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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
**Demographic patterns from an epilepsy clinic in Sri Lanka**

Ranjanie Gamage, Inuka Kishara Gooneratne

*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

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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 patients (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).
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. Most studies conducted in the Asia show one peak age for incidence in children and another peak age for prevalence in young adults. 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. 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. 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. 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. 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. Discrimination against people with epilepsy in the workplace and with respect to access to education is not uncommon. 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. 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. People with epilepsy also consistently appear at greater risk of problems in relation to educational achievement and employment. Issues of social withdrawal and isolation have been also reported with knockon effects for marriage and other close interpersonal relationships.

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 socioeconomic problems patients with epilepsy have to face. As mentioned in other studies social withdrawal and isolation may contribute towards these problems. 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. 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. From the available literature, the major causes seem to be: head injury, birth trauma, and intracranial infections, such as neurocysticercosis or meningoencephalitis. In places of greater socioeconomic development, head trauma and stroke are the leading causes of epilepsy. 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. 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. Neurocysticercosis was the cause of epilepsy in about 50% of patients in...
some studies\textsuperscript{34,35}. In Asia, many studies report the presence of cysticercosis\textsuperscript{36} but Neurocysticercosis is not found in Sri Lanka\textsuperscript{36}. This is unexpected when considering the geographical proximity of India which has a high prevalence of cysticercosis\textsuperscript{36}. 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\textsuperscript{28}. 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\textsuperscript{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\textsuperscript{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\textsuperscript{40}.

In Asia, post-traumatic epilepsy is one of the most common complications of head injury\textsuperscript{3}. A study claimed that post-traumatic epilepsy accounted for 5\% of total epilepsy and 20\% of symptomatic epilepsy\textsuperscript{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\textsuperscript{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\textsuperscript{42}. In many developing nations, notions about epilepsy are rooted not in medical sciences but in spiritual beliefs\textsuperscript{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 patients 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\textsuperscript{10} 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\textsuperscript{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**

Percutaneous vertebroplasty in vertebral crush fractures – a descriptive analysis

Devinda Lecamwasam¹, Ravi P. Ruberu², Mike Wilks¹, Ramon Pathi¹, Maria Dellamalva², Deepal Lecamwasam²

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. Vertebroplasty was first introduced in 1987 by Galibert and Deramond et al, pioneered to be used in aggressive vertebral angiomas. 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.

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.

Results

Baseline characteristics of the study participants are shown in Table. 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).
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).

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).

Table 1. Baseline characteristics of the study participants

<table>
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<tr>
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<tr>
<td>Total number of subjects</td>
<td>47</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
</tr>
<tr>
<td>Age range</td>
<td>65 to 90 years</td>
</tr>
<tr>
<td>Duration of back pain</td>
<td>2-21 days (mean 9.5)</td>
</tr>
<tr>
<td>Previous crush fractures</td>
<td>13</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>2-33 days</td>
</tr>
<tr>
<td>Indication for VP</td>
<td>Intractable pain despite analgesia 43 Intolerable to Opiates 4</td>
</tr>
<tr>
<td>Phone contact on follow up with patient</td>
<td>30</td>
</tr>
<tr>
<td>Phone contact on follow up with next of kin</td>
<td>17</td>
</tr>
</tbody>
</table>
Split modelling decision tree analysis revealed an association between improved pain perception, younger age, and pre-morbid 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 elderly5. 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 vertebra6, and cement leakage into the disk6. 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 vertebra 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 vein8. Bone cement leakage is by far the commonest reported complication7. Whilst this often is of benign nature, there have been significant number of case reports describing nerve root irritation4 pulmonary embolism9, cerebral cement embolism10, and fatalities11. Nevertheless, larger studies have demonstrated that VP recipients have much the same mortality rates as for untreated symptomatic patients12.

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 complications13. Operator experience have also shown to improve short term outcome of VP14.

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 area15,16.

