Sri Lanka Journal of Neurology

Official Journal of The Association of Srilankan Neurologists

Volume 2, Number 1, 2013

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.

Printed by **Ananda Press**
82/5, Sir Ratnajothi Saravanamuttu Mawatha, Colombo 13, Sri Lanka.
Tel: 0112 435975 Fax: 0112 385039 E-mail: anpress@sltnet.lk

SRI LANKA JOURNAL OF NEUROLOGY

Official publication of the Association of Srilankan Neurologists

Volume 2, Number 1, 2013

CONTENTS

Editorial

Misuse of gabapentin and pregabalin
Saman B Gunatilake 1

Papers

Demographic patterns from an epilepsy clinic in Sri Lanka
Ranjanie Gamage, Inuka Kishara Gooneratne 2

Percutaneous vertebroplasty in vertebral crush fractures – a descriptive analysis
Devinda Lecamwasam, Ravi P. Ruberu, Mike Wilks, Ramon Pathi, Maria Dellamalva, Deepal Lecamwasam 7

Review

Preventive pharmacologic treatment of migraine in adults
Ajini Arasalingam, Saman B Gunatilake 11

Case reports

Multiphasic disseminating encephalomyelitis (MDEM)
Bimsara Senanayake 17

The little old adie pupil
H P M C Caldera, I K Gooneratne, R Gamage 19

Cortical-hand syndromea
Uditha Dassanayake, Thashi Chang 21

Nummular headache
Tissa Wijeratne, Dilani Wijeratne 23

A stroke mimic
G N N Fernando, L J Jayaweera, B M T P Nawasiwaththa, S Bandusena, P S Gunarathna 25

Picture quiz

Stroke 27

Guidelines

Guidelines to authors 29

Answers

Answers to picture quiz on stroke 32

ISSN 2279-2295

Editorial

Misuse of gabapentin and pregabalin

Sri Lanka Journal of Neurology, 2013, **2**, 1

Neuropathic pain affects up to 8% of the population, causing significant distress and morbidity. Good evidence-based treatment is available, so early diagnosis is important. Recent publicity and guidelines, and increasing prevalences of age-related causes of neuropathic pain (including postherpetic neuralgia and diabetic neuropathy), have led to increasing rates of diagnosis and treatment at secondary and primary level of care. Gabapentin and pregabalin are the recommended mainstays of evidence-based treatment. Unfortunately, experience in US and UK suggests that gabapentin and pregabalin are now prevalent as drugs of abuse. The drug's effects vary with the user, dosage, past experience, psychiatric history, and expectations. Individuals describe varying experiences with gabapentin abuse, including: euphoria, improved sociability, a marijuana-like 'high', relaxation, and sense of calm, although not all reports are positive (for example, 'zombie-like' effects). Gabapentin is easily prescribed without restriction, and escalating doses are recommended. It is therefore easy to facilitate any misuse and addiction potential, and to stock the black market. Like opiates, gabapentin is fatal in overdose; unlike opiates, there is no antidote and the long half-life instills the need for prolonged, intensive management of overdose.

Pregabalin is licensed for neuropathic pain and also for general anxiety disorder. Pregabalin prescribing in the West has increased by 350% and gabapentin by 150% in last five years. This is big business. This trend is seen even in Sri Lanka evidenced by the large number of different generic brands being available in the country. A new name appears in the market almost every month. The use of these drugs is heavily promoted amongst the general practitioners as well. Pain is the commonest symptom known and is very subjective. Diagnosing a neuropathic pain needs special training and when to use these drugs has to be decided with extreme care. But what is seen now is even musculoskeletal pains like back ache, and headaches are being sometimes treated with these specific drugs by GPs, Rheumatologists and Orthopaedic surgeons. In some diabetic clinics use of gabapentin and pregabalin have become routine. The slightest complaint of numbness of a toe is treated.

Whether pregabalin and gabapentin are abused as recreational drugs in Sri Lanka is not known. But its free availability and widespread prescribing will lead to their abuse and we have to be cautious. Some form of control is required in the use of these drugs. Should we restrict their use to only hospital pharmacies?

Saman B Gunatilake
Editor in Chief

Paper

Demographic patterns from an epilepsy clinic in Sri Lanka

Ranjanie Gamage[1], **Inuka Kishara Gooneratne**[1]

Sri Lanka Journal of Neurology, 2013, **2**, 2-6

Abstract

Introduction: Over half of the 50 million people with epilepsy worldwide are estimated to live in Asia. Although much research is done in Asia, information about the recognition of the burden created by the disease is scarce. Better understanding of the demographic distribution of epilepsy would improve our knowledge and understanding of this disorder at the population level.

Method: A retrospective hospital-based study was conducted to determine demographic patterns in patients attending the epilepsy clinic at the National Hospital of Sri Lanka for one year. An interviewer based questionnaire was used to collect data on demographic characteristics.

Results: Data was gathered from 500 patients. Male to female ratio was 1.08:0.92. Two hundred and twelve patients (42.4%) belonged to the 16 to 30 age group while 140 (28%) were from the 31 to 45 age group. Most of the patients in the aforesaid age groups (n=352) were unemployed (n=211, 59.94%) and only 89 (25.3%) were employed. Two hundred and sixty four patients (75%) were unmarried while 7 (1.9%) were divorced. The number of patients who received primary and secondary education were 44 (24.4%) and 93 (51.6%) respectively. Two (1.1%) patients went to university. Forty one (22.8%) had no schooling.

The causes of epilepsy are: no identifiable cause 357 (71.4%), CNS infections 46 (9.2%), head trauma 25 (5%), peri-natal distress 32 (6.4%) stroke 22 (4.4%) and structural lesions 18 (3.6%).

Conclusion: Many epilepsy patients have fewer educational, marital, and employment opportunities which contributes towards poor interpersonal skills, social withdrawal and low self esteem.

CNS infections, though small in number in the above cohort remains an important cause of epilepsy. Early case detection and treatment of CNS infections may further lower the burden of epilepsy.

Index words: demographic patterns of epilepsy, burden of epilepsy in Sri Lanka, psychosocial consequences of epilepsy

Introduction

Epilepsy is a neurological condition that knows no geographic or social boundaries, occurring in men and women and affecting people of all ages. It has been estimated that at least 50 million people worldwide have epilepsy[1,2]. More than 80% of people with epilepsy live in developing countries, where effective treatment of this condition is scarce[3].

The incidence of epilepsy in developed countries is estimated as being between 40 and 70 per 100,000 persons per year[4-7]. The incidence in resource-poor countries is much higher often above 120/100,000/year[4]. Poor sanitation, inadequate health delivery systems, and higher risk of brain infections and infestations may contribute to this[4,8].

Over half of the 50 million people with epilepsy worldwide are estimated to live in Asia which is a heterogeneous and resource-constrained continent[9]. Although much research is done in Asia, information about the recognition of the burden created by epilepsy is scarce.

The exact number of people suffering from epilepsy in the South Asian Region is largely unknown. Although South Asian countries compile and publish health data, epilepsy is not included as it is not a notifiable disorder[10]. "How many suffer from epilepsy?" is thus a difficult question to answer. However, various hospital-based and community-based studies have reported that it is a commonly encountered problem. As per some studies in the region, it is known that prevalence of epilepsy varies from 2-10 per 1000 population[10]. Studies from different parts of India reveal that the prevalence varies from 9/1000 in Bangalore, 5/1000 in Mumbai, 3/1000 in Calcutta to 4/1000 in New Delhi. In a survey in the Kandy district of Sri Lanka, it was observed that 9 out of 1000 people had epilepsy. It is also reported that epilepsy is the second commonest neurological condition after headache, in terms of the number of people affected[10].

[1] *Institute of Neurology, National Hospital of Sri Lanka.*

Better understanding of the demographic distribution of epilepsy and prevalence of more specific forms of epilepsy in the community would improve our knowledge and understanding of this disorder at the population level. Such studies in Sri Lanka are scarce[10].

The present study was conducted to identify demographic patterns in patients attending the epilepsy clinic at the National Hospital of Sri Lanka situated in the capital city Colombo. This tertiary referral center provides specialized outpatient clinics in Neurology including epilepsy, and caters for patients from all over the island.

Method

A retrospective hospital-based study was conducted to determine demographic patterns in patients attending the epilepsy clinic at the National Hospital of Sri Lanka. An interviewer based questionnaire was used to collect data on demographic characteristics, seizure semiology, delays in treatment and its causes, and underlying aetiology of seizures. Data were collected from patients attending the above clinic from January 2002 to January 2003. Definitions for the classification of aetiology and semiology were adopted from the International League Against Epilepsy guidelines for epidemiologic studies on epilepsy[11].

Statistical analysis was done through SPSS version[11]. Informed consent was obtained from the study population. Ethical approval was obtained from Ethics Review Committee of the National Hospital of Sri Lanka.

Results

Data were gathered from 500 patients who attended the clinic during the stipulated study period. Of these patients 260 (52%) were males. Two hundred and twelve patients (42.4%) belonged to the 16 to 30 age group while 140 (28%) were between 31 and 45 years. Forty patients (8%) were over 45 years of age and 54 (10.8%) patients were between the ages of 11 and 15. Twenty two (4.4%) were from the 6 to 10 age group and 32 (6.4%) were 5 years and below. Most of the patients between 16 and 45 (n=352) were unemployed (n=211, 59.94%) and only a minority were employed (n=89, 25.3%). Fifty two (14.7%) were certified unemployable. Two hundred and sixty four patients (75%) in the aforesaid age group were unmarried while 7 (1.9%) were divorced. While the majority of patients who were above 30 years (n=180) had received secondary education (n=93, 51.6%), a significant proportion of patients (n=44, 24.4%) received only primary education. Only 2 (1.1%) patients went to university. Forty one (22.8%) had no schooling.

Seizure type was classified according to semiology and EEG findings, and was as follows: generalized tonic clonic (191, 38.2%), absence (31, 6.2%), complex partial (156, 31.2%), simple partial (38, 7.6%), myoclonic (21, 4.2%) and secondary generalized seizures (63, 12.6%).

The possible causes of epilepsy in the above cohort of patients were as follows: no identifiable cause 357 (71.4%), CNS infections 46 (9.2%), head trauma 25 (5%), perinatal distress 32 (6.4%) stroke 22 (4.4%) and lastly structural lesions including hippocampal sclerosis, congenital brain malformation and brain tumours 18 (3.6%).

A delay in treatment was defined as a delay in seeking western medical treatment for a period of over 3 months following the onset of epilepsy. Such a delay was only seen in 84 patents (16.8%). Of these patients 40 (47.6%) did not receive alternative treatment or did not sought relief in ritualistic practices. Only 4.8% (n=4) chose native medical treatment modalities ("Ayurveda" – a traditional medical practice in Sri Lanka). Spiritualistic healing by way of rituals such as *"Bali-Thovil"* and charms had been sought by 23.8% (n=20).

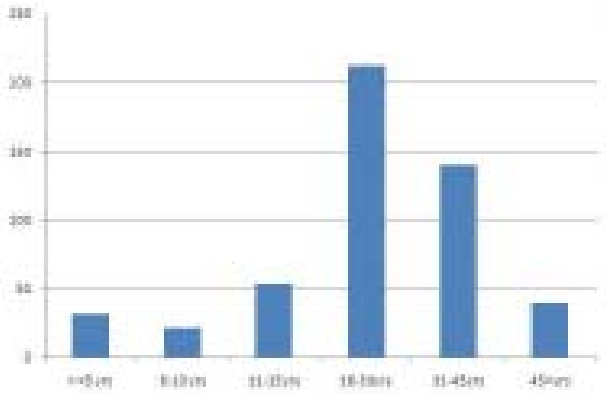


Figure 1. Age distribution in patients attending the epilepsy clinic.

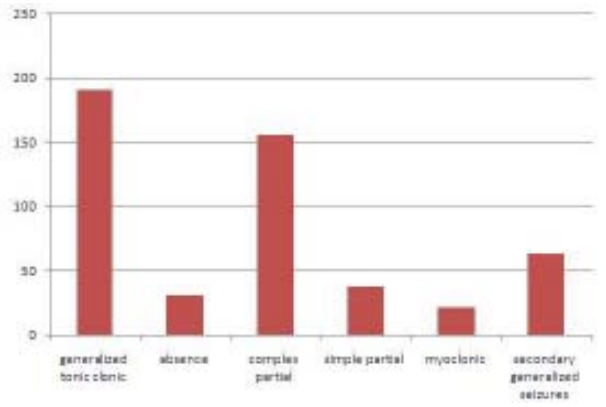


Figure 2. Seizure type.

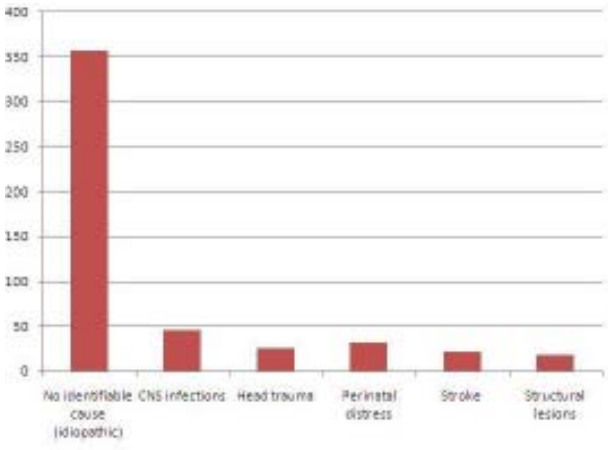


Figure 3. Causes of epilepsy identified.

Discussion

In developed countries, the incidence and prevalence of epilepsy both follow a bimodal distribution with a first peak in childhood and another in old age[9]. Most studies conducted in the Asia show one peak age for incidence in children and another peak age for prevalence in young adults[9, 12-19]. The postulated reason for the missing peak in the older age groups in many Asian countries is the relatively young population compared with that in more developed regions[9]. In the study population the absence of the old age peak may reflect this trend in Asia although Sri Lanka has population demographics which depict an increasing aging population[20]. The possible explanation for the low representation of very young age groups in the study population is that paediatric neurology clinics provide care for children with epilepsy.

