# Sri Lanka Journal of Neurology

Official Journal of The Association of Srilankan Neurologists

Volume 7, Number 1, 2020

# 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**
277, Hokandara Road, Thalawathugoda, Sri Lanka.
Tel: 0112774793 E-mail: anandapress65@gmail.com

ISSN 2279-2295

# SRI LANKA JOURNAL OF NEUROLOGY

Official publication of the Association of Srilankan Neurologists

**Volume 7, Number 1, 2020**

## CONTENTS



*(Continued)*

Editorial

# Cannabis in neurology

*Sri Lanka Journal of Neurology,* 2020, **7**, 1-3

Constituents of the cannabis plant, cannabinoids, may be of therapeutic value in neurologic diseases. The most abundant cannabinoids are D9-tetrahydrocannabinol (THC), which possesses psychoactive properties, and cannabidiol (CBD), which has no intrinsic psychoactive effects, but exhibits neuroprotective properties in preclinical studies. A small number of high-quality clinical trials support the safety and efficacy of cannabinoids for treatment of spasticity of multiple sclerosis, pain refractory to opioids, glaucoma, chemotherapy induced nausea and vomiting and rare severe forms of childhood refractory epilepsies. Lower level clinical evidence indicates that cannabinoids may be useful for dystonia, tics, tremors, epilepsy, migraine and weight loss. Data are also limited in regards to adverse events and safety.

Common nonspecific adverse events are similar to those of other CNS 'depressants' and include weakness, mood changes and dizziness. Cannabinoids can have cardiovascular adverse events and, when smoked chronically, may affect pulmonary function. Fatalities are rare even with recreational use. There is a concern about psychological dependence, but physical dependence is less well documented. Cannabis preparations may presently offer an option for compassionate use in severe neurologic diseases, but at this point, only when standard-of-care therapy is ineffective.

There is public (and producer) interest in cannabis containing medicinal products and currently there seems to be an interest in the Sri lankan community mostly in public and political domain to have these products available for illnesses in our patients. With the licensing of CBD for Dravet and Lennox Gastaut syndromes in USA and UK, two rare but severe forms of epilepsy resistant to other drugs, our colleague paediatricians are naturally interested in offering this treatment to selected patients of theirs, but they have justifiable concerns about exposing a group already vulnerable to mental health and neuro behavioural comorbidities to the associated additional risks associated with the use of cannabis products.

The cannabis plant produces at least 144 naturally occurring compounds known as cannabinoids. The most widely researched cannabinoids are THC and CBD. THC is the primary constituent of cannabis that causes the "high" whereas CBD is not intoxicating at typical doses. Several products exist for medicinal use and these differ in THC/CBD profile, formulation, licensed indications, and conditions for prescribing. Cannabis based products that were previously listed in Schedule 1 (Drugs belonging to schedule 1 are thought to have no therapeutic value and therefore cannot be lawfully possessed or prescribed) can now be prescribed by doctors on the General Medical Council Specialist Register in the UK, on a named patient basis. Currently, general practitioners in the UK cannot prescribe them. Some cannabis-based products were already available for medicinal use before rescheduling in 2018. Sativex, an oral spray derived from the cannabis plant containing THC and CBD in a 1:1 ratio, is licensed for the treatment of spasticity in multiple sclerosis in 29 countries, including the UK, Israel, Canada, Brazil, and Australia. However, a meta-analysis suggests its effectiveness may be limited and it is not recommended by the UK's National Institute for Health and Care Excellence (NICE) because of poor cost effectiveness.

Epidiolex, an oral CBD solution derived from the cannabis plant, was licensed by the US Food and Drug Administration in June 2018 for the treatment of seizures in two rare and severe forms of childhood epilepsy – Lennox-Gastaut syndrome and Dravet syndrome based on data from randomized controlled trials supported by selected case videos, and "emotional testimony" from parents. FDA has approved its use recently for seizures in tuberous sclerosis based on a recently completed trial. Of note is that two recently completed randomized controlled trials failed to show efficacy of CBD and CBDV for the treatment of refractory focal onset epilepsy in adults. With the licensing of cannabidiol for drug resistant seizures in Dravet and Lennox Gastaut syndromes in the United states in 2018, interest in the potential for cannabis-based-medicinal products to meet currently unmet needs for people with epilepsy continues to grow. Only pure cannabidiol formulations have been rigorously evaluated in controlled trials thus far, with modest but significant improvements in motor seizures.

In the last 2 years, five randomized controlled trials of pharmaceutical grade CBD have been completed. The first study reported on the use of CBD (Epidiolex) for the treatment of convulsive seizures in patients with Dravet syndrome. In this double-blind, placebo controlled study, patients were randomized to receive either CBD at 20 mg/kg/day or placebo in addition to their standard

AEDs. The primary outcome measure was the change in convulsive seizures over a 14-week treatment period compared to a 4-week baseline. The authors were able to show a significant decrease in convulsive seizures per month from 12.4 to 5.9 with CBD vs. 14.9 to 14.1 with placebo (p=0.01 after adjusting for baseline differences). The responder rate of convulsive seizures in this study was 43% for CBD vs. 27% for placebo (p=0.08). The authors also reported on the overall seizure frequency (all seizure types) which has improved in the CBD group (p=0.03). However, there was no significant improvement in the nonconvulsive seizures. There was an overall improvement in the Caregiver Global Impression of Change scale in 62% of the CBD compared to 34% of the patients treated with placebo. Of the two LGS studies, the first study included 171 patients with drop seizures who were randomized to receive either placebo or CBD (Epidiolex) at 20 mg/kg/day after a 4-week baseline; the primary endpoint was change from baseline in drop seizure frequency. After 14 weeks of treatment, the median percentage reduction in drop seizure frequency per month from baseline was 43.9%in the CBD group and 21.8% in the placebo group (p=0.0135). Forty-four percent of patients were considered responders in the treatment phase and 46% in the maintenance phase of the study with respect to a reduction of drop seizures. The second randomized and placebo-controlled study also evaluated the efficacy of CBD in LGS with the primary endpoint being change in the rate of drop seizures. In this dose ranging study, patients were randomized to placebo, 10 mg/kg/day or 20 mg/kg/day of CBD with response measured at 14 weeks when compared to 4-week baseline. Of the 225 enrolled patients, 41.9% in the 20 mg/kg/day CBD group, 37.2% in the 10 mg/kg/day CBD group, and 17.2% in the placebo group responded to therapy with comparisons between treatment and placebo groups being significant. Responder rates for drop seizures were 39%, 36%, and 14% in the 20 mg/kg/day, 10 mg/kg/day, and placebo groups, respectively.

Dronabinol and nabilone are synthetically produced medicinal products that mimic the effects of THC. Dronabinol has an identical structure to THC, while nabilone has a related structure and is more potent than dronabinol, requiring lower doses to achieve clinical efficacy. Countries including the US, the Netherlands, Germany, Austria, and Croatia have licensed the use of both products. They are licensed for the treatment of weight loss in patients with AIDS and of nausea and vomiting in people receiving chemotherapy who have failed to respond adequately to conventional antiemetics. Nabilone is licensed in the UK while dronabinol is not licensed but can be prescribed on a named patient basis.

A combination of △ 9-THC and CBD, nabiximols (Sativex), showed >20% improvement in spasticity in patients with MS after 4 weeks in over half of patients treated. This has led to approval of use of nabiximols in multiple sclerosis for management of severe spasticity. The preparation, nabiximols (Sativex) has currently attained regulatory approval in 30 countries for spasticity associated with multiple sclerosis (MS), and in Canada for central neuropathic pain in MS, and for opioid-resistant cancer pain. Recent surveys find usage rates for cannabis of 20%-60% among MS patients. Cannabis may improve quality of life in some patients with multiple sclerosis. Patients' perception of the benefit of cannabis is often vastly different from their clinicians.

Other areas where a keen interest exists in studying the value of cannabinoids are intractable epilepsy, brain tumors, Parkinson disease (PD), Alzheimer disease (AD) and traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE). Available studies and data in these conditions are of low quality mainly observational and needs further properly designed studies before considering use in these conditions.