Referrals for VP have declined in the United States of America17 since recent blinded placebo-controlled trials1,18. 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 others19 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


Preventive pharmacologic treatment of migraine in adults
Ajini Arasalingam¹, Saman B Gunatilake²

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Introduction
Migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours¹. Episodic migraine has a female predilection affecting 17% of women and 6% of men²-⁴. Episodic migraine is characterized by < 15 days of headache per month and chronic migraine by > 15 headache days per month¹. 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 productivity⁵. 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 medication². Several drug classes are used as preventive treatment in episodic migraine and they affect various aspects of migraine pathophysiology⁷,⁸.

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 prophylaxis⁹.

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 drugs 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 migraine¹⁰.

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 Administration¹¹. Novel antiepileptic drugs, calcium channel blockers, serotonin and noradrenaline reuptake inhibitors, glutamate blockers and drugs from several other classes are prescribed off-label by doctors¹². The NICE guidelines recommend topiramate and propranolol as preventive therapy for migraine¹³. 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 Prevalence 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 conditions¹³. 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.
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 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. However in a smaller study Gupta showed that 50 mg topiramate reduced headache frequency and increased the responder rate. Trials comparing topiramate 100 mg to placebo in 478 patients showed statistically significant superiority of topiramate. Four large trials comparing topiramate 200 mg to placebo showed statistically superiority for topiramate with regard to responder rate but only two studies showed a reduction in headache frequency. Two other smaller trials 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; topiramate 100 mg and flunarizine 5 mg; topiramate 50 mg and propranolol 80 mg; and topiramate 200 mg, 100 mg and propranolol 80 mg, 160 mg. There was a slight but significant advantage of topiramate 50 mg over sodium valproate 400 mg. 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 paresthesias, 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.

Sodium valproate

Two cross-over trials with a total of 63 patients showed that sodium valproate had a significant reduction in headache frequency compared to placebo. In one trial 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 compared different doses of sodium valproate by measuring serum sodium valproate concentrations. The study showed that lower (21-50 μg/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. Two smaller studies compared topiramate 50 mg with sodium valproate 400 mg 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. 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.

Gabapentin

Pooled data from 5 trials of gabapentin suggest that it is not efficacious for the prophylaxis of episodic migraine in adults. 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. Atenolol is a Level B drug according to the 2012 AAN and AHS guidelines.

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. However a trial with the lowest dose (80mg) of propranolol had the most positive result. Meta-analysis of 10 trials by the Cochrane group suggested that propranolol 160 mg might be slightly more effective than 120 mg. 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.

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

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 while another trial showed that metoprolol had similar efficacy compared with nebivolol in migraine prevention.

Calcium channel blockers

Flunarizine was efficacious in migraine prophylaxis when compared with a placebo but when compared with the beta-blockers propranolol, and metoprolol 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 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. 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. Amitriptyline was found to have similar efficacy to venlafaxine and topiramate.

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. Another study reported...
venlafaxine and amitriptyline to have similar efficacy in reducing headache frequency 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 and candesartan were possibly effective while telmisartan 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 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. Zolmitriptan 2.5 mg twice daily or three times daily significantly decreased the frequency of menstrually related migraine, however there was no advantage in the three times daily dosing over the twice daily dosing.

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. 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 overdose 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

Preventive pharmacologic treatment of migraine in adults


Multiphasic disseminating encephalomyelitis (MDEM)

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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. 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. A full recovery is seen in 50 to 75% of cases; while up to 70 to 90% recover with some minor residual disability. 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. When the patient suffers more than one disseminated demyelinating episode, it is called recurrent disseminated encephalomyelitis (RDEM) or multiphasic disseminated encephalomyelitis (MDEM). 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.

Discussion

Relapsing remitting multiple sclerosis (RRMS) and recurrent or multiphasic disseminated encephalomyelitis (MDEM) are considered different diseases. 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.

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

Figure 1. The MRI of the brain showing large bilateral subcortical and central white matter lesions which were not enhancing.
In a study comparing children with ADEM/MDEM complex with those with MS some features were, more commonly seen with ADEM/MDEM group.