In most studies in the region, epilepsy is slightly more common in men than in women but the sex-specific prevalence is not, in general, significantly different[9,13,15 16,19]. This trend is also reflected in the above study population.

People with disabilities are among the most vulnerable in any society. The psychosocial and economic consequences of epilepsy in less developed countries are generally acknowledged to contribute substantially to the burden of this disease as it is associated with social stigma[21]. Stigmatization leads to discrimination, and people with epilepsy have been the target of prejudicial behaviour in many spheres of life, over many centuries and in many cultures[22]. Discrimination against people with epilepsy in the workplace and with respect to access to education is not uncommon[21]. In a study done in Hong Kong 94.1% of respondents thought that people with epilepsy could be married, but only 67.8% would allow their child to marry a person with epilepsy[23]. Thus people with epilepsy may have fewer educational, marital, and employment opportunities. The findings of this study may lend support to the supposition that people with epilepsy in developing regions suffer social stigma with associated poor social and economic status.

It has also been shown that people with epilepsy are generally more prone to poorer self-esteem and higher levels of anxiety and depression than people without epilepsy[24]. People with epilepsy also consistently appear at greater risk of problems in relation to educational achievement[25-27] and employment[28-30]. Issues of social withdrawal and isolation have been also reported with knockon effects for marriage and other close interpersonal relationships[31,32].

The majority of the patients followed up at the clinic were between the ages of 15 and 30. The second largest patient population was between the ages of 30 and 45. These age categories contribute maximally towards the workforce. The majority in the above age categories were unemployed thus contributing poorly towards the workforce which in turn adds on to the economic burden of the country. Many of the patients in the above age categories were also unmarried and also showed poor educational achievements which reinforces the socio-economic problems patients with epilepsy have to face. As mentioned in other studies social withdrawal and isolation may contribute towards these problems[31,32]. Fewer educational, marital, and employment opportunities in turn worsens social withdrawal, thus a vicious cycle ensues.

In most regional studies the range of patients with generalised seizures was 50-69%, and 31-50% had partial seizures[9]. This trend was seen in the above study population as well. There are only few studies on the causes of epilepsy in Asian populations, and there are particularly only a few case-control or cohort studies[9]. From the available literature, the major causes seem to be: head injury, birth trauma, and intracranial infections, such as neurocysticercosis or meningoencephalitis[9]. In places of greater socioeconomic development, head trauma and stroke are the leading causes of epilepsy[9]. In this study in majority of the patients an identifiable cause was not detected. The high incidence of idiopathic epilepsy in this study is probably an over estimation and may indicate a shortage of more elaborate investigative procedures in finding a cause.

The prevalence of central nervous system infections was low in this study. In developing countries in other regions of the world, CNS infections seem to explain the high prevalence of epilepsy[9]. The listed causes of epilepsy are, malaria, tuberculosis, schistosomiasis, AIDS, and cysticercosis and among these, the latter seems to be the most common cause of epilepsy[33]. Neurocysticercosis was the cause of epilepsy in about 50% of patients in

some studies[34,35]. In Asia, many studies report the presence of cysticercosis[9] but Neurocysticercosis is not found in Sri Lanka[36]. This is unexpected when considering the geographical proximity of India which has a high prevalence of cysticercosis[35]. The unimpeded human migration to and from either country has not resulted in an increase in the prevalence of cysticercosis.

Malaria is still widely endemic in Asia, with more than 3 million cases per year[9]. In a retrospective survey in Thailand 7.7% of patients with childhood malaria (with or without the presence of cerebral malaria) had convulsions 37. In another study convulsions were found to be present in 60% of patients with cerebral malaria[38]. The link between epilepsy and malaria is supported by a case-control study in Gabon and a cohort study in Mali in Africa as well[39]. However in Sri Lanka the incidence of Malaria is negligible and has reached the pre-elimination stage due to effective treatment and preventive programmes[40].

In Asia, post-traumatic epilepsy is one of the most common complications of head injury[9]. A study claimed that post-traumatic epilepsy accounted for 5% of total epilepsy and 20% of symptomatic epilepsy[41]. In our study patients with epilepsy due to trauma are comparable with regional data. It may also be an underestimation due to the fact that most of patients with head trauma may be followed up at neuro-surgical clinics. Therefore the above numbers may be an underestimation of the true impact of trauma on epilepsy.

Ideas and opinions about treatment of epilepsy are often based on beliefs about the disease. Since epilepsy is often seen as a spiritual affliction, some patients with epilepsy or their carers assume that traditional treatment in the local community is appropriate. This is commonly seen in most developing nations[42]. An increase in the sustained use of effective treatment is closely linked to improved awareness of epilepsy, as beliefs and explanations about epilepsy influence health-seeking and treatment-seeking behaviour[42]. In many developing nations, notions about epilepsy are rooted not in medical sciences but in spiritual beliefs[43]. In Sri Lanka such spiritual beliefs do exist and are reflected in ritualistic practices such as *"Bali-Thovil"* and various types of charms. In our study a treatment delay was seen in only a minority of patients and of these patients only a small proportion of people had sought relief in such spiritualistic practices. Such ritualistic practices had a small role to play in causing treatment delays in the above population which might suggest better health seeking behaviour observed among Sri Lankan communities compared to communities in other developing nations. This may be due to greater awareness of the disease which in turn may be due to high literacy rates observed in Sri Lanka[20] and effective health education programmes. However this observation may also be due to selection bias.

Conclusion

Utilization of a healthcare system depends on socio-demographic factors, social structures, level of education, cultural beliefs and practices, gender discrimination, status of women, economic and political systems, environmental conditions, the disease pattern and attributes of the healthcare system itself. When considering the healthcare system itself health seeking behaviour is influenced by availability, accessibility, affordability and acceptability[44]. The data above suggest that the healthcare system in Sri Lanka may have the above attributes, thus providing the necessary confidence to the community towards such health seeking behaviour.

Although health seeking behaviour remains high in the above cohort it seems epilepsy may still be highly stigmatized. Many patients in the above population have fewer educational, marital, and employment opportunities which contributes towards poor interpersonal skills, social withdrawal and low self esteem. This emphasises that epilepsy is a chronic disabling neurological disorder which causes many psychosocial tribulations that need to be addressed by healthcare professionals.

CNS infections, though small in number in the above cohort remains an important cause of epilepsy. Early case detection and prompt treatment of CNS infections may contribute towards further lowering the burden of epilepsy.

While this study represents institutional data and may have an element of referral bias it highlights psychosocial tribulations in epilepsy patients and the need for intervention. However further community based epidemiological studies are necessary to assess the burden of epilepsy in the community.

References

1. World Health Organization. International Classification of Functioning Disability and Health: ICF. Geneva: WHO; 2001.
2. Leonardi M, Ustun TB. The global burden of epilepsy. *Epilepsia* 2002; **43**(Suppl. 6): 21-5.
3. Leonardi M, Ustun TB. The global burden of epilepsy. *Epilepsia* 2002; **43** (Suppl 6): 21-25.
4. Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol* 2003; **16**: 165-70.
5. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000; **123**: 665-76.
6. Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe: a systematic review. *Eur J Neurol* 2005; **12**: 245-53.
7. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet* 2006; **367**: 1087-100.

8. Sander JW. Infectious agents and epilepsy. In: Knobler S, O'Connor S, Lemon SM, Najafi M, editors. The infectious etiology of chronic diseases: defining the relationship, enhancing the research and mitigating the effects. Washington, DC: National Academies Press; 2004. p. 93-9.
9. Mac TL, Tran D, Quet F, Odermatt P, Preux PM, Tan TC. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. *Lancet Neurol* 2007; **6**: 533-43.
10. Satishchandra P, Gururaj G, Mohammed QD, Senanayake N, Silpakit O. Global campaign against epilepsy: out of the shadows – from prejudice to hope. World Health Organization publication 2001.
11. Guidelines for Therapeutic Monitoring on Antiepileptic Drugs: Commission on Antiepileptic Drugs. *International League Against Epilepsy* 1993; **34**: 585-7.
12. Li SC, Schoenberg BS, Wang CC, et al. Epidemiology of epilepsy in urban areas of the People's Republic of China. *Epilepsia* 1985; **26**: 391-4.
13. Fong GCY, Mak W, Cheng TS, et al. A prevalence study of epilepsy in Hong Kong. *Hong Kong Med J* 2003; **9:** 252-7.
14. Radhakrishnan K, Pandian JD, Santhoshkuma T, et al. Prevalence, knowledge, attitude and practice of epilepsy in Kerala, South India. *Epilepsia* 2000; **41**: 1027-35.
15. Aziz H, Guvener A, Akhtar SW, et al. Comparative epidemiology of epilepsy in Pakistan and Turkey: population based studies using identical protocols. *Epilepsia* 1997; **38**: 716-22.
16. Sridharan R, Murthy BM. Prevalence and pattern of epilepsy in India. *Epilepsia* 1999; **40**: 631-6.
17. Mannan MA. Epilepsy in Bangladesh. *Neurol Asia* 2004; **9**: 18.
18. Radhakrishnan K, Nayak SD, Kumar SP, et al. Profile of antiepileptic pharmacotherapy in a tertiary referral center in South India: a pharmacoepidemiologic and pharmaco-economic study. *Epilepsia* 1999; **40**: 179-85.
19. Tsang KL, et al. Clinical characteristics of adult epilepsy patients in the 1997 Hong Kong epilepsy registry. C*hin Med J (Engl)* 2001; **114**: 84-7.
20. Department of Census and Statistics, Available from: http://www.statistics.gov.lk/page.asp?page=Population%2and%20Housing. [Cited on 2011 Feb 1]. [Last updated on 2010, December 24].
21. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. *Epilepsy & Behavior* 2008; **12**: 540-6.
22. Pahl K, de Boer HM. Epilepsy and rights. In: Atlas: epilepsy care in the world. Geneva: WHO; 2005. p. 72-3.
23. Fong CY, Hung A. Public awareness, attitude, and understanding of epilepsy in Hong Kong Special Administrative Region, China. *Epilepsia* 2002; **43**: 311-16.
24. Arntson P, Drodge D, Norton R, Murray E. The perceived psychosocial consequences of having epilepsy. In: Whitman, S. and Hermann, B. (Eds.) Psychopathology in Epilepsy: Social Dimensions. Oxford: Oxford University Press. 1986.
25. Thompson PJ. Educational attainment in children and young people with epilepsy. In Oxley J., Stores G (eds) Epilepsy and Education. London. The Medical Tribune group. 1987; 15-24.
26. Hauser W, Hesdorffer DC. Epilepsy: Frequency, Causes and Consequences. Maryland: Epilepsy Foundation of America. 1990.
27. Aldenkamp AP. The impact of epilepsy on cognitive development during focal and generalised epileptiform EEG activity Brain 1995; **107**: 293-308.
28. Elwes RDC, Marshall J, Beatty A, Newmann PK. Epilepsy and Employment: A community based survey in an area of high unemployment. *Journal of Neurology, Neurosurgery and Psychiatry* 1991; **54**: 200-3.
29. Thompson PJ and Oxley J. Social aspects of epilepsy. In Laidlaw J, Richens A, Chadwick DW (eds) A textbook of epilepsy. 4th edition London. Churchill Livingstone 1993; 661-704.
30. Jacoby, A. Epilepsy and Employment Status: finding from a UK study of people with well-controlled epilepsy. *Epilepsy Research* 1995; **21**: 125-32.
31. Dansky LV, Andermann E, Andermann F. Marriage and fertility in epileptic patients. *Epilepsia* 1980; **21**: 261-71.
32. Scambler G, Hopkins A. Being epileptic: coming to terms with stigma. S*ociology of Health and Illness* 1986; **8**: 26-43.
33. Commission on Tropical Diseases of the International League Against Epilepsy. Relationship between epilepsy and tropical diseases. *Epilepsia* 1994; **35**: 89-93.
34. Preux PM, Druet-Cabanac M: Epidemiology of epilepsy in sub-Saharan Africa. *Lancet Neurol* 2005; **4**: 21-31.
35. Rajshekhar V, Joshi DD, NQ Doanh, et al. Taenia solium taeniosis/cysticercosis in Asia: epidemiology, impact and issues. *Acta Trop* 2003; **87**: 53-60.
36. Juyal PD, Sharma R, Singh NK, Singh G. Epidemiology and Control Strategies Against Cysticercosis (due to Taenia solium) with Special Reference to Swine and Human in *Asia. J. Vet. Anim. Sci.* 2008; **1**: 1-10.
37. Wattanagoon Y, Srivilairit S, Looareesuwan S, et al. Convulsions in childhood malaria. *Trans R Soc Trop Med Hyg* 1994; **88**: 426-28.
38. Faiz MA, Rahman MR, Hossain MA, et al. Cerebral malaria – a study of 104 cases. *Bangladesh Med Res Counc Bull* 1998; **24**: 35-42.
39. Ngoungou EB, Dulac O, Poudiougou B, et al. Epilepsy as a consequence of cerebral malaria in area in which malaria is endemic in Mali, West Africa. *Epilepsia* 2006; **47**: 873-79.
40. Rajakaruna RS, Alifrangis M, Amerasinghe PH, Konradsen F. Pre-elimination stage of malaria in Sri Lanka: assessing the level of hidden parasites in the Population. *Malaria Journal* 2010; **9**: 25.
41. Hui AC, Kwan P. Epidemiology and management of epilepsy in Hong Kong: an overview. *Seizure* 2004; **13**: 244-6.
42. Coleman R, Loppy L, Walraven G. The treatment gap and primary health care for people with epilepsy in rural Gambia. *Bull World Health Organ* vol.80 no.5 Genebra 2002.
43. Whyte SR. Constructing epilepsy: images and contexts in East Africa. In: Ingstad B, Whyte SR, editors. Disability and culture. Berkeley and Los Angeles (CA): University of California Press; 1995: 226-45.
44. Ahmed SM. Exploring health seeking behaviour of disadvantaged populations in rural Bangladesh. Division of international health, department of public health sciences, Karolinska institute, Stockholm, Sweden. Karolinska University Press. 2005.