Adverse effects of CBD include diarrhoea, somnolence and reduced appetite, with mostly acceptable tolerability, but a not insignificant (up to 1 in 23) risk of serious adverse events. Recognized drug interactions include with valproate (increased risk of hepatotoxicity) and clobazam (contributing to somnolence, increased secretions, probably chest infections, and potentially efficacy).

A significant gap exists between the actual evidence, and public beliefs, fueled by media and anecdote. Pro cannabis lobby brings out sympathy and emotional aspects of the illnesses to promote their cause. Continued education of the public, policymakers, researchers and healthcare providers about what is and isn't yet known, together with on-going good quality research is essential to counter future potential risks, particularly in relation to vulnerable populations like disabled MS patients, severe epilepsies, and patients with intractable pain syndromes.

Based on current evidence in terms of efficacy or tolerability it is not yet a "game changer", and there is much still to be done. There are justifiable concerns about the use of THC containing products, particularly in children and adolescents and moreover being used for unlicensed conditions resulting in wide abuse with significant drawbacks and repercussions. So when the evidence is not strong and the consequences can be detrimental to the cause, best is to practice caution – "*Primum non nocere*".

## References

1. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med.* 2018; **378**: 1888-97. RCT of cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome.
2. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug resistant seizures in the Dravet syndrome. *N Engl J Med.* 2017; **376**: 2011-20.
3. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018; **391**: 1085-96. syndrome.
4. Gaston TE, Szaflarski JP. Cannabis for the Treatment of Epilepsy: an Update. Current Neurology and Neuroscience Reports (2018) 18: 73. https://doi.org/10.1007/s11910-018-0882-y.
5. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex). *European Journal of Neurology.* 2011; **18**: 1122-31.

**Saman B. Gunatilake**

*Editor*

E-mail: saman.gunatilake@hotmail.com

Review

# Palliative care in neurology

**David Oliver**[1]

*Sri Lanka Journal of Neurology,* 2020, **7**, 4-7


## Abstract

Palliative care is a very important part of the care for people with neurological disease, and their families. This may be appropriate in any patient group, but is particularly helpful for patients with progressive neurological disease and when the disease is progressing towards the end of life. A multidisciplinary approach allows the assessment and management of the various issues facing patients – physical, such as symptom management, psychological, social and spiritual. In this way the quality of life of patients can be maintained and preparations made for the end of life, so that they are able to have their symptoms managed effectively and die peacefully.


## Introduction

Although palliative care has often been associated with the care of people with cancer there has been increasing awareness of neurological palliative care and in 2016 the European Academy of Neurology and the European Association for Palliative Care collaborated in producing a Consensus document[1]. This document emphasises the increasing importance of palliative care for neurological patients, and their families, and the need for neurologists to become involved.

Palliative care is defined by the World Health Organisation as "An approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering, early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"[2]. Thus, neurologists are very closely involved in providing palliative care as many patients do have a life-threatening illness – this may be a progressive disease such as motor neurone disease (MND) or in acute situations when death may occur suddenly, such as in acute stroke or infections. In all patient care it is important to ensure good communication with patient and family, share decision making and goal setting and provide symptom management. Specialist palliative care may be needed for some more complex patients, where the team would provide palliative care as their main activity and have received specialist training and continuing education[3].

## Palliative care assessment

The assessment of the patient and family will involve all aspects of care, as described in the WHO Definition:

- Physical – the various symptoms that may be experienced by the patient, including pain, breathlessness, dysphagia, dysarthria, mobility issues, tremor, confusion, agitation, anxiety, depression. There is a need to be proactive in looking for symptoms, as patients and families may be reluctant to talk about some issues. The careful elucidation of the cause of the symptom is essential before treatment – which may be using medication or non-pharmacological[1].

  The assessment may need to be of mobility and positioning, as the patient becomes less mobile and more dependent, and the wider multidisciplinary team should be involved.

- Psychological – patients will have their own concerns about their diagnosis, disease progression or their future. This may present as anxiety or depression, but other issues may need to be heard and addressed appropriately.

- Social – most people are part of larger family groups, who will have their own particular concerns and for whom the patients may have concerns. It is important that these issues are heard and support given.

- Spiritual – patients may have specific religious concerns but more often may express their worries about the future, or issues related to their illness – such as "why me?", "how will I cope", "what happens as I am dying or after death"[4]. These may be openly expressed or discussed in less obvious ways, as concerns about other aspects of life. The wider multidisciplinary team may be able to respond and support the person and their family and allow expression of these issues.

This assessment of all of the issues that are important to the person, and their family, will often involve the wider multidisciplinary team. It is important that the team members liaise and can involve other members of the team appropriately.

## Effectiveness of palliative care

There is increasing evidence for the effectiveness of palliative care, although this is limited. A Cochrane

[1]*Professor, Tizard Centre, University of Kent, Cornwallis North East, University of Kent, Canterbury, Kent, CT2 2NF UK.*
Correspondence: David Oliver E-mail: drdjoliver@gmail.com

Library Systematic review of 23 studies that evaluated home palliative care for people with advanced illness did show that people were more likely to die at home and there was evidence that symptom burden was reduced[5]. A similar Cochrane Review of palliative care interventions for people with multiple sclerosis (MS) showed no clear evidence of any effect on quality of life or hospital admissions[6]. Within cancer care there has been evidence that early palliative care involvement improves quality of life and mood and length of survival[7].

There have been studies looking at the effectiveness of palliative care for people with neurological disease. A short-term palliative care intervention was found to lead to improvement of symptoms for people with MS, whereas the control group deteriorated, and this was associated with improvement in caregiver burden and was found to be cost effective[8,9]. The provision of extra training in palliative care for specialist MS nurses was shown to help in symptom management but did not affect quality of life or other outcomes[10]. A randomized controlled trial of multidisciplinary palliative care for people with advanced neurological disease, including MND, MS and Parkinson's disease (PD), found an improvement in quality of life and symptoms – pain control, breathlessness, sleep disorders and bowel symptoms – and there were trends for improvement in other symptoms[11].

There is also increasing evidence for the effectiveness of multidisciplinary team (MDT) care. Within the care of MND two studies have shown that the MDT approach may lead to an increase in length of life[12,13]. It is unclear as to the most important aspect of the MDT approach but it may be due to the closer working relationships, the development of trust between team members and the ability of close collaboration and sharing of information. This may be partly supported by the evidence on neurological palliative care where the involvement of a wider multidisciplinary team on an intensive basis, with regular visits and support[11], was more effective that a short-term intervention[8,10].

A multidisciplinary palliative care out-patient clinic for people with PD has been shown to improve quality of life, non-motor symptoms, the severity of motor symptoms and the completion of advance care planning documents[14]. There were improvements in caregiver anxiety and care giver burden but these were only significant after 12 months and were less conclusive. There was also evidence that the benefits were greater for people who were found to have a higher level of palliative care needs[14].

## Care at the end of life

Although palliative care may be appropriate, according to the needs of the patient and family, at any time during the disease progression there is a particular need to ensure that a full assessment is undertaken as the person becomes iller and approaches the final stages of their illness. It has been suggested that there are certain triggers that may indicate that the end of life, the last 6 to 12 months, is approaching. These are swallowing problems, recurring infection (especially aspiration pneumonia), marked decline in functional status, first episode of aspiration pneumonia, cognitive difficulties, weight loss and significant complex symptoms, as well as the overall impression of the professional team[15]. Although these were initially decided by consensus within a group of experts, a retrospective survey of patients who had died with neurological disease showed that the number of triggers increased as death approached[16]. A particularly significant trigger was aspiration pneumonia which was seen primarily in the last 6 months of life and may reflect a patient who is deteriorating, with reduced generalised weakness, poor swallowing, reduced cough and increased breathing issues.

The recognition of the end of life phase is important as it allows the multidisciplinary team to focus particularly on symptoms, other physical issues and psycho-social concerns, and facilitate communication with the patient, if this is possible, the family and all the professionals involved in the person's care. In this way potential crises may be anticipated and plans made to ensure that the patient's wishes are met. There is also the opportunity for all involved to discuss the situation and be more prepared for the death. It is particularly important for the family to become more aware, together with the patient, if they are able to be involved in these conversations.

