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

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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.

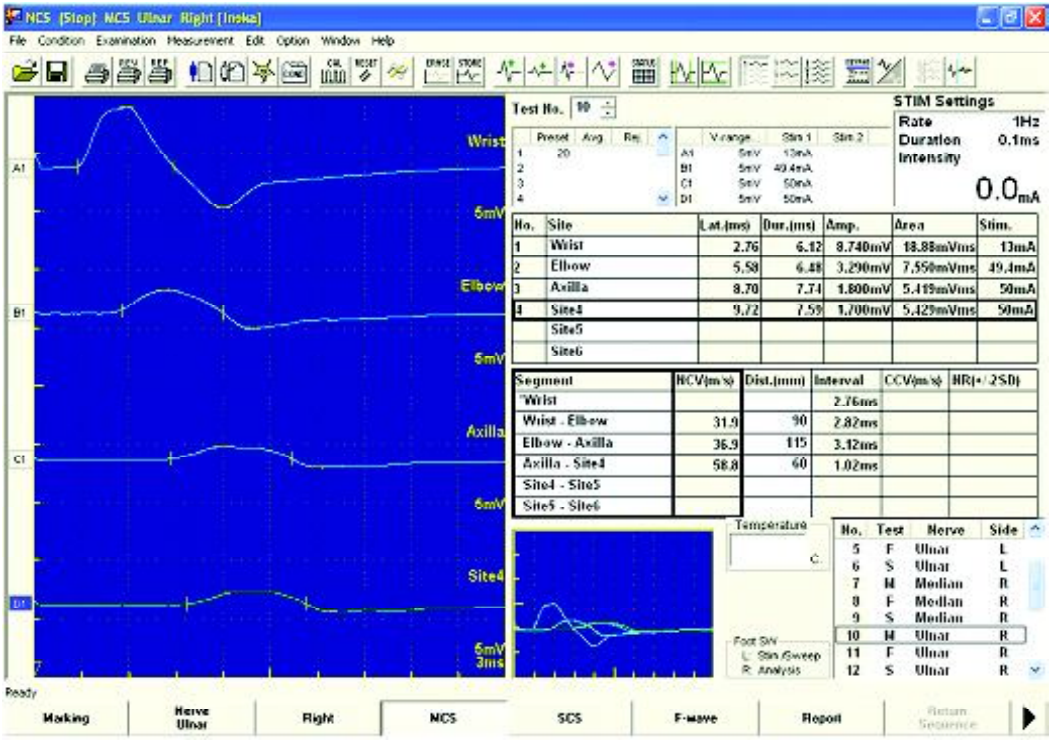

Figure 2. Ulnar motor studies.

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.

References

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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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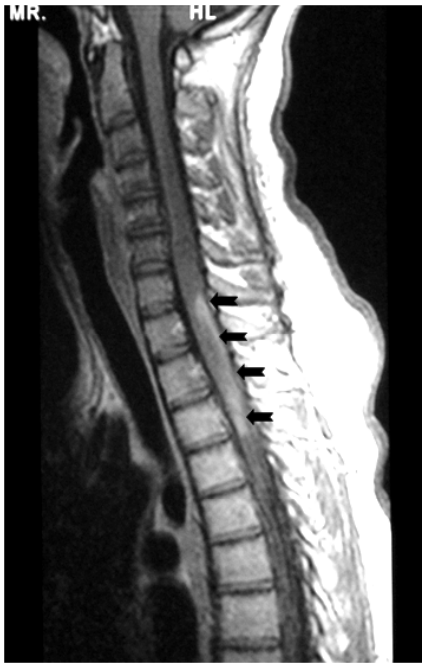

Figure 1. Satgital T1-weighted MR image of the spine shows a longitudinally-extensive, expansile lesion in the upper thoracic cord with enhancement following intravenous gadolinium administration (arrows).

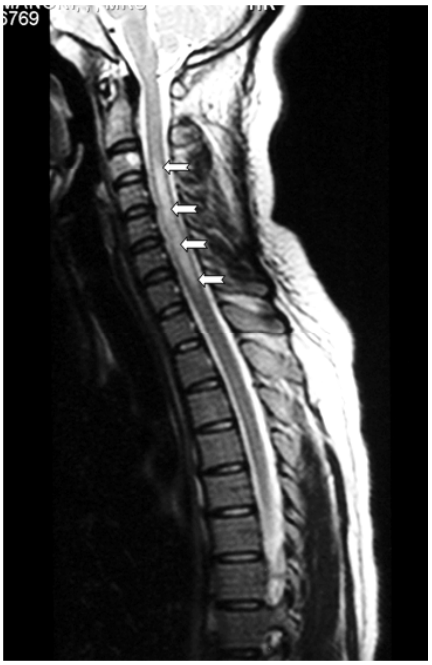

Figure 2. Satgital T2-weighted MR image of the spine shows a longitudinally-extensive, centrally located lesion in the cervical cord (arrows).

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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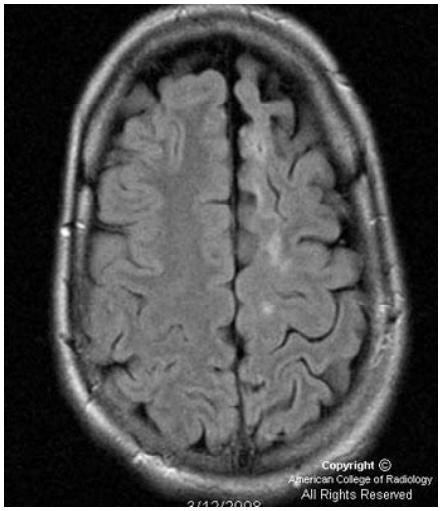
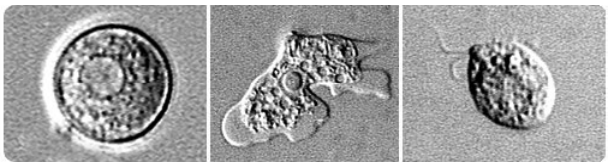
Epilepsy

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

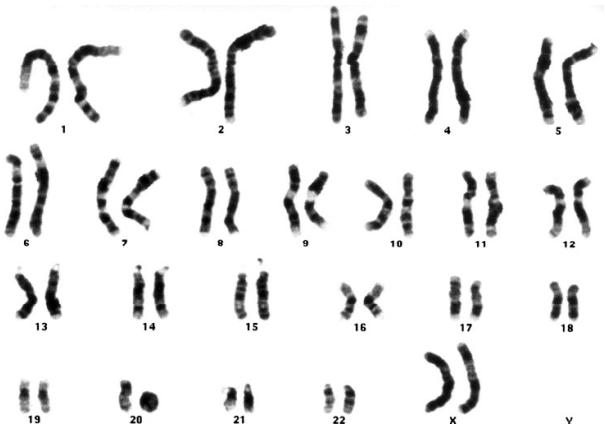
1. This 5-year old girl has epilepsy and learning disability. What is the diagnosis?



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).

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

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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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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.

Miscellany

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).

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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

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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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Informed consent

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.

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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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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.

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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.