Paper

Percutaneous vertebroplasty in vertebral crush fractures – a descriptive analysis

Devinda Lecamwasam[1], Ravi P. Ruberu[2], Mike Wilks[2], Ramon Pathi[2], Maria Dellamalva[2], Deepal Lecamwasam[2]

Sri Lanka Journal of Neurology, 2013, **2**, 7-10

Abstract

Introduction: Efficacy of Vertebroplasty (VP) in acute vertebral crush fractures has been questioned. We support that VP is an effective treatment in selected patients.

Method: Retrospective study of 47 (37 female) patients admitted to a private hospital between 2006 to 2011 with pain due to acute vertebral crush fractures and received VP were interviewed by phone following reviewing of notes.

Results: Forty seven (65-90y) were of two distinct populations, younger group was 67 to 70y. Duration of pain was 9.5 days (range 2-21 days). Hospital length of stay (LOS) was 2-33 days. Total of 31 (66%), females 23, reported VP as satisfactory (good, very good, excellent). All had VP within 15 days of admission. Twenty two (71%) of 31 were independent prior to the back injury. Fifteen (48%) were over 85y (very elderly) and 15 (48%) were between 70 - 85y. Very elderly (5 males, 10 females) reported a favourable outcome and their LOS was 14-33 days. Twenty-two of the elderly (total 25) had LOS greater than 7 days and reported a favourable outcome. Two reported no effect.

Younger patients (7) were independent in daily activities. Five reported the procedure as satisfactory and were discharged within two weeks.

LOS increased with age. Majority (98%) received either rehabilitation (80%) or returned home (17%). Significant associations were noted in relation to younger age, post procedure pain perception, and premorbid independence with early discharge (CI 95%).

Conclusion: VP is a safe and a useful treatment where conservative management has failed.

Background

Approximately 1-4 million patients present with vertebral compression fractures worldwide every year leading to significant pain, disability, diminished quality of life as well as increase risk of further vertebral fractures[1]. Vertebroplasty was first introduced in 1987 by Galibert and Deramond et al, pioneered to be used in aggressive vertebral angiomas[2]. Subsequent work has shown it to be of value in treating osteoporotic compression fractures. Although the early literature related to VP treatment in osteoporotic vertebral crush fractures have shown some success, there has been notable criticism in relation to the treatment efficacy[3].

Method

A retrospective study of 47 (10 male, 37 female) patients admitted to a private hospital between 2006 to 2011 with back pain due to vertebral crush fractures and received VP were interviewed by phone following reviewing of case notes. Where possible patients were contacted or otherwise their carers were interviewed. Descriptive statistics and multiple variable analyses using split modelling decision tree were performed using JMP 10 statistical software. Pain perception was grouped as Excellent (resolution of pain within 24h), very good (resolution of pain within 48h), good (resolution of pain within 96h), and no effect when satisfactory pain resolution was not achieved.

Two experienced interventional radiologists carried out the VPs. Procedure was performed by placing a 11 or 13 gauge needle as close to the centre of the vertebral body, directing the bevel toward either the centre, or superior/ inferior endplate as may be required for particular fracture morphology using a transpedicular approach. The injection of cement (polymethylmethacrylate) was performed under lateral screening, carefully watching for any retrograde flow of cement toward or into the epidural space. Intermittent antero-posterior screening was used to check for the position of cement.

Results

Baseline characteristics of the study participants are shown in Table[1]. Age range of the 47 patients were 65-90 years and was of two distinct populations as noted by normal quantile plot analysis, where the younger age group was between 67 to 70 years. The mean duration of back pain on presentation was 9.5 days (range 2-21 days).

[1] *Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, SA, 5011, Australia,* [2] *Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia.*

Table 1. Baseline characteristics of the study participants

Total number of subjects	47
Male	10
Female	37
Age range	65 to 90 years
Duration of back pain	2-21 days (mean 9.5)
Previous crush fractures	13
Hospital length of stay	2-33 days
Indication for VP	Intractable pain despite analgesia 43 Intolerable to Opiates 4
Phone contact on follow up with patient	30
Phone contact on follow up with next of kin	17

Hospital length of stay ranged between 2-33 days. There were no adverse outcomes noted as a direct result of the VP procedure. Total of 31 (66%) patients (males 8, females 23) reported the outcome of VP as satisfactory (good, very good, excellent). All had VP within 15 days of admission and 4 had the procedure within 2 days. Twenty two (71%) of 31 patients were independent prior to the back injury and 9 were semi-independent. Fifteen (48%) were over 85 years of age (very elderly) and 15 (48%) patients were between 70-85 years (elderly). All very elderly (5 males, 10 females) reported a favourable outcome and their length of hospital stay ranged between 14 to 33 days (Figure 1).

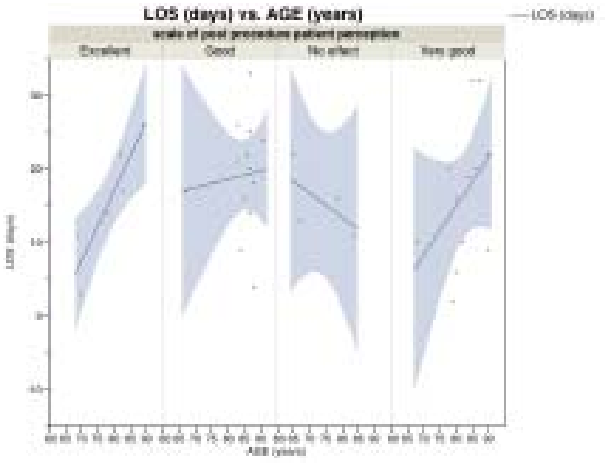


Figure 1. Graphical representation of length of stay in days vs. age in years plotted against perceived outcome of VP. 43 of 47 patients were satisfied of the outcome of VP.

Twenty-two of the elderly (total 25) group had a length of hospital admission greater than 7 days and all reported a favourable outcome. Two patients reported that procedure had no effect and one patient was from high-level residential care.

Of the younger patients (65-70 years), all seven were independent in daily activities and five were ambulating unaided prior to the injury. One used a walking stick and the other a walking frame. All had acute vertebral crush fractures and two were bedridden. Five reported the procedure as satisfactory and were discharged within 2 weeks.

Overall length of hospital stay increased with age in the study population. Majority (98%) received either rehabilitation (80%) or returned home (17%) following discharge from the hospital (Figure 2).

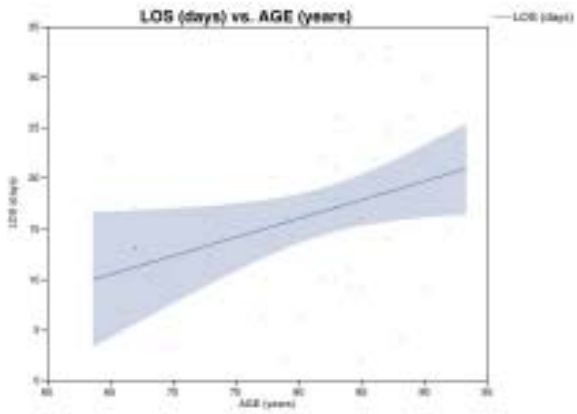


Figure 2. Graph showing the increase in length of stay in day with increase in age.

Split modelling decision tree analysis revealed an association between improved pain perception, younger age, and premorbid degree of independence in decreasing order as statistically significant associations in relation to early discharge (CI 95%). Patient variables such as sex, cohabitants, support where patient was admitted from, and post injury disability did not show a significant association with early discharge.

Discussion

Our case series show that VP is a safe and an effective procedure often providing rapid pain relief in the frail elderly. All subjects reported no adverse outcome, or dissatisfaction. Of 47 patients, 45 reported a favourable outcome, which included the very elderly group. Of the two patients who reported no change to pain, post procedure, one was a high level of care nursing home resident with advance arthritis. As expected, overall length of stay increased with advancing age and every one over the age of 85y received rehabilitation. There is a considerable body of literature upholding efficacy of VP in reducing pain and improving quality of life both in the elderly and the very elderly[4]. Fractures of the adjacent vertebral bodies to that of the VP treated vertebral body have been of some concern. However, this is a rare complication. In one study adjacent fracturing to the treated was associated with higher height restoration of the treated vertebra, location of the adjacent vertebra in the TL junction, the shorter distance between the treated and the adjacent vertebra[5], and cement leakage into the disk[6]. In their study of 104 consecutive patients and predictors of new vertebral body fractures, Komemushi et al has shown that increased fracture risk was not associated with age, gender, bone mineral density, the number of vertebrae treated per procedure, the cumulative number of vertebrae treated, the presence of a single untreated vertebrae between treated vertebrae, the presence of multiple untreated vertebrae between treated vertebrae, the amount of bone cement injected per procedure, the cumulative amount of bone cement injected, cement leakage into the soft tissue around the vertebrae, and cement leakage in to the vein[6]. Bone cement leakage is by far the commonest reported complication[7]. Whilst this often is of benign nature, there have been significant number of case reports describing nerve root irritation[8] pulmonary embolism[9], cerebral cement embolism[10], and fatalities[11]. Nevertheless, larger studies have demonstrated that VP recipients have much the same mortality rates as for untreated symptomatic patients[12].

Care with accurate needle placement, adequate barium radio-opacification of bone cement, viscous low pressure delivery, delivery under direct fluoroscopic visualisation, and use of appropriate delivery systems have reduced these complications[13]. Operator experience have also shown to improve short term outcome of VP[14]. In our study, approximately two third of patients were followed over 24 months and none were noted to have had an adjacent vertebral fracture. Furthermore, two of the authors of our study group are highly experienced interventional radiologists who have performed VP for over 5 years and have had no significant adverse effects. Contraindications to VP include unstable fracture, lack of definable vertebral collapse, radicular pain, cord compression, destruction of the posterior wall of the vertebral body, and infection in the area[15,16].

Referrals for VP have declined in the United States of America[17] since recent blinded placebo-controlled trials[3,18]. We believe this to be true in Australia as well. These two randomised control trials (RCTs) published in the *New England Journal of Medicine* concluded that there was no significant difference in pain relief between VP group and the control group one month following treatment. We believe the patient cohort in these studies is different to that of ours. The patients enrolled in these studies had duration of pain for far too long and the RCTs took over 4 years to complete. Whilst it is conceivable from these studies that long duration of pain and inadequate imaging techniques could potentially cause treatment failure, careful patient selection with duration of pain less than 6-8 weeks (not adequately controlled by analgesics or analgesic intolerability) and appropriate use of imaging to identify acute fractures (bone scan or MRI) has proven in our case series as well as in others[19] to be key factors in high success rate.

In experienced hands, with careful case selection, the procedure carries a low risk of short term and long-term morbidity. The overall impression is a positive one and we believe improvement in quality of life is sustained.

References

1. Wardlaw D, Meirhaeghe JV. Another chapter for vertebral compression fractures. *The Lancet* 2010; **376**: 1031-3.

2. Galibert P, Deramond H, Rosat P, Le Gars D. [Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty]. *Neuro-Chirurgie* 1987; **33**: 166-8.

3. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *The New England Journal of Medicine* 2009; **361**: 557-8.

4. Cahana A, Seium Y, Diby M, Martin JB, Ruefenacht D, Dietrich PY. Percutaneous vertebroplasty in octogenarians. Results and follow-up. *Pain Practice the Official Journal of World Institute of Pain* 2005; **5**: 316-23.

5. Kim SH, Kang HS, Choi JA, Ahn JM. Risk factors of new compression fractures in adjacent vertebrae after percutaneous vertebroplasty. *Acta Radiologica* 2004; **45**: 440-5.

6. Komemushi A, Tanigawa N, Kariya S, Kojima H, Shomura Y, Komemushi S, Sawada S. Percutaneous vertebroplasty for osteoporotic compression fracture: multivariate study of predictors of new vertebral body fracture. *Cardiovascular and Interventional Radiology* 2006; **29**: 580-5.

7. Anselmetti GC, Zoarski G, Manca A, Masala S, Eminefendic H, Russo F, Regge D. Percutaneous vertebroplasty and bone cement leakage. Clinical experience with a new high-viscosity bone cement and delivery system for vertebral augmentation in benign and malignant compression fractures. *Cardiovascular and Interventional Radiology* 2008; **31**: 937-47.

8. Kelekis AD, Martin JB, Somon T, Wetzel SG, Dietrich PY, Ruefenacht DA. Radicular pain after vertebroplasty. Compression or irritation of the nerve root? Initial experience with the "cooling system". *Spine* 2003; **28**: 265-9.

9. Krueger A, Bliemel C, Zettl R, Ruchholtz S. Management of pulmonary cement embolism after percutaneous vertebroplasty and kyphoplasty. A systematic review of the literature. *European Spine Journal.* Official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 2009; **18**: 1257-65.

10. Scroop R, Eskridge J, Britz GW. Paradoxical cerebral arterial embolization of cement during intraoperative vertebroplasty: case report. *American Journal of Neuroradiology* 2002; **23**: 868-70.

11. Chen HL, Wong CS, Ho ST, Chang FL, Hsu CH, Wu CT. A lethal pulmonary embolism during percutaneous vertebroplasty. *Anesthesia and Analgesia* 2002; **95**: 1060-1062, table of contents.

12. McDonald RJ, Achenbach SJ, Atkinson EJ, Gray LA, Cloft HJ, Melton LJ, 3rd, Kallmes DF. Mortality in the vertebroplasty population. *American Journal of Neuroradiology* 2011; **32**: 1818-23.

13. Perrin C, Jullien V, Padovani B, Blaive B. [Percutaneous vertebroplasty complicated by pulmonary embolus of acrylic cement]. *Revue des maladies respiratoires* 1999; **16**: 215-17.

14. McDonald RJ, Gray LA, Cloft HJ, Thielen KR, Kallmes DF. The effect of operator variability and experience in vertebroplasty outcomes. *Radiology* 2009; **253**: 478-85.