As the disease progresses and death approaches careful consideration should be given to medication. There may be existing medications that are no longer appropriate, such as statins, which may be stopped. Medication may need to be prescribed so it is readily available to cope with new anticipated symptoms. For instance, for a patient at home it is important to ensure that medication is in the home to cope with pain, choking, breathlessness or distress is important – often an analgesic, anti-emetic, a relaxant and an anticholinergic, to reduce chest secretions. If these are readily available any professional can administer them or on occasions, with training, the family may be able to give the medication and minimise distress at the end of life.

As patients with neurological disease deteriorate, they may face reduced communication and / or cognition. Thus, advance care planning (ACP) is particularly important when a person, while they have capacity to make decisions, expresses their wishes about the treatment they would wish to receive or not receive if they lose capacity – due to cognitive changes, loss of communication or severe weakness or loss of consciousness[17]. This may be as a specific Advance Directive, where the

person states the treatments they do not wish to receive, or the appointment of a proxy, or advocate, to make decisions on their behalf if they lose capacity – the professionals may ask the proxy for their view of the person's wishes. In these ways the person, who has lost capacity is able to influence the care they receive and this is often reassuring for the patient and relieves the burden from family[1].

## Conclusion

Palliative care should be available according to need, rather than just restricted to a specific period towards the end of life. The needs of patients will vary over time and palliative care may be appropriate at certain times. For instance, a patient with MND may have greater palliative care needs at diagnosis, as they face the challenge of coping with the disease and the fears it may engender, when gastrostomy is considered, when respiratory support is discussed and towards the end of life. This may, for many patients with MND, be over a period of two to three years, although for some it may be over a longer timescale. A person with PD may have similar varying needs, perhaps related to pain, non-motor symptoms, disability, aspiration pneumonia and in the later stages of the disease progression, but this may be over 10 to 15 years, or even longer. Specialist palliative care or hospice care may be needed at any time if these needs are more complex and the specialist MDT may provide other care during the periods between this involvement.

There is a need for all involved in the care of neurological patients and their families to increase their skills – for neurologists to learn more about the management of symptoms and palliative care and for palliative care specialists to understand more about the issues for neurological patients[1]. In this way there can be greater collaboration and interaction between teams and improved care for patients and families. In Europe a EAN / EAPC online survey found that there was often collaboration between neurology and palliative care for people with MND and brain tumours and less often with MS and PD[18]. The level of collaboration varied greatly, from occasional contacts to joint clinics.

Discussions about care at the end of life may take place throughout the disease progression whenever patients and families would like to do so and particularly at times when decisions are made about future management, including diagnosis or if interventions are being considered, such as gastrostomy or non-invasive ventilation[1].

There is discussion of the role of the neurologist as a palliative care provider[19] and that the role of the neurologists is changing from being purely a diagnostician to the provision of ongoing care for patients and their families, sharing in their growth and decline, and supporting them in their deterioration and later stage[20]. This will encompass primary palliative care – discussing serious news, managing symptoms, ensuring treatment is aligned to the patients' wishes, preparing for end of life and working as part of the wider multidisciplinary team.

This is a challenge for the future but palliative care and neurology need to collaborate, so that the quality of life of patients, and their families, can be maintained at as good a level as possible and enabling them to die peacefully.

### References


1. Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. *European Journal of Neurology* 2016; **23**: 30-8.
2. World Health Organization. (2002). Palliative care www.who.int/cancer/palliative/definition/en/
3. Radbruch L, Payne S, et al. White Paper on standards and norms for hospice and palliative care in Europe: part 1. *European Journal of Palliative Care* 2009; **16**: 278-89.
4. Lambert R. Spiritual care. In Oliver D, Borasio GD, Johnston W (eds). *Palliative care in amyotrophic lateral sclerosis – from diagnosis to bereavement*. 3rd edition. 2014. Oxford. Oxford University Press. Pp 171-86.
5. Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. *Cochrane Database of Systematic Reviews* 2013; (6): CD0077760. Published 29013 Jun 6. Doi: 10.1002/14651858.CD007760.pub2
6. Latorraca COC, Martimbianco ALC, Pachito DV, et al. Palliative care interventions for people with multiple sclerosis. *Cochrane Database of Systematic Reviews* 2019 (10): Art. No. CD012936. Doi: 10.1002/14651858.CD012936.pub2.
7. Temel JS, Greer JA, Muzikansky, et al . Early palliative care for patients with metastatic non-small-cell lung cancer. *New England Journal of Medicine* 2010; **19**: 733-42.
8. Edmonds P, Hart S, Gao W, Vivat B, Burman R, Silber E, Higginson I. Palliative care for people severely affected by multiple sclerosis: evaluation of a novel palliative care service. *Multiple Sclerosis Journal* 2010; **16**: 627-36.
9. Higginson IJ, McCrone P, Hart S, et al. Is short-term palliative care cost-effective in multiple sclerosis? A randomized phase II trial. *Journal of Pain and Symptom Management* 2009; **38**: 816-26.
10. Solari A, Giordano G, Patti F, Grasso G, Confalonieri P, et al. Randomised controlled trial of a home based palliative approach for people with severe muliple sclerosis. *Multiple Sclerosis Journal* 2017; **24**: 663-74.

11. Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, Oliver DJ. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. *BMJ Supportive and Palliative Care* 2017; **7**: 164-72.

12. Aridegbe T, Kandler R, Walters SJ, et al. The natural history of motor neuron disease: Assessing the impact of specialist care. *Amyotrophic Lateral Sclerosis* 2013; **14**: 13-19.

13. Rooney J, Byrne S, Heverin M, et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. *Journal of Neurology, Neurosurgery and Psychiatry* 2015; **86**: 496-503.

14. Kluger BM, Miyaskai J, Katz M, et al. Comparison of integrated outpatient palliative care with standard care in patients with Parkinson disease and related disorders. *Journal of the American Medical Association Neurology* 2020; doi: 10.1001/jamaneurol.2019. 4992

15. *End of life care in long term neurological conditions: a framework for implementation*. National End of Life Care Programme 2010.

16. Hussain J, Adams D, Allgar V, Campbell C. Triggers in advanced neurological conditions: prediction and management of the terminal phase. *BMJ Supportive and Palliative Care* 2014; **4**: 30-7.

17. Chapman S. Advance Care planning. In: Oliver D (ed). End of life care in neurological disease. 2013. London Springer. 133-42.

18. Oliver D, Hepgul N, Borasio GD, et al. Collaboration between neurology and palliative care; a European survey. Poster at the 5th European Academy of Neurology Congress, Oslo. June 2019.

19. Creutzfeldt CJ, Robinson MT, Holloway RG. Neurologists as palliative care providers. Communication and practice approaches. *Neurology* 2016; **6**: 40-8.

20. Gursahani R. Palliative care and the Indian neurologist. *Annals of the Indian Academy of Neurology* 2016; **19**(Suppl 1): S40-S44.

Review

# Rehabilitation of Neuro-mobility

**Uditha Jayatunga**[1]

*Sri Lanka Journal of Neurology,* 2020, **7**, 8-12

Neurological disability is multi-dimensional. These include mobility limitations, upper limb dysfunction, swallowing, speech, vision, hearing, continence, cognition and behavioural issues. Out of all these, regaining mobility is of paramount importance to most patients. Regaining mobility is vital for patients not only to walk but also get back to normal life as much as possible, to maintain family, work and social responsibilities as well as to live independently as possible. Additionally, there are psychological and physiological benefits of maintaining bipedal mobility.

Normal gait requires that many systems, including strength, sensation and coordination function in an integrated fashion. Locomotion in humans is based on spinal pattern generators, which are regulated by supraspinal control. Corticofugal, basal ganglia, cerebellar, vestibulospinal and reticulospinal controls are all important in normal bipedal walking. The control of walking must thus involve motor cortex (possibly the supplementary motor area on the medial surface of the frontal lobe which gives rise to diagonally opposite movements of arms or legs when stimulated), the cerebellum, subthalamic region, midbrain, noradrenergic reticulospinal tract and the spinal locomotor centre. Neurological mobility disorders could be due to isolated motor weakness, paralysis, spasticity, ataxia, sensory deficits, dyskinetic movements, coordination and balance disturbances or a combination of many factors.

