitute publication. References to articles or books accepted for publication but not yet published must include the title of the journal (or name of the publisher) and the year of expected publication. Unpublished work (personal communication, papers in preparation) may be cited by inserting a reference within parentheses in the text; authors must submit a letter of permission from the cited persons to cite such communications.

Sample references below are in the style required by the *SLJN*.

Journals: List all authors when 4 or fewer; when 5 or more, list only the first 3 and add et al.

1. Standard article.

   Bernstein H, Gold H. Sodium diphenylhydantoin in the treatment of recurrent arrhythmias. *Journal of the American Medical Association* 1965; **19**1: 695-9.

2. Corporate author.

   The Royal Marsden Hospital Bone Marrow Transplantation Team. Failure of syngeneic bone marrow graft without preconditioning in posthepatitis marrow aplasia. *Lancet* 1977; **2**: 242-4.

3. Special format.

   Cahal DA. Methyldopa and haemolytic anaemia (Letter). *Lancet* 1975; **1**: 201.

Books: List all authors or editors when 4 or fewer; when 5 or more, list only the first 3 and add et al.

1. Author.

   Eisen HN. Immunology: *An introduction to molecular and Cellular Principles of the Immune Response*. 5th ed. New York: Harper and Row,1974.

2. Editors.

   Dausset J. Colombani J, eds. *Histocompatibility Testing* 1972. Copenhagen: Munksgaard, 1973.

3. Chapter in a book.

   Hellstrom I, Helstrom KE. Lymphocyte-mediated cytotoxic reactions and blocking serum factors in tumor-bearing individuals. In: Brent L, Holbrow J, eds. *Progress in immunology* II. v. 5. New York: American Elsevier, 1974: 147-57.

Other citations in Reference List:

1. In press (must have journal title).

   Dienstage JL. Experimental infection in chimpanzees with hepatitis A virus. *Journal of Infectious Diseases* 1975. In press.

2. Magazine article.

   Roueche B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971. Sep 4: 66-81.

In-text citations of unpublished material (to be placed within parentheses):

1. Personal communication.
   (Strott CA, Nugent CA. Personal communication).

2. Unpublished papers.

   (Lerner RA, Dixon FJ. The induction of acute glomerulonephritis in rats. In preparation). (Smith J. New agents for cancer chemotherapy. Presented at the Third Annual Meeting of the American Cancer Society, June 13, 1983, New York).

Tables

All tables must be typed double-spaced. Tables should be numbered with arabic numerals, in the order in which they are cited in the text. A table title should describe concisely the content of the table.

Figures

Figures should be professionally drawn or prepared using a computer and high-resolution printer. Lettering should be uniform in style. Free hand or typewritten lettering is not acceptable. Number the figures in the order in which they are cited in the text. Photomicrographs should have scale markers that indicate the degree of magnification. Submit three glossy prints of each figure. Indicate on a label the name of the first author of the paper, the figure number, and the top of the figure: then paste the label on the back of the figure. Do not mount figures on backing board.

Colour figures may be submitted and will be published if essential.

Legends for figures

Reduce the length of legends by using partial sentences. Explain all abbreviations and symbols on the figure, even if they are explained in the text. Stain and magnification should be given at the end of the legend for each part of the figure. If there is no scale marker on the figure, the original magnification used during the observation should be given, not that of the photographic print.

Acknowledgements

Acknowledge only persons who have contributed to the scientific content and provided financial or technical support. Authors must submit written permission from persons acknowledged for other than financial or technical support.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *New England Journal of Medicine* 1991; **324**: 424–8.
2. Young D. Implementation of SI units for clinical laboratory data: style specifications and conversion tables. *Annals of Internal Medicine* 1987; **106**: 114–29.

Answers to picture quiz

Sri Lanka Journal of Neurology, 2012, **1**, 61

1. **Rett syndrome** is a neurodevelopmental disorder of the grey matter of the brain that almost exclusively affects females but has also been found in male patients. The clinical features include small hands and feet and a deceleration of the rate of head growth (including microcephaly in some). Repetitive stereotyped hand movements, such as wringing and/or repeatedly putting hands into the mouth, are also noted. People with Rett syndrome are prone to gastrointestinal disorders and up to 80% have seizures. They typically have no verbal skills, and about 50% of individuals affected are not ambulatory. Scoliosis, growth failure, and constipation are very common and can be problematic.

   Genetically, Rett syndrome (RTT) is caused by mutations in the gene MECP2 located on the X chromosome, and can arise sporadically or from germline mutations. In less than 10% of RTT cases, mutations in the genes CDKL5 or FOXG1 have also been found to resemble it. Rett syndrome was initially diagnosed by clinical observation, but the diagnosis is definitive when there is a genetic defect in the MECP2 gene. In some very rare cases, no known mutated gene can be found suggesting changes in MECP2 that are not identified by presently used techniques or mutations in other genes that may result in clinical similarities.