15. Peh WC, Gilula LA. Percutaneous vertebroplasty. Indications, contraindications, and technique. *The British Journal of Radiology* 2003; **76**: 69-75.

16. Satre TJ, Mackler L, Birch JT, Jr. Clinical inquiries. Who should receive vertebroplasty? *The Journal of Family Practic*e 2006; **55**: 637-8.

17. Luetmer MT, Kallmes DF. Have referral patterns for vertebroplasty changed since publication of the placebo-controlled trials? *American Journal of Neuroradiology* 2011; **32**: 647-8.

18. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *The New England Journal of Medicine* 2009; **361**: 569-79.

19. Gangi A, Clark WA. Have recent vertebroplasty trials changed the indications for vertebroplasty? *Cardiovascular and Interventional Radiology* 2010; **33**: 677-80.

Review

Preventive pharmacologic treatment of migraine in adults

Ajini Arasalingam[1], **Saman B Gunatilake**[2]

Sri Lanka Journal of Neurology, 2013, **2**, 11-16

Introduction

Migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours[1]. Episodic migraine has a female predilection affecting 17% of women and 6% of men[2-5]. Episodic migraine is characterized by < 15 days of headache per month and chronic migraine by > 15 headache days per month[1]. Migraine headaches may be moderate to severe or debilitating. Migraine affects the physical, psychological and social well being of patients and can restrict daily activities resulting in lost work time and diminished productivity[6]. Forty percent of adults with episodic migraine and all patients with chronic migraine might benefit from preventive medication, however only 12% of adults take preventive medication[2]. Several drug classes are used as preventive treatment in episodic migraine and they affect various aspects of migraine pathophysiology[7,8].

Several classes of drugs are used for migraine prophylaxis. The European Federation of Neurological Societies recommends the beta-blockers metoprolol and propranolol, calcium channel blockers flunarizine and the antiepileptic drugs sodium valproate and topiramate as the first line drugs and amitriptyline, venlafaxine, naproxen and bisoprolol as drugs of second choice for migraine prophylaxis[9].

The American Headache Society and the American Academy of Neurology in the updated guidelines of 2012 recommends sodium valproate, topiramate, metoprolol, timolol, propranolol and frovatriptan as the dugs with established efficacy (based on at least 2 class 1 trials) and amitriptyline, venlafaxine, atenolol, nadolol, naratriptan and zolmitriptan as drugs that are probably effective in the prevention of migraine[10].

Of the several drug used by the medical professional the beta blockers propranolol and timolol and the antiepileptic drugs topiramate and sodium valproate (divalproex sodium) are the only four that are approved by the US Food and Drug Administration[11]. Novel antiepileptic drugs, calcium channel blockers, serotonin and noradrenaline reuptake inhibitors, glutamate blockers and drugs from several other classes are prescribed off-label by doctors[11]. The NICE guidelines recommend topiramate and propranolol as preventive therapy for migraine[12]. If both are unsuitable or ineffective NICE recommends trying a course of acupuncture 10 sessions over 5-8 weeks or gabapentin according to patient preference.

Goal for preventive treatment

The 2000 US Headache Consortium defined the goals of preventive treatment as "50% decrease in attack frequency and decrease in intensity and duration; improve responsiveness to acute therapy; improve function and decrease disability and prevent occurrence of medication overuse headache and chronic daily headache".

Indications to commence prophylactic treatment

The American Migraine Prevalance and Prevention Study recommends prophylactic treatment to be commenced when a patient has at least 6 headache days per month or at least four headache days with at least some impairment or at least three headache days with severe impairment or requiring bed rest. Preventive medication is not advised with less than four headache days per month with no impairment in functioning or one or two headache days per month regardless of severity.

Therapeutic principles when prescribing preventive treatment

Preventive treatment is usually commenced at a low dose and titrated gradually till therapeutic outcome is achieved, maximal tolerable dose is reached. An adequate trial of more than two months for each preventive medication is recommended. Medication should be re-evaluated and patient should be followed up. The patient should be involved in the care to improve compliance. The choice of medication will be influenced by comorbid problems. Contraception should be discussed with women in childbearing age and the potential risk of teratogenicity and risks to the fetus should be discussed. The drug should be chosen based on efficacy, patient's preferences, headache profile, the drugs side effects and the presence or absence of coexisting or co-morbid conditions[13]. In this review we hope to analyze the evidence for the different medications used for prevention of migraine with emphasis on the drugs available in Sri Lanka.

[1] *Consultant Neurologist, Teaching Hospital, Peradeniya,* [2] *Consultant Neurologist and Professor of Medicine, University of Sri Jayewardenepura and Colombo South Teaching Hospital.*

Antiepileptic Drugs

The antiepileptic drugs studied most with respect to migraine prophylaxis have been sodium valproate, topiramate, gabapentin, lamotrigine and oxcarbazepine.

Topiramate

Data analyzed from 9 trials[14-22] with 1737 participants showed that topiramate reduced headache frequency by about 12 attacks per 28 days compared to placebo and that topiramate doubled the proportion of responders relative to placebo. Topiramate 50 mg compared with a placebo showed a significant increase in number of responders but no significant decrease in monthly headache frequency in two trials[14, 21]. However in a smaller study Gupta[19] showed that 50 mg topiramate reduced headache frequency and increased the responder rate. Trials[14-17,20,21,23] comparing topiramate 100 mg to placebo in 478 patients showed statistically significant superiority of topiramate. Four large trials[14,16,21,24] comparing topiramate 200 mg to placebo showed statistically superiority for topiramate with regard to responder rate but only two studies[14,21] showed a reduction in headache frequency. Two other smaller trials[18,22] on topiramate and placebo did not reveal a significant difference. When topiramate was compared with active comparators there was no significant difference in efficacy between maximal doses of topiramate and amitriptyline[25]; topiramate 100 mg and flunarizine 5 mg[26]; topiramate 50 mg and propranolol 80 mg[27]; and topiramate 200 mg, 100 mg and propranolol 80 mg, 160 mg[16]. There was a slight but significant advantage of topiramate 50 mg over sodium valproate 400 mg[28,29]. The trials comparing flunarizine and sodium valproate were underpowered.

Topiramate does not give an unexpectedly high rate of adverse events when used for migraine prophylaxis. Significant adverse effects of topiramate include paresthaesias, memory and concentration problems, glaucoma, hyperchloremic acidosis, renal stones, poor appetite and weight loss.

Meta-analysis (2012) of above studies showed that topiramate in a 50 or 100 mg/day dose is effective in reducing headache frequency and was reasonably well tolerated in adult patients with migraine[30].

Sodium valproate

Two cross-over trials[31,32] with a total of 63 patients showed that sodium valproate had a significant reduction in headache frequency compared to placebo. In one trial[32] responder rate with sodium valproate was significantly superior to placebo. The number needed to treat was 3. In these trials the doses ranged from 150 mg/day to an individualized target dose of maximum 1200 mg/day. A parallel group trial[33] compared different doses of sodium valproate by measuring serum sodium valproate concentrations. The study showed that lower (21-50μg/ml) serum levels gave a slightly but significantly lower headache frequency compared to higher (>50 μg/ml) serum levels and recommended a daily dose of 500-600 mg as effective.

When sodium valproate was compared with flunarizine there was no significant difference between the two in the proportion of responders, but data was insufficient to calculate significance in headache frequency[34]. Two smaller studies compared topiramate 50 mg with sodium valproate 400 mg[28,29] and found no significant difference in efficacy between the two drugs. However the pooled results of these two studies indicate a significant difference in favour of topiramate. There was no significant difference in Migraine Disability Assessment (MIDAS) scores between sodium valproate and topiramate[28]. The main adverse effects were asthenia/fatigue, dizziness/vertigo, nausea, tremor and weight gain.

A recently published Cochrane review on 10 trials on sodium valproate concluded that valproate is effective in reducing headache frequency and is reasonably well tolerated in adult patients with episodic migraine[35].

Gabapentin

Pooled data from 5 trials of gabapentin suggest that it is not efficacious for the prophylaxis of episodic migraine in adults[36]. Doses of 900 mg to 2400 mg were used in these trials.

Other antiepileptic drugs

A recent Cochrane review did not show robust conclusions regarding the efficacy of other antiepileptic drugs (acetazolamide, carisbamate, clonazepam, lamotrigine, oxcarbazepine and vigabatrin) in the prophylaxis of episodic migraine in adults.

Beta-blockers

Beta-blockers are one of the commonly prescribed groups of drugs used in migraine prophylaxis. Of the beta-blockers propranolol, metoprolol and timolol are considered effective (Level A) based on the evidence from at least 2 high quality randomized controlled trials[10]. Atenolol is a Level B drug according to the 2012 AAN and AHS guidelines[10].

Propranolol

Propranolol is the commonest drug used in migraine prophylaxis. The Cochrane study group reviewed 26 trials, which compared propranolol with a placebo and

concluded that the proportion of responders was higher with propranolol than with placebo, and the responder ratios tended to be higher in trials with higher doses of propranolol[37]. However a trial with the lowest dose (80mg) of propranolol had the most positive result[38]. Meta-analysis of 10 trials by the Cochrane group suggested that propranolol 160 mg might be slightly more effective than 120 mg[37]. The authors conclude that propranolol is superior to placebo showing clear short-term effects. The meta-analysis of propranolol versus other beta-blockers (nadolol, metoprolol), calcium antagonist (9 trials with flunarizine, 1 each with a combination of propranolol and flunarizine, nimodipine and nifedipine) and other drugs (including amitriptyline and naproxen) did not show statistically significant difference between propranolol and the comparator. Evidence on long-term effects of propranolol is limited[37].

Propranolol was found to be as effective as topiramate[27] and another study showed similar efficacy between topiramate 100 and 200 mg / day and propranolol 160 mg /day[16].

Metoprolol

The more recent large trials showed statistically significant effects of metoprolol resulting in it being classified as a Class I drug in the 2012 AAN guidelines. A recent trial showed that metoprolol 200mg / day was superior to aspirin 300 mg/ day[39] while another trial showed that metoprolol had similar efficacy compared with nebivolol in migraine prevention[40].

Calcium channel blockers

Flunarizine was efficacious in migraine prophylaxis when compared with a placebo but when compared with the beta-blockers propranolol[41], and metoprolol[42] there was no difference between the beta-blockers and flunarizine. Recommended flunarizine dose is 5-10 mg per day.

Studies on nimodipine and nifedipine as prophylaxis for migraine were equivocal and general consensus is that nimodipine and nifedipine are ineffective as prophylaxis.

Trials on verapamil were not rigorous randomized control trials and thus the evidence for use in migraine is not strong. Studies are insufficient to recommend diltiazem.

Common side effects of the group include dizziness, depression, vasomotor changes, tremor, gastrointestinal side effects, peripheral oedema and hypotension. Patients may complain of an initial increase in headache, which improves, with a few weeks of treatment. Sedation, weight gain, dry mouth, dizziness, hypotension, occasional extrapyramidal reactions, exacerbation of depression and abdominal pain are the common adverse effects associated with flunarizine.

In the 2012 guidelines both verapamil and nimodipine were downgraded because of confounding data on these drugs.

Antidepressants

Of the antidepressants amitriptyline and venlafaxine are the only drugs recommended in the 2012 AHS/AAN guideline and the EFNS guidelines and they are recommended as second line drugs.

Amitriptyline is efficacious in migraine prophylaxis and there is no significant difference between amitriptyline and topiramate. Venlafaxine is probably effective in migraine prophylaxis and evidence with regards to fluoxetine is conflicting. One study showed fluoxetine to be better than placebo[43] however overall the other studies on fluoxetine have been negative or equivocal.

Amitriptyline

Amitriptyline is a tri-cyclic antidepressant which up until recently was recommended as having proven benefit in migraine prophylaxis. In the 2012 AAN/ AHS guidelines it is classified as a Level B medication for migraine prophylaxis.

There was no significant difference between amitriptyline and propranolol[44]. Some studies showed that amitriptyline was more efficacious than propranolol in patients with mixed migraine and tension type headache while propranolol was significantly better in patients with migraine alone[45]. Amitriptyline was found to have similar efficacy to venlafaxine[46] and topiramate[47,48].

Amitriptyline is a tertiary amine and is usually started at a dose of 10 mg at bedtime. The dose ranges from 10 to 300mg a day. Tricyclic antidepressants are sedating and thus should be started with a low dose at bedtime. Common side effects encountered when using tricyclic antidepressants include orthostatic hypotension, dry mouth, a metallic taste, epigastric distress, constipation, dizziness, mental confusion, tachycardia, palpitation, blurred vision, urinary retention and weight gain. Tremors, confusion and delirium are particularly common in the elderly.

Venlafaxine

Venlafaxine is a 5HT-norepinephrine reuptake inhibitor with some evidence of efficacy in migraine prophylaxis. Significant reduction in headache days was reported in a study at a dose of 150 mg / day while a dose of 75 mg /day was ineffective[49]. Another study reported

venlafaxine and amitriptyline to have similar efficacy in reducing headache frequency[46] at doses of 150 mg and 75 mg respectively but the latter group had more side effects. Adverse effects included nausea with VLF and hypersomnia, poor concentration with AMT.

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers

The 2012 AHS/AAN guidelines have recommended lisinopril and candesartan as level C drugs in the prevention of episodic migraine, as the trials are not robust. These were not recommended in the 2000 guidelines as there were no studies but in the past decade there have been three studies published, one each for candesartan, lisinopril and telmisartan. Lisinopril[50] and candesartan[51] were possibly effective while telmisartan[52] was ineffective.

Triptans

Frovatriptan, zolmitriptan and naratriptan are efficacious in the short-term prevention of menstrual migraine. The triptan is started 2-3 days before the menstrual period or expected onset of menstrual migraine and continued for 5-6 days and stopped. This prevents migraine occurring at menses only.

Two class 1 trials established the efficacy of frovatriptan[53,54] in preventing menstrual migraine. A dose of 2.5 mg twice daily after a loading dose of 10 mg was used in the studies. In another Class 1 study the number of migraine days and perimenstrual migraines were reduced in patients receiving oral naratriptan 1 mg twice daily for 5 days commencing 2 days before menses onset[55]. Zolmitriptan 2.5 mg twice daily or three times daily significantly decreased the frequency of mens-trually related migraine, however there was no advantage in the three times daily dosing over the twice daily dosing[56].