From a Rehabilitation Medicine management of neuro-mobility, many facets need to be addressed in order to optimise mobility. Observing how patient is mobilising is the most important part of neurological examination. Types of gait disorders are hemiplegic or diplegic scissoring gait in spastic conditions, festinent gait in Parkinsons, Trendelenburg or waddling gait or lordotic gait in muscle disorders, high stepping gait in sensory disorders, broad based ataxia in cerebellar disorders, choreiform gait in hyperkinetic gait disorders. When observing their gait, it is important to look at the speed, stride length and cadence. Beyond this you need to look at spasticity related altered body postures, bed and wheel chair seating postures, seating balance, ability to stand from seating posture, transferability and technique, ability to remain standing and the standing posture. A wide base may indicate cerebellar or proprioceptive loss.

There are many mobility related scales we use such as Rivermead Mobility Index which is a 15-point scale which assesses the ability to turn in bed to running 10 meters. Depending on the condition of the patient, we could use many other simpler scales such as 6-meter timed walk test or Timed up and Go (TUG) test or other mobility associated scales such as Berg balance scale looking at the balance of the patient. At the higher end of the spectrum, we could use facilities such as Gait analysis to optimize and fine tune mobility of some patients. Beyond this, we also need to look at social mobility including getting back to driving.

Any improvement in the ladder of such mobility scales will improve the quality of life and independence. Hence a patient who could not turn in bed independently (Rivermead 1) to improve up to being able to sit at the edge of bed independently (Rivermead 3) could be considered significant progress. Such improvement will also reduce the patient getting pressure sores, ability to eat seated as well as improving lung functions. Similarly if a patient improves from being able to walk 10 meters (Rivermead 7) to walking on uneven ground (Rivermead 12) is a significant improvement though overall mobility is much less than if they previously had normal mobility.

For a successful mobility neuro-rehabilitation program, it should have access to not only to multi-disciplinary teams but also many other facilities. These include orthotics (splinting), walking aids, specialist wheelchair services, medications and spasticity services, a gait lab, functional electrical stimulation service, access to orthopaedic and neurosurgical services and disability driving assessment service. Such facilities are very important to maximize the potential of the patients, which is the overall goal in Rehabilitation Medicine. It is also vital to recognize the environmental limitations patients have which could limit their mobility. It is routine for our occupational therapists to look at home as well as work environments if needed to maximize their potential.

It is important to recognize that any underlying condition causing mobility problem needs appropriate management where possible – such as in spinal cord compression, Guillain Barre Syndrome or Parkinson disease.

[1]*Consultant in Rehabilitation Medicine, University Hospitals of Derby and Burton NHS Trust, UK.*
Correspondence: E-mail: udithajayatunga@ntlworld.com

**Therapy**

In neuro-rehabilitation, multidisciplinary input is essential at all stages for holistic management which includes mobility disorders.

For mobility issues, this MDT team should generally consist of a physiotherapist, occupational therapist, orthotist and the Rehabilitation Medicine consultant. At times depending on the issues, others have to be incorporated such as the orthopaedic surgeon, wheel chair OT/technologist, psychologist and gait analysis team members. Specific achievable goals should be planned and discussed within the MDT team as well as with the patient. Many patients need long term follow up by the Rehabilitation Consultant who may in turn get either the MDT or individual therapy members involved depending on the specific issues. For many long term conditions, patients cannot be given life long therapy input due to limited resources. Such patients are given therapy exercises for them to maintain their potential. If patients deteriorate due to natural progression of the condition or due to any other factors, then patients should be able to access top up therapy.

**Drug management**

Drug management of mobility issues are predominantly related to management of spasticity. In generalized spasticity affecting mobility, we would use many antispastic agents such as Baclofen, Gabapentin, Tizanidine, Danthrolene and Diazepam. It is important to remember that spasticity in some circumstances will help the patient to maintain mobility and hence needs careful evaluation.

Botulinum toxin is used for focal spasticity. Commonly in lower limbs, the adductor, hamstrings, gastrosoleus muscle and posterior tibial muscles are injected. These most often need to be used in combination with suitable splinting. Some patients may have troublesome striatal toe or toe clawing which needs treatment. Botulinum toxin is expensive and hence it is vital to make sure goals are clarified and met for continuation of treatment. For patients who are wheelchair bound, Botulinum toxin injections can help to improve seating posture, prevent pressure sores and hence improve overall quality of life. Injecting the upper limbs too could potentially help mobility. An example is, if we could help them to extend their forearm by injecting biceps or brachio-radialis, it may help them to use a Zimmer frame.

There is a small group of patients with conditions such as spinal injuries or multiple sclerosis where it is difficult to manage their spasticity with either oral medications or Botulinum toxin injections. They have to be considered for intrathecal baclofen pump (ITB) which is highly effective in controlling underlying spasticity. It is very expensive and usually they need a test dose before implanting the pump. Few patients can get back to bipedal mobility but for majority of patients, ITB will help with their wheel chair seating and mobility. Troublesome spasms or postures could be some of the reasons where they cannot sit out for a long time, which could be well controlled with ITB pump (as below). These pumps are not only very effective but also could give hourly varying doses to fine tune their management. Once stable, side effects are minimal, however they need regular filling of their pump port which is usually placed in the anterior abdominal wall.

**Before ITB**

**After ITB**

### Gait analysis

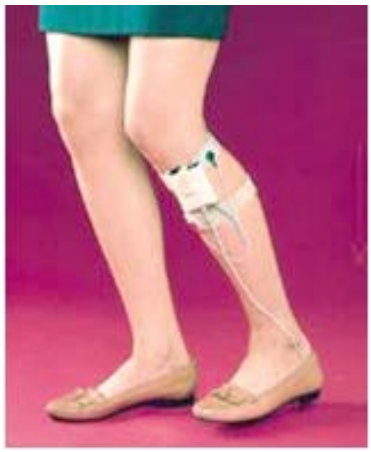
This is an important tool in the management of complex mobility problems such as in cerebral palsy patients. About 85% of cerebral palsy patients do have spasticity related gait disorders. In others who have cerebral palsy related dyskinesia or ataxia, complex gait analysis is less useful. Gait analysis is time consuming, but we could get multiple data from dynamic force plate, 3D motion analysis, surface EMG, joint angles and pedar pressure monitoring. From gait analysis we could objectively assess the deviation from normal mobility at all levels. A typical gait cycle is broadly divided into the swing phase and the stance phase. Walking requires an upright position with fully functioning anti-gravity muscles and intact postural reflexes. A greater amount of time is spent in the stance phase with the stance phase contributing to about 60% of the gait cycle and the swing phase contributing to 40%.

Gait analysis is a very important tool for assessment of complex gait, to monitor progress, plan treatment and interventions, monitor effectiveness of treatment and prevent complications. The interventions following gait analysis, may include injections for spasticity, Functional Electrical Stimulation (FES), orthotics, physiotherapy, surgical interventions or a combination of the above.

### Functional Electrical Stimulation

This is a technique which is now being widely used in rehabilitation. Many patients who are mobile with underlying spasticity may have spastic foot drop. Such pattern is typically seen in stroke patients who have hemiplegic gait with spastic foot drop, circumduction and hip hiking. If you fail to control with simple AFO and other therapeutic measures, they could be considered for single channel FES where the common peroneal nerve is stimulated using a switch in the insole to produce dorsiflexion of the foot during swing phase of the gait cycle.

**FES system**



In some patients it could have a dramatic effect. In general, in stroke patients, FES improves walking speed by 16%, reduces the effort of walking by 29%, improves confidence and reduces falls. Bilateral FES and multi-channel FES systems are also in use but they are more complicated to use and need a lot of determination by the patient. Advanced systems are being implanted, which have more user friendly versions and they give better results.