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 periventricular 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 T2-weighted images show abnormalities than in T1-weighted images. The lesions were predominantly in the white matter. Absolute and relative sparing of the periventricular white matter occurred in 56 and 78% of images, respectively. Involvement of the deep and subcortical white matter was nearly universal. The supratentorial white matter lesions were universally asymmetrical. In MS T2 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.

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**Case report**

The little old adie pupil

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**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 Holmes-Adie’s syndrome (HAS)¹. When HAS is associated with hypohidrosis it is called Ross Syndrome, although some consider it as a variant of HAS². 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 pupillary abnormality as a manifestation of oculomotor nerve palsy is an extremely rare occurrence without diplopia, squints or ptosis³.

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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. 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 oculo-parasympathetic lesion confirms postganglionic oculo-parasympathetic lesion and excludes a third nerve palsy in our patient.

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. 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.

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 effect of pupil constricts 0.5 mm more than the normal pupil or the relatively larger abnormal pupil becomes the smaller pupil after the instillation. 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. Cholinergic supersensitivity is absent in about 20% of tonic pupils.

After the acute denervation, short ciliary nerve fibers tend to reinnervate to reach their end organs. During this process, sprouting accommodative fibers innervate the ciliary muscle and improve near vision. Relative abundance of accommodative fibers in comparison to pupilconstrictor 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 pupilconstrictor 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 demonstrated 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. In HAS involvement of the fellow pupil is at a rate of 4% per year. 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. Refractory correction and pilocarpine eye drops for the dilated eye can be considered to correct the near vision.

References
Introduction

The term 'pseudo-peripheral palsy' was first coined by Lhermitte in 1909 to describe the predominant weakness of fingers following a stroke. 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. The pattern of weakness may be global, ulnar-predominant or radial-predominant. The syndrome is usually caused by infarcts involving the motor control area for the hand (the 'knob') in the precentral gyrus. However, lacunar infarcts and small intracerebral haemorrhages have also been found to present with isolated hand weakness in some cases.

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.
Indeed, the diagnosis would have been mostly clinical before the advent of magnetic resonance imaging (MRI) since CT scans are negative in up to 40% of patients presenting with monoparesis. Diffusion-weighted magnetic resonance imaging is the most sensitive diagnostic investigation for a small acute infarct (Figure 1). In most cases of cortical-hand syndrome, a potential source of embolization had been recognized, 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.

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

Nummular headache

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Introduction

Nummular headache (NH) was first described in 2002 by Pareja et al. 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). The diagnostic criteria for NH were updated in the current ICHD-3 beta classification, which is in press (available on line). 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. 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.

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.

In a series of 59 patients with NH, five patients had associated trophic changes on the site of the pain. 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, paraesthesia 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.

In one hospital series, incidence of NH was 6.4/100,000 per year. 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. 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.

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. 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. Carba-
mazepine, Indomethacin, Topiramate have also been used with successful results in some patients in the past11,14,15.

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 scalp, 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, dysesthesia, paraesthesia, allodynia and/or tenderness.

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


References
A stroke mimic

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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/mm3, lymphocytes 330/mm3) 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/mm3, lymphocytes 30/mm3). 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 around4. 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

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stroke caused by vasculitis. TBM was associated with cerebral infarctions in 47% and cryptococcal meningitis in 32% 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. This 25-year-old patient presented with a stroke. MRI brain and muscle biopsies are shown. What is the diagnosis?

![MRI and muscle biopsy images]

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?

![MRI and skin biopsy images]

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?

![MRI and eye images]
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 accompanied 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.
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.

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.
2. Editors.

Other citations in Reference List:
1. In press (must have journal title).
2. Magazine article.

In-text citations of unpublished material (to be placed within parentheses):
1. Personal communication.
   (Strott CA, Nugent CA. Personal communication).
2. Unpublished papers.

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. 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 neuropsychopathy 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