Onabotulinumtoxin A

Onabotulinumtoxin A is currently being used as prophylaxis for chronic migraine, defined as 15 or more headache days per month, with 4 or more headache hours per day[57]. Cost remains a potential barrier to its use. The clinical effect of onabotulinumtoxin A may be delayed or transient after the first set of injections and a second set of injections is warranted before concluding that the therapy is unhelpful. Repeat injections, initially every 3 months, are usually required to maintain benefit.

Conclusion

When selecting an appropriate drug for prevention of migraine one should consider the frequency, severity and disability due to migraine. One should also consider the level of evidence for efficacy, adverse effect profile and patient comorbidities. Treatment failures can be due to various reasons including unrealistic expectations of the patient, poor drug compliance and overuse of acute medication in the treatment of migraine.

Based on current evidence the AAN/AHS guidelines and the EFNS guidelines recommend topiramate, sodium valproate, propranolol and metoprolol as first line drugs and atenolol, venlafaxine and amitriptyline as the second line drugs. The EFNS guidelines recommend flunarizine as a first line drug in addition to the ones mentioned in the AAN/AHS guidelines.

References

1. Headache Classification Committee of the International Headache Society. The International Classification of headache disorders, 3rd edition. *Cephalalgia* 2013; **33**: 629-808.
2. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. *Headache* 2007; **47**(3): 355-63.
3. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002; **58**(6): 885-94.
4. Bigal ME, Lipton RB, Winner P, et al. Migraine in adolescents: association with socioeconomic status and family history. *Neurology* 2007; **69**(1): 16-25.
5. Hernandez-Latorre MA, Roig M. Natural history of migraine? in childhood. *Cephalalgia* 2000; **20**(6): 573-9.
6. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med.* 1999; **159**(8): 813-8.
7. Sprenger T, Goadsby PJ. Migraine pathogenesis and state of pharmacological treatment options. *BMC Medicine* 2009; **7**: 71.
8. Sanchez-Del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. *Curr Opin Neurol* 2006; **19**(3): 294-8.
9. Evans S, Afra J, Frese A, et al. The EFNS guideline on the drug treatment of mograine (revised report of an EFNS task force). *European Journal of Neurology* 2009; **16**: 968-81.
10. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012; **78**: 1337-45.
11. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. *Neurol Sci.* 2008; **29** Suppl 1: S110-22.
12. National Institute for Health and Care Excellence (2012). Headaches – Diagnosis and management of headaches in young people and adults. CG 150. London: National Institute for Health and Care Excellence.

13. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia* 2002; **22**(7): 491-512.

14. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; **291**(8): 965-73.

15. de Tommaso M, Marinazzo D, Nitti L, Pellicoro M, Guido M, Serpino C, et al. Effects of levetiracetam vs topiramate and placebo on visually evoked phase synchronization changes of alpha rhythm in migraine. *Clinical Neurophysiology* 2007; **118**(10): 2297-304.

16. Diener HC, Tfelt-Hansen P, Dahlöf C, Lainez MJA, Sandrini G, Wang SJ, et al. Topiramate in migraine prophylaxis: results from a placebo-controlled trial with propranolol as an active control. *Journal of Neurology* 2004; **251**(8): 943-50.

17. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *Lancet Neurology* 2007; **6**(12): 1054-62.

18. Edwards KR, Glantz MJ, Norton JA, Cross N. Prophylactic treatment of episodic migraine with topiramate: a double-blind, placebo-controlled trial in 30 patients. *Cephalalgia* 2000; **20**(4): 316.

19. Gupta P, Singh S, Goyal V, Shukla G, Behari M. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). *Headache* 2007; **47**(3): 402-12.

20. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, et al. Topiramate intervention to prevent transformation of episodic migraine: the topiramate. INTREPID study. *Cephalalgia* 2011; **31**(1): 18-30.

21. Silberstein SD, Neto W, Schmitt J, Jacobs D, for the MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. *Archives of Neurology* 2004; **61**(4): 490-5.

22. Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001; **41**(10): 968-75.

23. Mei D, Capuano A, Vollono C, Evangelista M, Ferraro D, Tonali P, et al. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. *Neurological Sciences* 2004; **25**(5): 245-50.

24. Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. *Clinical Therapeutics* 2006; **28**(7): 1002-11.

25. Dodick DW, Freitag F, Banks J, Saper J, Xiang J, Rupnow M, et al. For the CAPSS-277 Investigator Group. Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clinical Therapeutics* 2009; **31**(3): 542-59.

26. Luo N, Di W, Zhang A, Wang Y, Ding M, Qi W, et al. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. *Pain Medicine* 2012; **13**(1): 80-6.

27. Ashtari F, Shaygannejad V, Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. *Acta Neurologica Scandinavica* 2008; **118**(5): 301-5.

28. Afshari D, Rafizadeh S, Rezaei M. A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. *International Journal of Neuroscience* 2012; **122**(2): 60-8.

29. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. *Headache* 2006; **46**(4): 642-8.

30. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010610. DOI: 10.1002/14651858.CD010610.

31. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992; **12**(2): 81-4.

32. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. *Neurology* 1994; **44**(4): 647-51.

33. Kinze S, Clauss M, Reuter U, Wolf T, Dreier JP, Einhaupl KM, et al. Valproic acid is effective in migraine prophylaxis at low serum levels: a prospective open-label study. *Headache* 2001; **41**(8): 774-8.

34. Mitsikostas DD, Polychronidis I. Valproate versus flunarizine in migraine prophylaxis: a randomized, double- open, clinical trial. *Functional Neurology* 1997; **12**(5): 267-76.

35. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010611. DOI: 10.1002/14651858.CD010611.

36. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010609. DOI: 10.1002/14651858.CD010609.

37. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD003225. DOI: 10.1002/14651858.CD003225.pub2.

38. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. *Neurology* 1972; **22**(4): 366-9.

39. Diener HC, Hartung E, Chrubasik J, et al. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. *Cephalalgia* 2001; **21**(2): 120-128.

40. Schellenberg R, Lichtenthal A, Wohling H, Graf C, Brixius K. Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? *Headache* 2008; **48**(1): 118-25.

41. Lucking CH, Oestreich W, Schmidt R, Soyka D. Flunarizine vs propranolol in the prophylaxis of migraine: two double- blind comparative studies in more than 400 patients. *Cephalalgia* 1988; **8**: 21-6.

42. Grotemeyer KH, Schlake HP, Husstedt IW, Rolf LH. Metoprolol versus flunarizine: a double blind crossover study. *Cephalalgia* 1987; **7**: 465- 6.

43. Saper JR, Silberstein SD, Lake AE 3rd, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache* 1994; **34**(9): 497-502.

44. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis. A comparison of propranolol and amitriptyline. *Arch Neurol* 1987; **44**: 486-9.

45. Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. *Headache* 1981; **21**: 105 -9.

46. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg.* 2004; **107**(1): 44-8.

47. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther* 2009; **31**(3): 542-59.

48. Keskinbora K, Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. *Clin Neurol Neurosurg* 2008; **110**(10): 979-84.

49. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; **45**(2): 144-52.

50. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001; **322**(7277): 19-22.

51. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003; **289**(1): 65-9.

52. Diener HC, Gendolla A, Feuersenger A, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. *Cephalalgia* 2009; **29**(9): 921-7.

53. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004; **63**(2): 261-9.

54. Brandes JL, Poole A, Kallela M, et al. Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. *Cephalalgia* 2009; **29**(11): 1133-48.

55. Newman L, Mannix LK, Landy S, et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double- blind, placebo-controlled study. *Headache* 2001; **41**(3): 248-56.

56. Tuchman MM, Hee A, Emeribe U, Silberstein S. Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. *CNS Drugs* 2008; **22**(10): 877-86.

57. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010; **30**(7): 793-803.

Case report

Multiphasic disseminating encephalomyelitis (MDEM)

Bimsara Senanayake[1]

Sri Lanka Journal of Neurology, 2013, **2**, 17-18

Index words: Acute disseminating encephalomyelitis (ADEM), Multiphasic disseminating encephalomyelitis (MDEM), Post chicken pox CNS demyelination

Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune mediated disease of the brain which usually follows a viral infection or vaccination[1]. However it could occur following other infections or spontaneously. Although it affects all age groups, most reported cases are in children and adolescents, with an average age around 5 to 8 years[2]. A full recovery is seen in 50 to 75% of cases; while up to 70 to 90% recover with some minor residual disability[3]. The average time to recover is one to six months. It produces multiple inflammatory lesions in the brain and spinal cord, particularly in the white matter. Usually these are found in the subcortical and central white matter and cortical gray-white junction of both cerebral hemispheres, cerebellum, brainstem, and spinal cord[4]. When the patient suffers more than one disseminated demyelinating episode, it is called recurrent disseminated encephalomyelitis (RDEM) or multiphasic disseminated encephalomyelitis (MDEM)[5,6]. Such a case of MDEM following chicken pox infection in a 20-year-old Sri Lankan patient is reported here. Relapsing remitting multiple sclerosis (RRMS) is the closest differential diagnosis. MR imaging findings and the clinical history makes RRMS less likely in this case.

Case history

A 20-year-old female developed lower limb weakness with a mid thoracic sensory level i.e. features compatible with transverse myelitis in February 2012. She suffered from chicken pox a week prior to this initial neurological deficit. She was unable to walk and was bed bound with no sphincter control. She was treated with intravenous steroid pulses to which she responded. However her cognitive skills were poor with occasional confusion, but seizures were not reported. The MRIs showed large bilateral subcortical and central white matter lesions which were not enhancing (Figure 1). Periventricular lesions were not a prominent feature. She was readmitted in April 2012 with weakness of lower limbs for which she again received treatment with IV methyl prednisolone. She gradually improved from this event and was discharged. In September 2012 she again developed right upper limb weakness followed by right lower limb weakness – a 'stroke like' event. She was re-admitted and imaged again. The right 'hemiplegia' again improved with IV methyl prednisolone therapy. Repeat MRI did not show any new lesions or GAD enhancement. Previous brain lesions were seen along with the cervical cord lesions and cord swelling. Visual evoked responses were bilaterally normal. Cerebro spinal fluid analysis too did not reveal any abnormality.

Figure 1. The MRI of the brain showing large bilateral subcortical and central white matter lesions which were not enhancing.

Discussion

Relapsing remitting multiple sclerosis (RRMS) and recurrent or multiphasic disseminated encephalomyelitis (MDEM) are considered different diseases[5]. However ADEM could be confused with the first episode of MS and RRMS needs to be considered in cases of MDEM. However they differ in 2 important ways[5].

a) MS occurs in people who are genetically vulnerable, a feature noticeably lacking in ADEM. ADEM is usually post infectious or post vaccination

b) Even more importantly the sharp edges of the typical MS lesion have been recognized by neuropathologists as pathognomonic for MS; not described in ADEM

[1] *Institute of Neurology, National Hospital of Sri Lanka.*

In a study comparing children with ADEM/MDEM complex with those with MS some features **were, more commonly seen with ADEM/MDEM group**[6],

1. A pre-demyelinating infectious disease
2. Encephalopathy
3. Polysymptomatic presentation
4. Seizures – favoring a diagnosis of ADEM
5. Blood leucocytosis

MRI showed that subcortical white matter lesions were almost universal in both groups, though peri ventricular lesions were more common in multiple sclerosis. Follow-up MRI revealed complete or partial lesion resolution in 90% and no new lesions in the ADEM/ MDEM group. It has been demonstrated that relapses may occur immediately after ADEM. If these relapses are thought to represent part of the same acute monophasic immune process, the term 'multiphasic disseminated encephalomyelitis' (MDEM) is used.

MRI imaging is the most useful tool so far to differentiate RRMS from MDEM in the absence of any specific biomarker. In ADEM/MDEM, FLAIR sequence and T_2-weighted images show abnormalities than in T_1-weighted images. The lesions were predominantly in the white matter. Absolute and relative sparing of the peri ventricular white matter occurred in 56 and 78% of images, respectively. Involvement of the deep and subcortical white matter was nearly universal. The supra tentorial white matter lesions were universally asymmetrical. In MS T_2- images demonstrated the lesions best. A large majority of patients have periventricular lesions. The lesions were also prevalent throughout the subcortical white matter (92% of images). No patients had any cortical grey matter involvement. The thalami and basal ganglia were involved infrequently (25 and 8%, respectively). Fifty-eight per cent of the images had at least one lesion over 1 cm in size.

Post infectious acute disseminating encephalomyelitis with recurrent symptoms and CNS demyelination should be differentiated from RRMS. ADEM/MDEM complex generally has a good long term prognosis.

References

1. Garg RK. "Acute disseminated encephalomyelitis". *Postgrad Med J* 2003; **79**(927): 11-7.
2. Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ. "Clinical and neuro radiologic features of acute disseminated encephalomyelitis in children". *Neurology* 2001; **56**(10): 1308-12.
3. Menge T, Kieseier BC, Nessler S, Hemmer B, Hartung HP, Stüve O. "Acute disseminated encephalomyelitis: an acute hit against the brain". *Curr Opin Neurol* 2007; **20**(3): 247-54.
4. Wingerchuk DM. "Post infectious encephalomyelitis". *Curr Neurol Neurosci Rep* 2003; **3**(3): 256-64.
5. Poser CM. "Multiple sclerosis and recurrent disseminated encephalomyelitis are different diseases". *Arch Neurol* 2008; **65**(5): 674; author reply 674-5.
6. Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG (December 2000). "Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children". *Brain* 2000; **123**(12): 2407-22.

Case report

The little old adie pupil

H P M C Caldera[1], **I K Gooneratne**[1], **R Gamage**[1]

Sri Lanka Journal of Neurology, 2013, **2**, 19-20

Introduction

The Holmes-Adie pupil (HAP) consists of tonic pupil/s of unknown aetiology. When HAP is associated with arreflexia of lower limbs it is called Homes-Adie's syndrome (HAS)[1]. When HAS is associated with hypohidrosis it is called Ross Syndrome, although some consider it as a variant of HAS[2]. When there is bilateral tonic pupil and arreflexia it is important to differentiate whether the tonic pupils are due to HAS or peripheral neuropathy.