### Orthotics

Orthotics play a key role in the overall management of most patients, in both acute and chronic stages as well as in upper or lower motor neurone lesions and myopathies. Hence it is vital to have the back up of a good orthotic department. They could be used alone in lower motor lesions such as foot drop due to common peroneal nerve palsy or in combination with botulinum toxin or other medications in upper motor neurone lesions.

Orthotic prescription will be determined by a discussion with the patient and an assessment of gait kinetics, manual muscle testing and joint range of motion. There is a huge range of orthotics, from simple foot insoles to complex reciprocating gait orthosis where when one flexes while other knee extends, used by cerebral palsy patients. More extensive orthosis such as Knee Ankle Foot Orthosis (KAFO) or Hip Knee AFOs (HKAFO) are used by post-polio patients, patients with myo-pathies, spina bifida, spinal lesions and cerebral palsy. Most of these are individualised orthosis and they sometimes need perfecting over many sittings due to complex biomechanics of mobility. Many users of extended orthosis depend totally on their orthosis to maintain their limited mobility.

Commonest form of orthosis is Ankle Foot Orthosis (AFO) used for patients having foot drop. A range of these are available to address differing biomechanics of these patients. Some need regular tweaking from the orthotists to make sure they fit well. In acute stages, orthosis also have a critical role in the prevention of contractures and many patients are given night splints such as 'foot up' splints as a preventative measure. Some patients may also identify their walking problem as due to knee instability. This may be due to the knee giving way or related to hyperextension, which can cause pain. There is a lack of evidence on orthotics for the management of knee instability related to neuromuscular disorders on pain and falls but control of knee alignment through use of rigid AFOs or through knee braces can be successful.

Patients with polyneuropathy commonly present with changes to the alignment of joints, which can lead to pain, instability or callous build ups under the feet. Custom insoles are an effective treatment of cavus foot

pain and its associated limitation in function by reducing and redistributing abnormal ground reaction forces.

**Wheelchairs and specialist seating**

Wheelchairs are very important for many patients. Most spinal injury patients are totally dependent on them while others do use it intermittently for indoor or outdoor mobility. There are many categories of wheel chairs and most individuals with good seating balance and upper limb function can use a standard self-propelled wheel chair. Others who are dependent on wheelchairs all day, need many other modifications to keep them comfortable and prevent pressure sores. Uncomfortable wheelchairs also could precipitate troublesome spasms. This is where specialist seating systems are needed. Hence it is absolutely vital for a Neuro-rehabilitation service to have access to a specialist wheelchair service. One of my patients, who has Duchenne's Muscular Dystrophy with severe weakness and could easily have been bed bound, has a well-adapted power chair for his needs. With this he goes all over UK conducting inspirational talks and also been to the parliament to lobby ministers. None of this would have been possible, if he did not have his accommodating powered wheelchair which he controls by head movements. Within limitations, his wheelchair allows him to maximize his quality of living.

**Head, trunk and pelvic supports**

**Moulded seating**

For a quadriplegic spinal injury patient, he may need head, trunk, pelvic and foot supports. Additionally, he will need a suitable pressure relieving cushion to prevent pressure sores. For a severe cerebral palsy patient with scoliosis, he will need to moulded wheelchair to accommodate posture, if it cannot be corrected by surgery. Additionally, to improve quality of life, for patients who do not have good upper limb function to self propel, powered wheelchairs are available which could be operated by either a joystick or other means.

**Surgery**

Surgery plays a vital role in a small number of patients with mobility disorders. Surgical interventions could involve bone, muscle, joints, ligaments, tendons or nerves. The goals of surgery may be to improve pain, minimize impairment and maximize motor function, increase muscle strength and control tone as well as spasticity and to promote self-care. Some are to improve bipedal mobility whereas others could be to improve wheelchair mobility by improving seating such as scoliosis corrective surgery. Implantation of ITB pump also falls into surgical intervention category. In severe spasticity, some are referred for dorsal rhizotomy. In many complex mobility disorders such as cerebral palsy, surgical interventions are done either over many years as new problems develop or sometimes done as single event. Surgery needs to be followed by therapy input

including splinting to optimize benefits. Examples of lower limb surgical interventions include femoral and tibial derotational surgery, osteotomy, tendon releases, tendon transfer/ lengthening, arthrodesis as well as a variety of foot surgeries particularly in conditions such as Charcot Marie Tooth Syndrome.

### Mobility and other aids

Most bipedal patients use a wide variety of mobility aids depending in their overall mobility as well as balance. These have to be ideally assessed by the therapists. These include a simple walking stick to a gutter frame. Most help mobility by widening the base to give stability when walking. Additionally, for patients to function at home, some patients need hoists or stair lifts. Hence it is important for an occupational therapist to visit patients at home to make suitable recommendations.

### Driving adaptations

Getting back to driving is also an important goal for many who may have had an acute disability. Hence it is a vital part of disability assessments. They are referred to disabled driving services to make recommendations. There are multiple driving adaptations available directly reflecting on their neurological disability as well as various other transfer and storage adaptations for wheel chair bound drivers. All these help them to improve their quality of living by helping them to get back to work or earn a living or by giving better social mobility.

### Environmental adaptations

Environment itself disables many patients within their home as well as outside. Once again occupational therapist will have a huge role to play by assessing the home environment. For a person in a wheelchair even a small step will be a huge challenge. They may recommend simple ramps and grab rails to overcome some of these problems.

## Conclusion

Mobility in neuro-rehabilitation ranges from bed mobility to high end activities such as running. For some, due to lifelong disabling conditions and for others it could be following an acute event. Multiple interventional modalities from simple to complex ones are available in isolation or in combination which should be delivered within a MDT team taking holistic needs into consideration. Such a service delivery should be able to optimise mobility within the limitations of patient's background pathology.

### References

1. Abbruzzese G. The Medical Management of Spasticity. *Eur J Neurol.* 2002 May; 9 Suppl 1:30-4; discussion 53-61.
2. Ko CK, Ward AB, Management of Spasticity, *Br J Hosp Med* 1997; **58**(8): 400-5.
3. Creamer M, Cloud G, Kossmehl P, Yochelson M, Francisco GE, Ward AB, Wissel J, Zampolini M, Abouihia A, Calabrese A, Saltuari L. Effect of Intrathecal Baclofen on Pain and Quality of Life in Poststroke Spasticity. *Stroke* 2018; **49**(9): 2129-37.
4. Watanabe Y, Bakheit AM, McLellan DL. A Study of the Effectiveness of Botulinum Toxin Type A (Dysport) in the Management of Muscle Spasticity. *Disabil Rehabil.* 1998; **20**(2): 62-5.
5. Sharif F, Ghulam S, Nawaz Malik A. Saeed Q Effectiveness of Functional Electrical Stimulation (FES) Versus Conventional Electrical Stimulation in Gait Rehabilitation of Patients With Stroke. *J Coll Physicians Surg Pak.* 2017; **27**(11): 703-6.
6. Khouri N, Desailly E. Contribution of clinical gait analysis to single-event multi-level surgery in children with cerebral palsy. *Orthop Traumatol Surg Res.* 2017; **103**(1S): S105-S11.
7. Tyson SF, Sadeghi-Demneh E, Nester CJ. A systematic review and meta-analysis of the effect of an ankle-foot orthosis on gait biomechanics after stroke. *Clin Rehabil.* 2013; **27**(10): 879-91.

Case report

# Oculopalatal tremor and hypertrophic olivary degeneration

**W L S Mahapitiya[1], A E S Senanayake[2], Darshana Sirisena[2], Manjula C. Caldera[3]**

*Sri Lanka Journal of Neurology,* 2020, **7**, 13-15


## Abstract

***Background:*** Oculopalatal tremor is characterized by synchronous occurrence of palatal tremor and pendular nystagmus. Oculopalatal tremor (OPT) follows a destructive lesion in the Guillain-Mollaret triangle (GMT) and is associated with hypertrophic inferior olive degeneration (HOD).