2. ***Naegleria fowleri*** is a free-living excavate form of protozoa typically found in warm bodies of fresh water, such as ponds, lakes, rivers, and hot springs. It is also found in soil, near warm-water discharges of industrial plants, and unchlorinated or poorly chlorinated swimming pools in an amoeboid or temporary flagellate stage. There is no evidence of this organism living in ocean (salt) water. Rarely, it can appear in inadequately treated samples of home-based tap water that is not treated enough to be entirely potable, though this is not the usual method of contracting the illness unless the water is very deeply inhaled, usually deliberately.

   N. fowleri can invade and attack the human nervous system. Although this occurs rarely, such an infection nearly always results in the death of the victim. The case fatality rate is estimated at 98%. From July to October 2012, 22 people died in the southern part of Pakistan within a week from Naegleria infection. At least 13 cases has been reported in Karachi, Pakistan, who had no history of aquatic activities. Infection likely occurred through ablution with tap water. It may be attributed to rising temperatures, reduced levels of chlorine in potable water, or deteriorating water distribution systems.

   In humans, *N. fowleri* can invade the central nervous system via the nose (specifically through the olfactory mucosa and cribriform plate of the nasal tissues). The penetration initially results in significant necrosis of and haemorrhaging in the olfactory bulbs. From there, the amoeba climbs along nerve fibers through the floor of the cranium via the cribriform plate and into the brain. The organism begins to consume cells of the brain piecemeal by means of a unique sucking apparatus extended from its cell surface. It then becomes pathogenic, causing primary amoebic meningoencephalitis (PAM or PAME). PAM is a syndrome affecting the central nervous system. PAM usually occurs in healthy children or young adults with no prior history of immune compromise who have recently been exposed to bodies of fresh water. Amphotericin B is effective against *N. fowleri in vitro*, but the prognosis remains bleak for those who contract PAM, and survival remains less than 1%.

3. **Rasmussen's encephalitis,** also known as chronic focal encephalitis (CFE), is a rare inflammatory neurological disorder, characterized by frequent and severe seizures, loss of motor skills and speech, hemiparesis (paralysis on one side of the body), encephalitis (inflammation of the brain), and dementia. The disorder, which affects a single cerebral hemisphere, generally occurs in children under the age of 15.

   The cause of the inflammation is not known: infection by a virus has been suggested, but the evidence for this is inconclusive. In the 1990s it was suggested that auto-antibodies against the glutamate receptor GluR3 were important in causing the disease, but this is no longer thought to be the case. However, more recent studies report **the presence of autoantibodies against the NMDA-type glutamate receptor subunit GluRepsilon2 (anti-NR2A antibodies)** in a subset of patients with Rasmussen's encephalitis.

   The condition mostly affects children, with an average age of 6 years. However, one in ten people with the condition develops it in adulthood. There are two main stages, sometimes preceded by a 'prodromal stage' of a few months. In the acute stage, lasting four to eight months, the inflammation is active and the symptoms become progressively worse. These include weakness of one side of the body (hemiparesis), loss of vision for one side of the visual field (hemianopia), and cognitive difficulties (affecting learning, memory or language, for example). Epileptic seizures are also a major part of the illness, although these are often partial. Focal motor seizures or epilepsia partialis continua are particularly common, and may be very difficult to control with drugs. In the chronic or *residual stage*, the inflammation is no longer active, but the sufferer is left with some or all of the symptoms because of the damage that the inflammation has caused. In the long term, most patients are left with some epilepsy, paralysis and cognitive problems, but the severity varies considerably.

4. **Ring chromosome 20, ring-shaped chromosome 20** or **r(20) syndrome** is a rare human chromosome abnormality where the two arms of chromosome 20 fuse to form a ring chromosome. The syndrome is associated with epileptic seizures, behaviour disorders and mental retardation. When only one copy of chromosome 20 forms a ring, the individual suffers from ring 20 chromosomal mosaicism.

   Ring chromosome 20 syndrome is thought to be an underdiagnosed condition. Since chromosomal analysis or karyotype testing is not a routine investigation for patients with epilepsy, the diagnosis of ring chromosome 20 syndrome is typically delayed or unrecognized. Individuals from the ages of 0-17 years should be considered for ring 20 chromosome analysis if they have: predominantly complex partial seizures, medically refractory crytogenic epilepsy, Lennox-Gastaut-like features with no cause identified, frequent subtle nocturnal seizures, an EEG showing prolonged high voltage frontally dominant slowing intermixed with spikes or sharp waves, an EEG showing overlapping features of continuous slow spike and wave discharges in sleep (CSWS) and electrical status epilepticus in sleep (ESES), and/ or subsequent cognitive impairment/learning difficulties/mild retardation. These patients will typically have a normal childhood development until onset of epilepsy and lack evidence of dysmorphism or other congenital malformations.