Case report

A 56-year-old previously healthy female presented with dull right sided headache without sinister features for three days. She was reviewed in the neurology clinic 2 weeks later. She had anisocoria with right pupil 4 mm in size and the left 6 mm. Both pupils reacted poorly to light and slowly reacted to accommodation (Figure 1A, B & C). In the left pupil sector palsy was noted and segmental vermiform movements were noted on slit lamp examination and local pathology in the iris and anterior chamber was excluded. Patient's eye movements were full and ophthalmoscopy revealed normal discs with intact venous pulsations. Rest of the cranial nerve examination and the general neurological examination were normal except for absent ankle jerks. The patient did not have hypohidrosis or other autonomic manifestations.

Diluted (0.125%) pilocarpine constricted both pupils (Figure 1D). Fasting blood sugar, full blood count, blood picture, renal and liver function panel, thyroid function test, erythrocyte sedimentation rate, anti nuclear antibody test, magnetic resonance imaging of the brain with magnetic resonance angiogram and nerve conduction study of the lower limbs were all normal.

Discussion

Headache with dilated pupil is usually considered as a sinister sign. This patient did not have any other features to suggest a sinister headache. Her eye movements were full and there was no ptosis. Isolated pupilary abnormality as a manifestation of oculomotor nerve palsy is an extremely rare occurrence without diplopia, squints or ptosis[3].

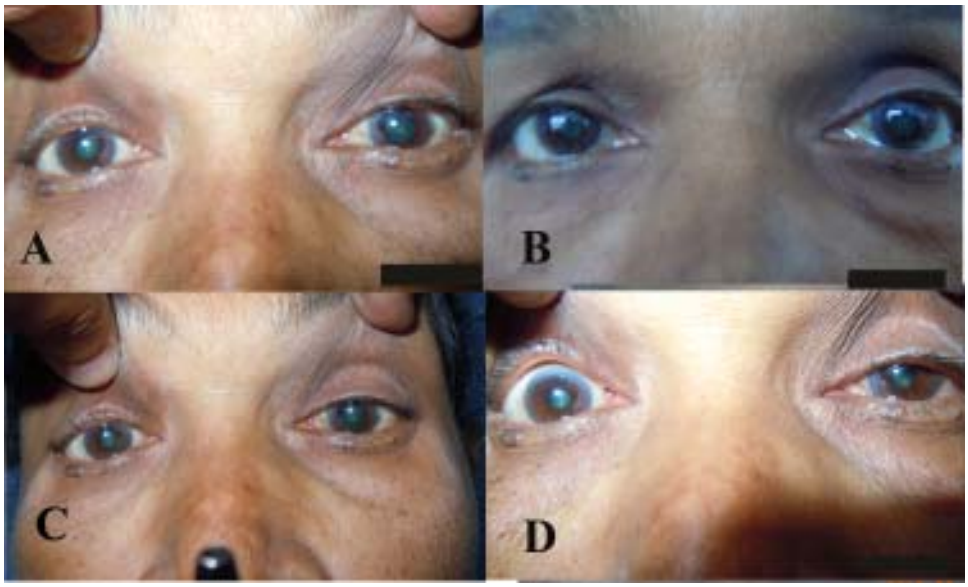


Figure 1. A: Pupils in light, B: Pupils in dim light, C: Pupils in accommodation, D: Pupils after diluted pilocarpine.

[1] *Institute of Neurology, National Hospital of Sri Lanka.*

When pupillary sizes differ more than 0.4 mm, it confirms anisocoria. To localize the abnormal pupil one can consider examination of the pupils in dim light which did not cause any change in size of the pupils in our patient (Fig 1B). Both pupils poorly reacted to light and slowly constricted to accommodation. There are a few causes to be considered in Light-Near dissociation (LND) syndromes such as Adie tonic pupil, Parinaud dorsal midbrain syndrome, Argyll Robertson pupils, oculomotor nerve aberrancy and peripheral neuropathy[4]. Argyll Robertson pupils are bilateral small pupils and are not keeping with this patient's findings. She did not have clinical features to suggest Perinaud syndrome or oculomotor nerve aberrancy. Segmental paralysis (sector palsy) of the iris sphincter with intact segments cons-tricting to light with vermiform movements observed on slit lamp examination in the absence of structural iris damage confirms postganglionic oculo-parasym-pathetic lesion and excludes a third nerve palsy in our patient[5].

Adie tonic pupil is caused by a lesion in the post-ganglionic parasympathetic pathway which is the ciliary ganglion or short ciliary nerves in the orbit. There are various aetiologies recognized such as trauma, tumour, ischemia, autoimmune, infection and idiopathic[6]. In the acute stage of the disease both iris sphincter and the ciliary muscle are paralyzed. The pupil does not react to light or accommodation initially. At this stage there may be photophobia, brow ache and blurring during near vision[6].

As in many denervated end organs the iris sphincter also develops denervation supersensitivity usually in about one week. Diluted pilocarpine (0.125%) would constrict the denervated pupil but not the normal at this stage. A positive response is considered as either the effected pupil constricts 0.5 mm more than the normal pupil or the relatively larger abnormal pupil becomes the smaller pupil after the instillation[6]. In our patient both pupils constricted to pilocarpine and confirmed bilateral denervated hypersensitivity. Diluted pilocarpine test is neither specific nor particularly sensitive for Adie Pupil. This test also becomes positive in preganglionic denervation that is seen in oculomotor nerve palsy[7]. Cholinergic supersensitivity is absent in about 20% of tonic pupils[6].

After the acute denervation, short ciliary nerve fibers tend to reinnervate to reach their end organs. During this process, resprouting accommodative fibers innervate the ciliary muscle and improve near vision. Relative abundance of accommodative fibers in comparison to pupiloconstrictor fibers results in aberrant reinnervation of the iris sphincter and restores the pupil near response in a few weeks. However the constriction movement and re-dilatation after a near effort is slow and it is called a tonic pupil. Because of the relative deficiency of pupiloconstrictor fibers, light reflex never improves. Due to the tonic firing of the accommodative fibers, baseline size of the Adie pupil reduces with time and become the smaller pupil ("Little old Adie") which was seen in the right pupil of this patient.

With clinical features of bilateral absent ankle jerks, Holms Adie Syndrome was considered in our patient. Although the nerve conduction test was normal small fiber neuropathy could not be excluded. When a patient present with unilateral tonic pupil and arreflexia who is otherwise healthy the diagnosis of HAS is straightforward. However our patient had bilateral tonic pupils with arreflexia which could be due to HAS or peripheral neuropathy in which it is utmost important to rule out the possibility of peripheral neuropathy causing the tonic pupils since HAS is a benign condition. A large European study (140 patients) with bilateral tonic pupils demons-trated that presence of sector palsy, anisocoria more than 1mm in light giving specificity (89.7%) to HAS and LND further increase the specificity to 92.3%. HAS affects one pupil first and may involve the fellow pupil often years later which makes anisocoria significant, where as the peripheral neuropathy affects both pupils together[8]. In HAS involvement of the fellow pupil is at a rate of 4% per year[4]. However bilateral tonic pupil at the initial presentation is rare and results in a diagnostic challenge. Presence of all these features in our patient led to a diagnosis of HAS. HAS remains a benign condition and patients do not progress to develop generalized neuropathy although the arreflexia would be permanent[8]. Refractory correction and pilocarpine eye drops for the dilated eye can be considered to correct the near vision.

References

1. Adie WJ. Tonic pupils and absent tendon reflexes. A benign disorder sui generis: its complete and incomplete forms. *Brain* 1932; **55**: 98-113.
2. Ross AT. Progressive selective sudomotor degeneration. *Neurology* 1958; **8**: 809-17.
3. Batleson JD, Trautmann JC, Sundt TM Jr. Minimal Oculomotor nerve paresis secondary to unruptured intracranial aneurysm. *Arch Neurol* 1986; **43**(10): 1015-20.
4. Wolintz RJ. Isocoric pupil dysfunction. CONTINUUM: Lifelong Learning in Neurology. *Neuro-Ophthalmology* 2009; **15**(4): 213-17.
5. Kardon RH, Corbett JJ, Thompson HS. Segmental denervation and reinnervation of the iris sphincter as shown by infrared videographic transillumination. *Ophthalmology* 1998; **105**(2); 313-21.
6. Kawasaki A. Anisocoria. CONTINUUM: Lifelong Learning in Neurology. *Neuro Ophthalmology* 2009; **15**(4): 218-35.
7. Jacobson DM, Vierkant RA. Comparison of cholinergic supersensitivity in third nerve palsy and Adie's syndrome. *J Neuroohthalmol* 1998; **18**(3): 171-5.
8. Bremner FD, Smith SE. Bilateral tonic pupils: Holmes-Adie syndrome or generalised neuropathy? *Br J Ophthalmol* 2007; **91**: 1620-3.

Case report

Cortical-hand syndrome

Uditha Dassanayake[1], **Thashi Chang**[1,2]

Sri Lanka Journal of Neurology, 2013, **2**, 21-22

Abstract

Isolated hand weakness (the cortical-hand syndrome) is a well-recognised, but rare presentation of stroke. The lesion has been isolated to the 'precentral knob' of the motor cortex of the brain. An embolic stroke mechanism has been considered the most frequent cause. The prognosis for recovery of hand function is considered good. A clinical diagnosis is imperative to decide on appropriate investigations and treatment. We describe a middle-aged man who presented with sudden-onset, isolated, global weakness of his left hand with a corresponding cortical infarct to illustrate the key clinical and radiological features in the diagnosis of the cortical-hand syndrome.

Index words: isolated hand weakness, monoparesis, cortical-hand

Introduction

The term 'pseudo-peripheral palsy' was first coined by Lhermitte in 1909 to describe the predominant weakness of fingers following a stroke[1]. The isolated paralysis of a limb following a cerebrovascular event can produce considerable diagnostic difficulty on first contact, especially as it is not universally recognized as a distinct stroke syndrome. Reports estimate that only less than 1% of ischemic strokes present with isolated upper limb weakness[2]. The pattern of weakness may be global, ulnar-predominant or radial-predominant[3]. The syndrome is usually caused by infarcts involving the motor control area for the hand (the 'knob') in the precentral gyrus[4]. However, lacunar infarcts and small intracerebral haemorrhages have also been found to present with isolated hand weakness in some cases[5].

Case presentation

A 57-year-old, right-handed man, with a background history of poorly-controlled diabetes mellitus, presented with an acute-onset isolated weakness of his left hand, which he noticed when he was unable to pick up a glass of water during a meal. The weakness was not progressive, but had remained static for over eight hours. There was no pain or numbness of the hand, no facial asymmetry, and the other limbs including his proximal left upper limb were functioning normally. He had no previous episodes of weakness or sensory loss, and no symptoms pertaining to his cervical spine.

On examination, he was found to be alert with no cognitive impairment and normal cranial nerve functions. There was MRC grade 2/5 weakness of all movements of his left hand below the wrist. The left shoulder and elbow power was MRC grade 5/5. The hand weakness was global and not localized to a single nerve distribution. The upper limb reflexes were normal and there was no associated sensory loss. The lower limbs were normal except for a stocking type sensory loss and diminished ankle reflexes, attributable to diabetic neuropathy. His general and other systemic examinations were normal; blood pressure was 160/90 mmHg.

Non-contrast computed tomography (CT) of the brain done ten hours after the onset of symptoms did not show any significant focal lesions. However, diffusion-weighted imaging of the brain showed a well-circumscribed, acute infarct in the right precentral gyrus (Figure 1). There was no significant stenosis of the internal carotid arteries on duplex scan, and the intracranial cerebral vessels were normal on MR angiogram. His ECG and echocardiogram were normal. Blood investigations including blood counts, liver and renal functions were normal but his HbA1c was 10.2% and his blood lipids were elevated.

He was treated with aspirin, atorvastatin and in addition to increasing the oral anti-diabetic medication. He was discharged from hospital six days after admission with improving hand and finger movements (MRC 3/5). On review two weeks later, his hand functions had further improved with a muscle power of 4/5.

Discussion

Isolated hand weakness due to stroke (the cortical-hand syndrome) is infrequently observed, and often misdiagnosed as peripheral nerve lesions. The acute onset, the global weakness involving median, ulnar and radial nerve movements in the hand and the absence of sensory signs, as illustrated in our patient, would favour a cortical-hand syndrome over a peripheral nerve lesion.

[1] *University Medical Unit, National Hospital of Sri Lanka, Colombo,* [2] *Department of Clinical Medicine, University of Colombo, Sri Lanka.*

Indeed, the diagnosis would have been mostly clinical before the advent of magetic resonance imaging (MRI) since CT scans are negative in up to 40% of patients presenting with monoparesis[6]. Diffusion-weighted magnetic resonance imaging is the most sensitive diagnostic investigation for a small acute infarct (Figure 1).

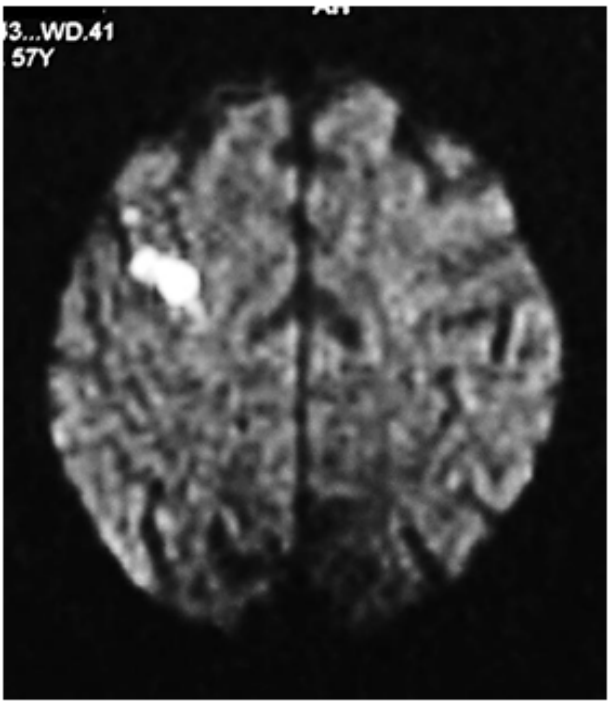


Figure 1. Diffusion-weighted magnetic resonance image of the brain showing an acute infarct in the right motor cortex.