***Case presentation:*** We report a case of 45 years-old patient with palatal tremor and pendular nystagmus without ear click. He has had a brainstem stroke 11 months back. He had right side pyramidal drift, left side lower motor neuron type facial weakness and left abducens nerve palsy and mild gait ataxia in addition to oculopalatal tremor. MRI showed hypertrophic inferior olive degeneration.

***Conclusion:*** Ear click is an infrequent finding in symptomatic palatal tremor. Additional clinical features may be present in OPT depending on topography of initial structural lesion. There is a wide variety of time intervals between the occurrence of anatomical lesions and recognition of palatal tremor.


**Key words:** oculopalatal tremor, pendular nystagmus, Guillain-Mollaret triangle.

## Background

Palatal tremor is a rare movement disorder. Initially it was most commonly referred to as “palatal myoclonus”. However, it was subsequently termed as “palatal tremor” considering its continuous, rhythmic nature of the jerks of the soft palate[1]. Palatal tremor is of two types: symptomatic palatal tremor (SPT) and essential palatal tremor (EPT)[2].

## Case presentation

A 45-year-old man presented with rhythmic movements in the soft palate for several weeks. He denies clicking sounds in both ears. He was a diagnosed patient with hypertension and has had a stroke 11 months before with sudden onset double vision, mouth deviation to right side and right upper limb and lower limb weakness. CT brain was normal at that time and was managed as an ischemic brainstem stroke at a local hospital. Physical examination revealed rhythmic movements of soft palate and patient was not able to control it voluntarily. Eye examination revealed mild abduction deficit on left eye and pendular nystagmus. There was mild lower motor neuron type facial weakness on left side and a right-side pyramidal drift. His right-side tendon reflexes were exaggerated with extensor plantar response on same side. Left side tendon reflexes and plantar response were normal. His gait was slightly ataxic with tendency to fall to left side. His speech and higher functions were normal.

His blood investigations including full blood count, erythrocyte sedimentation rate, blood picture, liver function tests, renal function tests and electrolytes were normal. Electrocardiogram, echocardiogram and carotid doppler were also unremarkable. MRI brain showed increased T2-weighted signal and enlargement of left inferior olive (Figure 1).

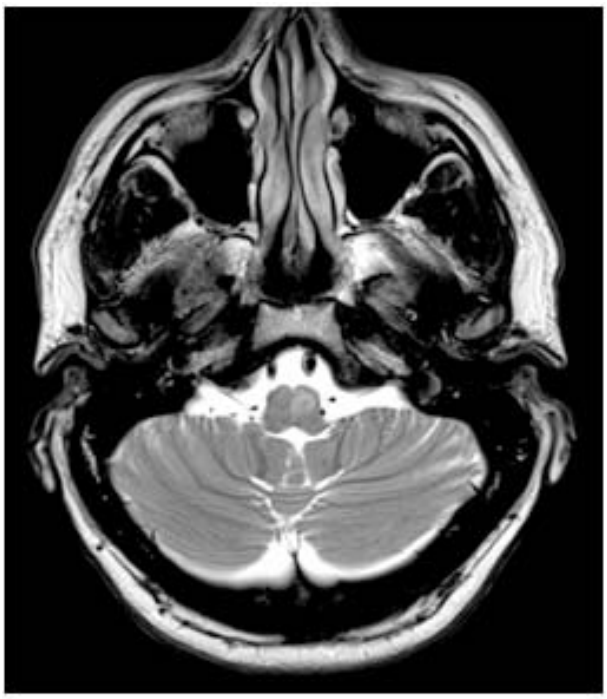


**Figure 1. Axial T2-weighted MRI image shows increased signal and enlargement of left inferior olive.**

[1]*Department of Neurology, National Hospital, Kandy, Sri Lanka,* [2]*Department of Neurology, National Hospital of Sri Lanka, Colombo, Sri Lanka,* [3]*Department of Neurology, Teaching Hospital Anuradhapura, Sri Lanka.*
Correspondence: W L S Mahapitiya E-mail: shyaman85@gmail.com

## Discussion

Rhythmic movements of soft palate in our patient are compatible with palatal tremor. Simultaneously, pendular nystagmus was also observed. His past history of combination of left abducens nerve palsy, lower motor type left facial palsy and contralateral hemiparesis point toward the lesion in the brainstem at pontine level. MRI findings are compatible with hypertrophic inferior olivary degeneration.

Palatal tremor (PT) comprises of two different entities: symptomatic palatal tremor (SPT) and essential palatal tremor (EPT). Palatal tremor may be unilateral, bilateral or asymmetrical[3]. Palatal movement in EPT results from activity of the tensor veli palatini muscle innervated by trigeminal nerve[4,5]. Tensor veli palatini muscle is attached to the lateral wall of the Eustachian tube and its rhythmic contraction is thought to be associated with repetitive opening and closing of the Eustachian tube, leading to the ear clicks[5,6]. In SPT, there is contraction of levator veli palatine muscle innervated by motor fibres from the facial nucleus or nucleus ambiguous causing palatal movements[4,5]. Levator veli palatine movement is also associated with ear click but it is not seen frequently[5]. Therefore, presence of ear clicks alone cannot differentiate between EPT and SPT.

Palatal tremor and ear click are the sole manifestations in EPT whereas in SPT, additionally, there may be ocular disorders and limb and gait ataxia. Oculopalatal (OPT) tremor refers to synchronous occurrence of palatal tremor and pendular nystagmus[4,7]. Pendular nystagmus is found to be present in 30% of SPT[2]. Vertical pendular nystagmus with varied combinations of torsional and horizontal components are typical for OPT[8,9]. Pendular nystagmus is most frequently asymmetric and dissociated in direction in the two eyes[10]. While PT is mostly asymptomatic, patients with pendular nystagmus may have decreased visual acuity and disturbing oscillopsia[4,10].

The site of the abnormality in EPT is unknown. However, SPT/OPT is believed to arise from destructive lesions in Guillain-Mollaret triangle (GMT), a triangle formed by the contralateral dentate nucleus, the ipsilateral red nucleus and the ipsilateral inferior olivary nucleus (ION)[4,7]. Afferent axons from contralateral dentate nucleus travel through contralateral brachium conjunctivum, cross the midline, turn around ipsilateral red nucleus, and descend in the ipsilateral central tegmental tract to reach the ipsilateral ION[4,7]. Efferent axons from ION cross midline, pass through contralateral inferior cerebellar peduncle to reach contralateral deep cerebellar nuclei. Central tegmental tract lesions are specifically associated with OPT compared to lesions of dentate nuclei/brachium conjunctivum where only PT is observed[8,10]. The most frequent etiology of structural lesions in brainstem or cerebellum is vascular, particularly hemorrhagic or ischaemic strokes. Other less common etiologies include brain trauma, brainstem tumours, surgical or gamma knife removal of brainstem cavernoma and multiple sclerosis[5,11].

SPT or OPT has been described in association with the anatomical observation of hypertrophic inferior olive degeneration (HOD)[4,12,13]. Olivary hypertrophy generally results from transynaptic deafferentation and loss of the inhibitory input from the contralateral dentate nucleus[5,12]. The hypertrophy of the ION appearing over a few months after the disruption of afferent fibers is accompanied by vacuolar changes in neurons and gliosis [5,12,13]. Neurons in the ION eventually become atrophied. However, gross olivary hypertrophy is constant[12,13]. These changes appear on MRI as signal changes on T2-weighted images and olivary hypertrophy with or without contrast enhancement. Increased olivary signal on T2-weighted images first appears approximately 1 month after the initial injury. Olivary hypertrophy develops 4 to 6 months after the acute event and resolved by 3 to 4 years[14,15]. Lesion in the dentate nucleus, superior cerebellar peduncle, or both cause contralateral HOD, but damage to the tegmental tracts leads to ipsilateral HOD[15].

There is a wide variety of time intervals between the occurrence of anatomical lesions and recognition of palatal tremor. It is observed that palatal tremor develops at least 1 month to 8 years after the initial insult (median between 10 and 11 months)[4,13,16], but nystagmus develops much earlier than PT[8]. Once PT or OPT is established, it persists for life[4]. However, few exceptional cases exist where PT or OPT have disappeared after many years[3]. 11 months later, it is noted palatal tremor in our patient.