The lesion in cortical-hand syndrome has been localised to an area in the precentral gyrus that is responsible for motor control of the hand. Functional MRI studies have identified this area as a knob-like structure in the precentral gyrus (the 'precentral knob') that appears shaped like an omega on axial scans of brain MRI[4]. However, it has been suggested that finger movements are controlled by a highly distributed network rather than by functionally and spatially discrete groups of neurons controlling each finger[7].

In most cases of cortical-hand syndrome, a potential source of embolization had been recognised[8], making it an important diagnosis to consider in view of treatment and secondary preventive measures. Although the underlying aetiology and the co-existent vascular risk factors would contribute to the outcome, the prognosis for recovery of hand function is generally considered good[9].

Our case report illustrates the key clinical features that would suggest the diagnosis in this uncommon presentation of stroke and highlights the importance of its diagnosis in terms of deciding appropriate investigations and treatment.

References

1. Lhermitte J. De la valeur semiologiqué des troubles de la sensibilité a` disposition radiculaire dans les lesions de l'encéphale. *Sem Méd* 1909; **24**: 277.
2. Castaldo J, Rodgers J, Rae-Grant A, et al. Diagnosis and neuroimaging of acute stroke producing distal arm monoparesis. *Journal of Stroke and Cerebrovascular Disease*s 2003; **12**(6): 253-8.
3. Chen PL, Hsu HY, Wang PY. Isolated hand weakness in cortical infarctions. *Journal of the Formosan Medical Association* 2006; **105**(10): 861-5.
4. Yousry TA, Schmid UD, Alkadhi H, et al. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 1997; **120**: 141-57.
5. Paciaroni M, Caso V, Milia P, et al. Isolated monoparesis following stroke. *Journal of Neurology, Neurosurgery, and Psychiatry* 2005; **76**(6): 805-7.
6. Melo TP, Bogousslavsky J, van Melle G, Regli F. Pure motor stroke: a reappraisal. *Neurology* 1992; **42**(4): 789-95.
7. Schieber MH, Santello M. Hand function: peripheral and central constraints on performance. *Journal of Applied Physiology* 2004; **96**(6): 2293-300.
8. Pikula A, Stefanidou M, Romero JR, Kase CS. Pure motor upper limb weakness and infarction in the precentral gyrus: mechanisms of stroke. *Journal of Vascular and Interventional Neurology* 2011; **4**(1): 10-13.
9. Alstadhaug KB, Sjulstad A. Isolated hand paresis: a case series. *Cerebrovascular Diseases Extra* 2013; **3**(1): 65-73.

Case report

Nummular headache

Tissa Wijeratne[1], **Dilani Wijeratne**[2]

Sri Lanka Journal of Neurology, 2013, **2**, 23-24

Introduction

Nummular headache (NH) was first described in 2002 by Pareja et al[1]. The term "nummular" was taken from the Latin "nummus" meaning 'coin'. Nummular headache is also known as coin shaped cephalgia. In 2004, NH was included in the research diagnostic criteria of the International Classification of Headache Disorders, 2nd edition (ICHD- 2)[2]. The diagnostic criteria for NH were updated in the current ICH 3 beta classification, which is in press (available on line)[3]. We present a 26-year-old woman who presented to us with the classic features of nummular headache and review the literature in this rare primary headache disorder.

Case history

A 26-year right-handed woman started suffering from focal head pain since January 2013. The painful area was perfectly circular with the diameter of about five cm in the right parietal region. She described the pain as moderately severe, pressure like pain which was continuous with the intensity fluctuating[2,3]. The pain was not specifically worse in the morning. There was no exacerbation with laughing, coughing, sneezing or straining. There were no positive constitutional symptoms in her history. Her clinical neurological examination was unremarkable. MRI, MRV, MRA brain was unremarkable. Her blood tests, electrocardiography, psychiatric tests (assessed by the second author) were unremarkable.

Clinical diagnosis of NH was made and detailed explanation was given to the patient. Her main concern of something sinister in her brain was alleviated through the diagnosis and reassurance. Simple analgesics (Ibuprofen 400 mg, prn) were used intermittently. Patient is stable with occasional symptoms in her right parietal region, which does not disturb her daily life at present.

Pareja et al described the first series of patients with NH in 2002. NH was described as a chronic, mild to moderate, pressure like pain in a circumscribed cranial area of approximately 2 to 6 cm diameter in his paper consisting of 13 patients. Head pain was exclusively affecting a circumscribed cranial area. Headache had a benign process with unknown origin[1].

NH presents a typical clinical picture of chronic pain that is exclusively felt in a round or oval area of the surface of the head, usually 2-6 cm diameter. It is usual for the symptomatic area to remain unchanged in size and shape. Exact etiology of NH is not known. Pareja et al raised the possibility that NH is a headache probably arising from epicranial structures[4].

In a series of 59 patients with NH, five patients had associated trophic changes on the site of the pain[4]. Four of these patients were women. They were 65, 50, 59 and 32 years of age respectively. The fifth patient with trophic changes was a man. He was 59 years old. All five patients had pain localized to the right parietal region. All five patients had sensory dysfunction such as hyperalgesia, paraestheisa on the site. Skin depression was the commonest trophic change, which was noted on all five patients. Three patients had hair loss on the site. Local temperature was increased in three patients. Color change was also observed on the same three patients. These three patients underwent skin biopsy with no specific changes seen. These findings suggest that the clinical spectrum of NH is likely to be a peripheral headache syndrome[1, 4-7].

In one hospital series, incidence of NH was 6.4/ 100,000 per year[7]. A further study 8 in general neurology outpatients, 1.25% of all patients with headaches had NH. In a large series of 72 patients with NH from Spain showed female predominance with a mean age of onset around 40 years with a slight occipital predominance[9,10]. NH seems to be a local pain disorder with peripheral sensitization localized to the site. Sensory symptoms and signs such as spontaneous pain, paroxysmal pain, trophic changes, evoked pain has been described in NH[11].

In many patients with NH a simple explanation of the benign nature of the headache is adequate with no specific treatment. Some patients may need standard dose of simple analgesics such as in our case we described here.

There are patients with NH with inadequate response to analgesics who may benefit from preventative therapy. Large case series from Spain confirmed 58% of their series were prescribed with a preventative medication[10]. Gabapentin was the most prescribed drug in this series. There are no clear guidelines on use of preventative therapy in NH.

Botulinum toxin type A has been used in small number of cases with successful outcome[12,13]. Carba-

[1] *Department of Neurology, Western Hospital and University of Melbourne, Footscray, Victoria 3011, Australia,* [2] *Department of Psychiatry, Adult Inpatient Unit, Austin Hospital, Heidelberg, Victoria, Australia.*

mazepine, Indomethacin, Topiramate have also been used with successful results in some patients in the past[11,14,15].

Table 1. IHS diagnostic criteria for nummular headache

Previously used term:

Coin- shaped headache

Description

Pain is of a highly variable duration, but often chronic, in a small circumscribed area of the scalp in the absence of structural lesion.

Diagnostic criteria

A. Continuous or intermittent head pain fulfilling criterion B
B. Felt exclusively in an area of sclap, with all of the following four characteristics
    1. Sharply contoured
    2. Fixed in size and shape
    3. Round or elliptical
    4. 1-6 cm in diameter
C. Not better accounted for by another ICHD-3 diagnosis

Comments

The painful area may be localized in any part of the scalp, but usually in the parietal region. Rarely 4.8 *Nummular headache* is bi- or multifocal, each symptomatic area retaining all the characteristics of nummular headache. Pain intensity is generally mild to moderate, but occasionally severe. Superimposed on the background pain, spontaneous or triggered exacerbation may occur. Duration highly variable: in up to 75% of published cases, the disorder has been chronic (present for longer than 3 months), but cases have also been described with duration of seconds, minutes, hours or days.

The affected area commonly shows variable combination of hypaesthesia, dysaesthesia, paraesthesia, allodynia and /or tenderness.

Other causes, in particular structural and dermatological lesions, must be excluded by history, physical examination and investigation

(**With permission from: International Headache Society. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*: an international journal of headache 2013;33:629-808.)**

References

1. Pareja JA, Caminero AB, Serra J, et al. Numular headache: a coin-shaped cephalgia. *Neurology* 2002; **58**: 1678-9.
2. Headache Classification Subcommittee of the International Headache S. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. An International Journal of Headache 2004; **1**: 9-160.
3. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. An International Journal of Headache 2013; **33**: 629-808.
4. Pareja JA, Cuadrado ML, Fernandez-de-las Penas C, Nieto C, Sols M, Pinedo F. Nummular headache with trophic changes inside the painful area. *Cephalalgia*. An International Journal of Headache 2008; **28**: 186-90.
5. Pareja JA, Montojo T, Alvarez M. Nummular headache update. *Current Neurology and Neuroscience Reports* 2012; **12**: 118-124.
6. Pareja JA, Pareja J. Nummular headache: diagnosis and treatment. *Expert Review of Neurotherapeutics* 2003; **3**: 289-92.
7. Pareja JA, Pareja J, Barriga FJ, et al. Nummular headache: a prospective series of 14 new cases. *Headache* 2004; **44**: 611-614.
8. Guerrero AL. Representation of the nummular headache in general consultation in neurology. *Neurologia* 2008; **23**: 474.
9. Grosberg BM, Solomon S, Lipton RB. Nummular headache. *Current Pain and Headache Reports* 2007; 11: 310-12.
10. Guerrero AL, Cortijo E, Herrero-Velazquez S, et al. Nummular headache with and without exacerbations. Comparative characteristics in a series of 72 patients. *Cephalalgia*. An International Journal of Headache 2012; **32**: 649-53.
11. Ruscheweyh R, Buchheister A, Gregor N, Jung A, Evers S. Nummular headache: six new cases and lancinating pain attacks as possible manifestation. *Cephalalgi*a. An International Journal of Headache 2010; **30**: 249-53.
12. Alvaro LC, Garcia JM, Areitio E. Nummular headache: a series with symptomatic and primary cases. *Cephalalgia*. An International Journal of Headache 2009; **29**: 379-83.
13. Mathew NT, Kailasam J, Meadors L. Botulinum toxin type A for the treatment of nummular headache: four case studies. *Headache* 2008; **48**: 442-7.
14. Moon J, Ahmed K, Garza I. Case series of sixteen patients with nummular headache. *Cephalalgia.* An International Journal of Headache 2010; **30**: 1527-30.
15. Baldacci F, Nuti A, Lucetti C, Borelli P, Bonuccelli U. Nummular headache dramatically responsive to indomethacin. *Cephalalgia*. An International Journal of Headache 2010; **30**: 1151-2.

Case report

A stroke mimic

G N N Fernando[1], L J Jayaweera[1], B M T P Nawasiwaththa[1], S Bandusena[1], P S Gunarathna[1]

Sri Lanka Journal of Neurology, 2013, **2**, 25-26

Abstract

Cryptococcal meningitis (CM) is an invasive mycosis with high morbidity and mortality. If unsuspected, particularly in immune-competent individual, delayed diagnosis may lead to poor outcome. High prevalence of tuberculous meningitis which shares similar clinical manifestations, further results in delayed diagnosis of CM. Stroke is a known complication of CM. Nevertheless, infection as a cause of stroke is poorly appreciated. We report a case of cryptococcal meningitis complicated by stroke to emphasize the complexities of management and value of early diagnosis for better outcome.

Case report

A 44-year-old, previously well man, presented with headache, and low grade fever for one month. He developed a generalized tonic clonic seizure on admission. In the recent past he has had an aviary of love birds for 2 years and has abandoned it as all birds died about 6 months back. Additionally, he handled chicken excreta as a fertilizer at his home cultivation.

He was febrile and had neck stiffness. He was alert and rational. There were no focal neurological signs. His cerebrospinal fluid analysis (protein 96 mg/dl, sugar 2.4 mg/dl, neutrophils 80/mm^3, lymphocytes 330/mm^3) and the leptomeningeal enhancement of the MRI brain with gadolinium contrast supported tuberculous meningitis. He was commenced on Anti Tuberculous Therapy (ATT) and oral prednisolone and made a gradual but partial recovery.

Two weeks later he suddenly deteriorated and developed double vision, unsteady gait and slurring of speech. He remained febrile with nuchal rigidity and Glasgow coma scale was 13 /15. Pupils were unequal, had R/S gaze palsy, and an ataxic gait with normal limb power. Over next 24 hours his GCS deteriorated to 6 /15 and developed right sided hemiparesis. CT scan of brain showed multiple bilateral infarctions. Repeat MRI brain showed basal patchy meningeal enhancement worse than previously and multiple bilateral infarctions including in the cerebellum and left internal capsule.

Repeat CSF examination showed predominant polymorphs (protein 89mg/dl, polymorphs 100/mm^3, lymphocytes 30/mm^3). TB screening, fungal and bacterial studies were repeatedly negative. His cardiovascular risk factor assessment was unremarkable. CSF for cryptococcal antigen became positive with a titer of 1:100 with a subsequent positive culture. The diagnosis of cryptococcal meningitis was made and IV amphotericin was commenced following which the patient made a dramatic recovery. Investigations ruled out HIV and other immunodeficiency states. In 6 months he had no residual disability.

Discussion

This case report highlights the complexities involved with arriving at the early definitive diagnosis of chronic meningitis particularly in resource constraint settings. TB meningitis is the leading cause of chronic meningitis in Sri Lanka. Low sensitivity of specific laboratory investigations has made it a diagnosis made with high assumption. Hence the patient was commenced on ATT. Detecting organism in CSF on direct examination with India ink and isolating in culture are the locally available tests for definitive diagnosis of CM. However, India ink staining would be falsely negative in about 50% particularly if concentration of fungi are low as well as due to variation in the thickness of the capsule which is demonstrable as an unstained rim around[1]. Delay in culturing the organism has made it least helpful for therapeutic decision making. Further, 20-40 ml CSF sampling is required for culture.

When he deteriorated further, his CSF India ink stain remained negative and culture reports were not available. Soluble cryptococcal antigen detection by agglutination on latex particle which became positive is highly sensitive up to 92-98%[2,3]. As such, the reported case highlights the need for investigations with high specificity and sensitivity in investigating chronic meningitis. Contact history of birds supported the diagnosis of cryptococcal meningitis, but specific therapeutic interventions become possible only once the definitive diagnosis is established.

Many CNS infections including TB, syphilis, aspergillus meningitis are known to be complicated by

[1] *Institute of Neurology Unit 2, National Hospital of Sri Lanka, Colombo.*

stroke caused by vasculitis[4]. TBM was associated with cerebral infarctions in 47% and cryptococcal meningitis in 32%[5] suggesting CNS infections as an important cause of infarctions particularly in developing countries.

Conclusion

The case highlights the need to pursue cryptococcal meningitis as a differential diagnosis of tuberculous meningitis. Availability of highly specific and sensitive investigations will help in early diagnosis and having a better outcome. Further, it brings to light infections as an important cause of stroke in developing countries.

References

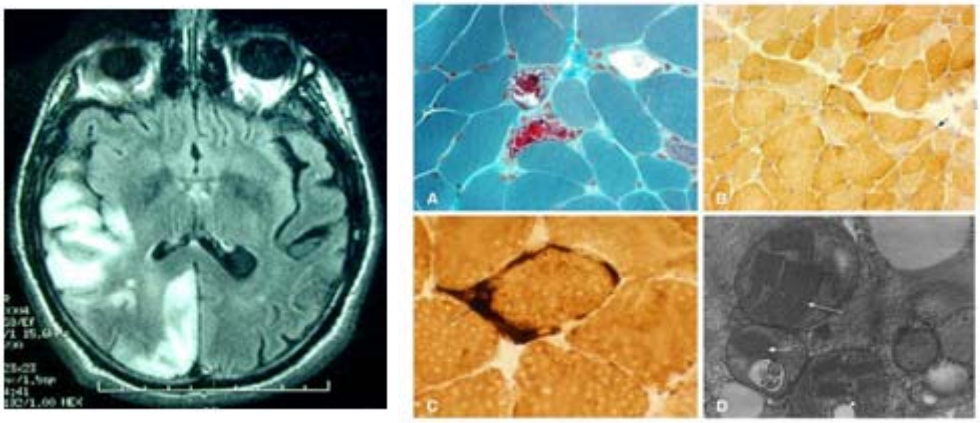
1. Allan H Ropper, Martin A Samuels, In: Adams and Victor, Principles of Neurology, 9th edition, McGraw Hill, 2009; **32**: 700-1.
2. Piens MA, Bianchi M, Prat C, Persat F, Mojon M. Detection of cryptococcal antigen in human serum. *Med Mycol Med* 1996; **6**: 123-8.
3. Mehrenberger M, Kamar N, Borde JS, et al. Vertigo after renal transplantation: a sign of pauci symptomatic cryptococcal meningitis. *Exp Clin Transplant* 2006; **4**: 525.
4. Allan H Ropper, Martin A Samuels, In: Adams and Victor, Principles of Neurology, 9th edition, McGraw Hill, 2009; **32**: 747.
5. Lan SH, Chang WN, Lu CH, Lui CC, Chang HW. Cerebral infarction in chronic meningitis: a comparison of tuberculous meningitis and cryptococcal meningitis. *Q J Med* 2001; **94**: 247-53.

Picture quiz

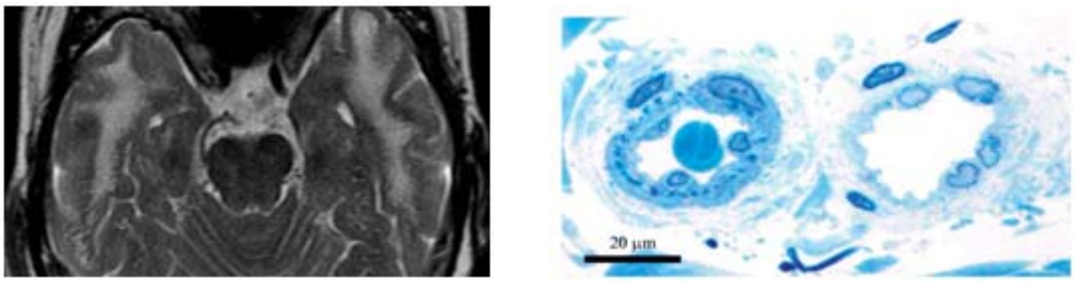
Stroke

Sri Lanka Journal of Neurology, 2013, **2**, 27-28

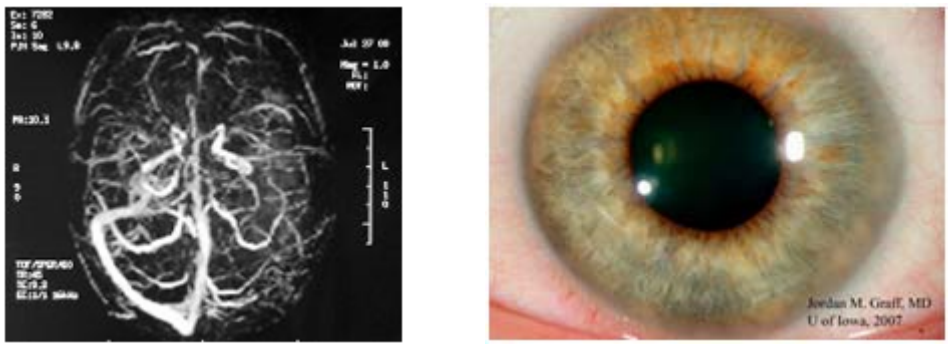
1. This 25-year-old patient presented with a stroke. MRI brain and muscle biopsies are shown. What is the diagnosis?



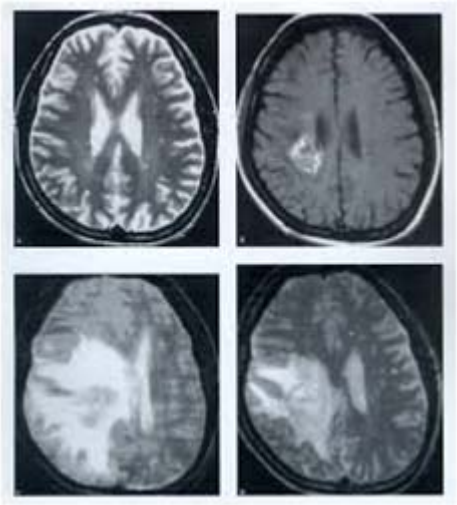
2. This 40-year-old man presented with a stroke. He gave a history of a previous stroke 2 years back and had been having frequent headaches. MRI brain and skin biopsy are shown. What is the diagnosis?

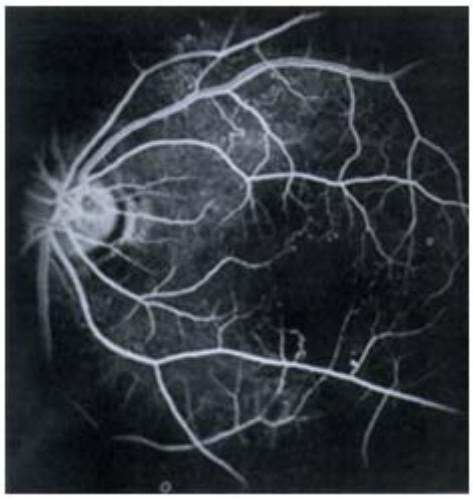


3. This 30-year-old female presented with acute hemiparesis. She was also found to have peripheral neuropathy, recent onset vertigo and hearing impairment. What is the unifying diagnosis?

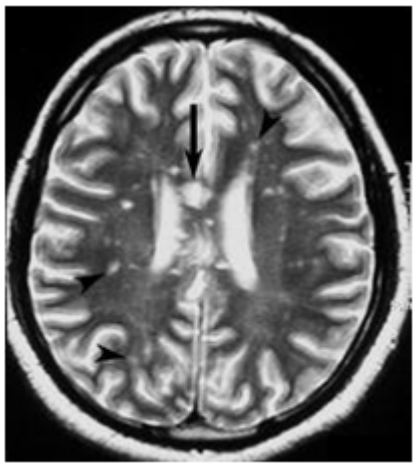


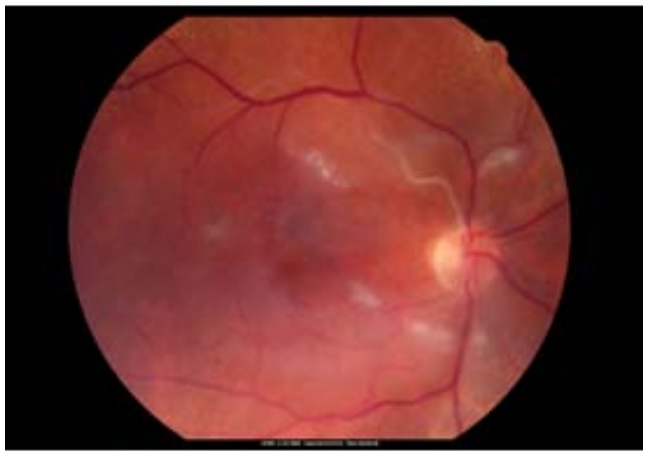
4. Given is the MRI finding and retinal arteriogram of a 50-year-old male who presented with proteinuria and progressive renal impairment. He developed a stroke 2 days ago. What is the unifying diagnosis?





5. Below are the fundal photograph and MRI scan of a 40-year-old woman who presented with right arm weakness and abnormal behavior for the past one week. She has lost her hearing in the left ear 4 weeks back. What is the unifying diagnosis?





(Answers on page 32

Guidelines to authors

Sri Lanka Journal of Neurology, 2013, **2**, 29-31

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.

Leading articles and reviews

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.

Perspectives and points of view

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).

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.

Previous publication of some content of a paper does not necessarily preclude it being published in the *SLJN*, but the editors need this information when deciding how to make efficient use of space in the Journal, and regard failure of a full disclosure by authors of possible prior publication as a breach of scientific ethics.

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.

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.

Peer review

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.

Editorial board

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.

Preparation of manuscript

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.

References

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, 2013, **1**, 32

1. **Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes** – abbreviated to MELAS – is one of the family of mitochondrial cytopathies, which also include MERRF, and Leber's hereditary optic neuropathy. It was first characterized under this name in 1984. A feature of these diseases is that they are caused by defects in the mitochondrial genome which is inherited purely from the female parent. The disease can manifest in both sexes. Muscle biopsy of a person diagnosed with MELAS shows (a) Modified Gomori trichrome stain showing several ragged red fibers (arrowhead). (b) Cytochrome c oxidase stain showing Type-1 lightly stained and Type II fibers, darker fibers, and a few fibers with abnormal collections of mitochondria (arrowhead). Note cytochrome c oxidase negative fibers as usually seen in mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS). (c) Succinate dehydrogenase staining showing a few ragged blue fibers and intense staining in the mitochondria of the blood vessels (arrow). (d) Electron microscopy showing abnormal collection of mitochondria with paracrystalline inclusions (arrowhead), osmiophilic inclusions (large arrowhead) and mitochondrial vacuoles (small arrowhead).

2. **CADASIL ("Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy"**) is the most common form of hereditary stroke disorder, and is thought to be caused by mutations of the *Notch 3* gene on chromosome 19. The disease belongs to a family of disorders called the Leukodystrophies. The most common clinical manifestations are migraine headaches and transient ischemic attacks or strokes, which usually occur between 40 and 50 years of age, although MRI is able to detect signs of the disease years prior to clinical manifestation of disease. The definitive test is sequencing the whole Notch 3 gene, which can be done from a sample of blood. However, as this is quite expensive and CADASIL is a systemic arteriopathy, evidence of the mutation can be found in small and medium-size arteries. Therefore, skin biopsies are often used for the diagnosis.

3. **Cogan syndrome**

   Cogan syndrome or disease is a rare predominantly affecting young to middle aged adults. It is considered to be part of the spectrum of vasculitis involving small and medium size vessels in multiple organ systems. Ocular manifestations include interstitial keratitis, episcleritis, scleritis and retinal vasculitis. Hearing loss and vestibulo-auditory dysfunction, systemic vasculitis (aortitis, inflammatory bowel disease and pericarditis) and neurological manifestations such as neuropathy and mental changes are the usual manifestations. Stroke including cerebral venous thrombosis are rare complications of Cogan syndrome.

   The MRI venogram shows cerebral venous thrombosis. Limbal stromal opacity and episcleritis is evident in the eye.

4. **HEARNS disease** (Hereditary Endotheliopathy with Retinopathy Nephropathy and Stroke).

   HEARNS is an autosomal dominant, multisystem disease presenting with leukoencephalopathy, progressive visual loss, nephropathy and stroke. Initial presentation is progressive visual loss during the third and fourth decade followed by focal neurological deficits within 4 to 10 years.

   MRI shows an ischaemic stroke and the retinal photograph shows retinopathy.

5. **Susac syndrome**

   Susac syndrome is a triad of hearing loss, branched retinal artery occlusion and encephalopathy. A rare autoimmune condition that affects small vessels of the brain, retina and cochlea. This syndrome has a female predilection and usually presents between 20 and 40 years.

   MRI findings show infratentorial and supratentorial small multifocal white matter lesion with corpus callosum involvement. These lesions do not enhance with gadolinium. Cortical micro infarctions are seen.

   The MRI shows multiple small white matter lesions and micro infarcts. Fundal photograph shows branch retinal artery occlusion.

Compiled by Saman B Gunatilake & Ajini Arasalingam