Additional clinical features may be present in OPT depending on topography of initial structural lesion. Contralateral hemiplegia, contralateral hemi-hypoesthesia or spinothalamic syndrome, ipsilateral facial palsy and ipsilateral kinetic cerebellar syndrome are frequent findings[4]. Patients also frequently have eye movement abnormalities, such as fascicular abducens nerve palsy, internuclear ophthalmoplegia, one and a half syndrome and nuclear abducens syndrome[4,17].

Pendular nystagmus is the most symptomatic consequence of OPT. Hence, most of clinical trial have been mainly performed on acquired pendular nystagmus. Gabapentin and memantine are found to be effective in reducing nystagmus amplitude and frequency irregularity[18]. Some authors have also observed sustained decrease of nystagmus velocity in some patients[4]. Botulinum toxin have been tested for treatment of PT and acquired nystagmus with variable results[19,20,21].

## References


1. Zadikoff C, Lang AE, Klein C. The 'essentials' of essential palatal tremor: a reappraisal of the nosology. *Brain* 2006; **129**: 832-40.
2. Deuschl G, Toro C, Valls-Sole J, Zeffiro DS, Hallett M. Symptomatic and essential palatal tremor. Clinical, physiological and MRI analysis. *Brain* 1994; **117**: 775-88.
3. Pradeep S, Grewal P, Jahan S, Raslau FD, Slevin JT. Pearls & Oysters: Progressive ataxia and palatal tremor: Imaging and disease course. *Neurology* 2020; **94**(13).
4. Tilikete C, Desestret V. Hypertrophic olivary degeneration and palatal or oculopalatal tremor. *Front Neurol* 2017; **8**: 302.
5. Samuel M, Torun N, Tuite PJ, Sharpe JA, Lang AE. Progressive ataxia and palatal tremor (PAPT): clinical and MRI assessment with review of palatal tremors. *Brain* 2004; **127**: 1252-68.
6. Deuschl G, Lohle E, Heinen F, Lucking C. Ear click in palatal tremor: its origin and treatment with botulinum toxin. *Neurology* 1991; **41**: 1677-9.
7. Borruat FX. Oculopalatal tremor: current concepts and new observations. *Curr Opin Neurol.* 2013; **26**(1): 67-73.
8. Kim JS, Moon SY, Choi KD, Kim JH, Sharpe JA. Patterns of ocular oscillation in oculopalatal tremor: imaging correlations. *Neurology* 2007; **68** (14): 1128- 35
9. Nakada T, Kwee IL. Oculopalatal myoclonus. *Brain* 1986; **109** (Pt 3): 431-41.
10. Tilikete C, Jasse L, Pelisson D, Vukusic S, Durand-Dubief F, Urquizar C, et al. Acquired pendular nystagmus in multiple sclerosis and oculopalatal tremor. *Neurology* 2011; **76**(19): 1650-7.
11. Yun JH, Ahn JS, Park JC, Kwon DH, Kwun BD, Kim CJ. Hypertrophic olivary degeneration following surgical resection or gamma knife radiosurgery of brainstem cavernous malformations: an 11-case series and a review of literature. *Acta Neurochir* 2013; **155**(3): 469-76.
12. Jellinger K. Hypertrophy of the inferior olives. Report on 29 cases. *Z Neurol* 1973; **205**: 153-74.
13. Matsuo F, Ajax ET. Palatal myoclonus and denervation supersensitivity in the central nervous system. *Ann Neurol* 1979; **5**(1): 72-8.
14. Goyal M, Versnick E, Tuite P, et al. Hypertrophic olivary degeneration: meta analysis of the temporal evolution of MR findings. *AJNR Am J Neuroradio*l 2000; **21**: 1073-77.
15. Patay Z , Enterkin J , Harreld JH, et al. MR imaging evaluation of inferior olivary nuclei: comparison of postoperative subjects with and without posterior fossa syndrome. *AJNR Am J Neuroradiol* 2014; **35**(4): 797-802.
16. Legros B, Sheikoleslam Z, Hildebrand J, Baleriaux D, Manto MU. Palatal myoclonus appearing 8 years after removal of a cerebellar low-grade astrocytoma. *J Neurol* 2001; **248**: 990-2.
17. Itoh Y, Sakata E. Acquired pendular oscillation after brain-stem hemorrhage. *Acta Otolaryngol Suppl* 1989; **468**: 205-8.
18. Shaikh AG, Thurtell MJ, Optican LM, Leigh RJ. Pharmacological tests of hypotheses for acquired pendular nystagmus. *Ann N Y Acad Sci* 2011; **1233**: 320-6.
19. Penney SE, Bruce IA, Saeed SR. Botulinum toxin is effective and safe for palatal tremor: a report of five cases and a review of the literature. *J Neurol* 2006; **253**(7): 857-60.
20. Repka MX, Savino PJ, Reinecke RD. Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; **112**(10): 1320-4.
21. Talks SJ, Elston JS. Oculopalatal myoclonus: eye movement studies, MRI findings and the difficulty of treatment. *Eye* 1997; **11**: 19-24.

Case report

# Nonketotic hyperglycemic hemichorea – a diagnostic challenge for the treating physician

**K U I S Gunathilake[1], S R Jayarathne[2], V Sivasadana[2], M I M Rifath[2], S C Weerasinghe[2]**

*Sri Lanka Journal of Neurology,* 2020, **7**, 16-17


## Abstract

Non-ketotic hyperglycemic hemichorea (NHH) is a rare phenomenon occurring in patients with type II diabetes mellitus. The exact mechanisms for NHH is unclear. There are several proposed mechanisms involving GABA pathways. We report a case of a 63-year-old female who presented with Choreiform movements with characteristic CT changes of NHH, whose abnormal movements rapidly resolved with good glycaemic control.


**Key words:** chorea, non-ketotic hyperglycemic hemichorea, diabetes, basal ganglia hyperdensity

## Introduction

Non-ketotic hyperglycemic hemichorea also known as diabetic striatopathy or chorea-hyperglycaemia basal ganglia (C-H-BG) syndrome is a rare phenomenon occurring in patients with type II diabetes mellitus[1]. It is more common among females, specially of east Asian descent[2]. It is often missed or misdiagnosed as a haemorrhagic stroke completely diverting the management strategy. We report a case of NHH, which was successfully treated.

## Case report

A 63-year-old female presented to Teaching Hospital Anuradhapura with uncontrolled rhythmic movements of left side upper and lower limbs of one-week duration. The patient gave a history of type 2 diabetes mellitus for more than 5 years but the control of blood sugar was poor.

Her choreiform limb movements were disturbing her daily activities and causing significant psychological distress. A non-contrast CT scan of the brain revealed an abnormal hyperdensity in the right putamen and globus pallidus (Figure 1).

At presentation her random blood sugar was 348 mg/dl with HbA1C value of 14.2%. Arterial blood gas was normal and urine ketone bodies were negative. Her full blood count, liver function tests, ECG, 2D echo and carotid Doppler were normal. She was started on sub cutaneous insulin and risperidone. She made a complete recovery in one week with complete resolution of CT findings (Figure 2).

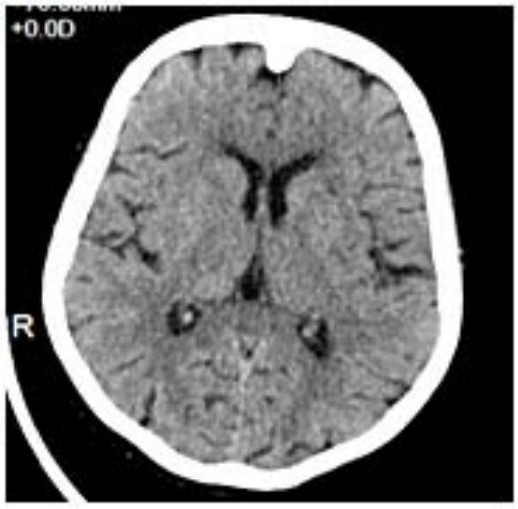



**Figure 1. NCCT showing right side basal ganglia hyper density.**

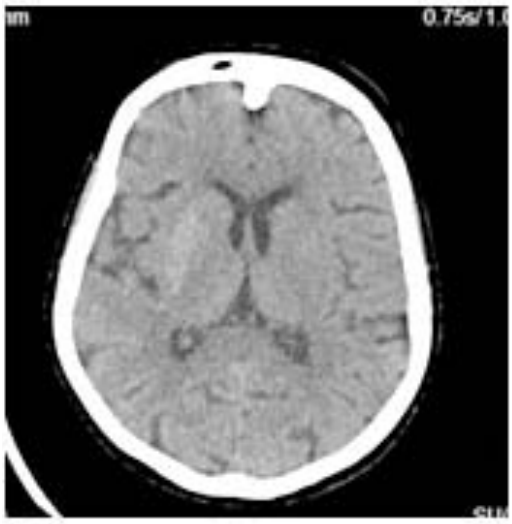


**Figure 2. Repeat NCCT brain.**

[1]*Postgraduate Institute of Medicine, University of Colombo, Sri Lanka,* [2]*Teaching Hospital, Anuradhapura, Sri Lanka.*

## Discussion

NHH is a rare complication of poorly controlled diabetes[1]. Typical patient with NHH chorea will have the triad: nonketotic hyperglycemia, hemichorea, and basal ganglia increased signal in T2MRI or high density in CT scan[5].

The exact mechanisms for NHH is unclear, however there are several postulated hypotheses. One theory suggests reduced activity of Gamma Ammino Butayric Acid (GABA), the main inhibitory neurotransmitter in the basal ganglia, due to cerebral hypo perfusion along with hyper viscosity due to hyper glycaemia. Direct metabolic effect of increased plasma glucose and augmented response to dopamine due to receptor hypersensitivity is also suggested to play a role[2,3].

NHH has a characteristic appearance in NCCT where basal ganglia show hyper density[4]. The diagnosis of NHH can be missed in clinical setting as the hyper density may not be clearly visible and clinician may attribute the movement disorder to a lacunar infarct in the background of diabetes mellitus[5]. Even when its visible it may be mistaken for a basal ganglia hemorrhage unless you are aware of NHH[3,6]. These diagnostic errors lead to erroneous management of this condition. Proper glycaemic control with normalization of blood sugar is the mainstay of management.

## Conclusion

Awareness of the NHH could cut down extensive testing on a typical presentation of this functionally debilitating but treatable condition. The general treatment measures include improving control of blood glucose and the use of neuroleptic drugs if necessary.

### References

1. Non-ketotic hyperglycaemic hemichorea | Radiology Reference Article | Radiopaedia.org [Internet]. [cited 2020 Jul 11]. Available from: https://radiopaedia.org/articles/non-ketotic-hyperglycaemic-hemichorea
2. Expert Opinion: Chorea in the Setting of Hyperglycemia – A Case Report and Review of the Literature – Practical Neurology [Internet]. [cited 2020 Jul 11]. Available from: https://practicalneurology.com/articles/2010-mar-apr/expert-opinion-chorea-in-the-setting-of-hyperglycemia--a-case-report-and-review-of-the-literature
3. Wilson TJ, Than KD, Stetler WR, Heth JA. Non-ketotic hyperglycemic chorea-hemiballismus mimicking basal ganglia hemorrhage. *J Clin Neurosci.* 2011; **18**(11): 1560-1.
4. Suranji GLASN, Weerasinghe SC, Peiris PJ. Unilateral basal ganglia hyper intensity in a patient with poorly controlled diabetes. *Sri Lanka J Diabetes Endocrinol Metab* [Internet]. 2018 Apr 17 [cited 2020 Jul 11]; 8(1): 53. Available from: https://sjdem.sljol.info/article/10.4038/sjdem.v8i1.7353/
5. Chang X, Hong W, Yu H, Yao Y. Chorea associated with nonketotic hyperglycemia: A case report with atypical imaging changes. *Medicine* (Baltimore). 2017; **96**(45): e8602. doi:10.1097/MD.0000000000008602
6. Hegde AN, Mohan S, Lath N, Lim CCT. Differential diagnosis for bilateral abnormalities of the basal ganglia and thalamus. *Radiographics* 2011; **31**(1).

Case report

# A unique pattern of memory deficits in reversible dementia induced by B12 deficiency

**K D Pathirana[1], W G S G Karunaratna[1], E A W Sewwandi[1], S Thotagamuwa[1], P W Kodituwakku[2]**

*Sri Lanka Journal of Neurology,* 2020, **7**, 18-19

## Introduction

Although there is a large body of literature on B12 deficiency-induced dementia, relatively little is known about its neuropsychological characteristics[1,2]. We report a middle-aged male vegan with dementia showing unique pattern of learning and memory deficit on detailed assessment due to B12 deficiency. He completely recovered with parenteral vitamin B12 therapy.

## Case report

A 45-year-old, right-handed, male working in a printing press was admitted with altered behavior and confusion. He complained of a tremor in hands and obsession about cleanliness and neatness. At the time of admission, he had stopped going to work. He had been a strict vegan for over 25 years due to an aversion to animal foods.

On examination he was slightly pale, pigmented and had a fine tremor on outstretched hands. He was not making eye contacts. The rest of the general medical examination, cardiovascular and respiratory system were normal. He scored 19/30 in the Mini-Mental State Examination. Motor and sensory examination of the limbs as well as the reflexes were normal.

Pre-treatment investigations showed, Hb: 10 g/dL, MCV: 129.9fL (80-100), WBC: 7600 /$mm^3$ with normal differential count, platelet count: 140,000 /$mm^3$, reticulocyte count: 0.4%, blood picture: oval macrocytes and hypersegmented neutrophils, ESR: 25 mm $^{st}$ hr, $Na^+$:135 mmol/L, $K^+$: 4.6 mmol/L, $Ca^{++}$: 1.19 mmol/L (1.12-1.32), Magnesium: 2.5/dL (1.7-2.7), FBS: 88 mg/dl, serum vitamin B12 level was 235 pg/mL (223-925), VDRL: non-reactive, antibody to HIV 1 and 2: negative.

MRI and CT scans of the brain, EEG, and cerebrospinal fluid analyses were normal, as were renal and liver functions tests.

## Assessment of memory

His memory was assessed with Lankan Verbal Learning Test (LVLT) and Modified Enhanced Cued Recall Test (MECRT). LVLT is a list learning test in which the patient was required to recall a list of 12 words drawn from 3 categories (spices, clothing items, and furniture) over 3 learning trials. Following a 20-minute filled delay, memory for the words was tested by means of free recall and recognition memory methods. MECRT comprises 4 cards, each showing 4 line-drawings of common items[3]. The test is administered by showing one card at a time, instructing the patient to name each item in response to a semantic cue (e.g. "One of these is a vegetable. What is its name?"). Once the patient had named the 4 items on a card, the examiner removed it and asked him to recall them. The patient was asked to recall all the items soon after the administration of the 4 cards (immediate recall) and then following a 20-minute delay (delayed recall). Thus, in the latter test the examiner provided more support for learning than in the former. While patients with Alzheimer's disease do not benefit from such support[4], those with memory problems due to attentional issues are known to benefit from it. Accordingly, the two memory tests allowed assessing memory as a function of the level of learning support.

## Results of the memory tests

Based on norms established for Sri Lankan older persons, the patient's raw scores were converted to T scores, which have a mean of 50 and standard deviation of 10. As shown in Table 1, the patient performed in markedly impaired range at baseline on the LVLT which provided low-level support. However, performance on this test significantly improved and maintained after B12 supplementation.

[1] *University of Ruhuna, Faculty of Medicine, Galle, Sri Lanka,* [2]*University of New Mexico School of Medicine, Albuquerque, USA.* Correspondence: K D Pathirana E-mail: kdpathirana@hotmail.com

**Table 1. Memory as a function of low and high-levels of cognitive support**

| *Cognitive tests* | *Baseline* | *2-month* | *7-month* | *12-month* |
|---|---|---|---|---|
| Low-level support | | | | |
| **LVLT** | | | | |
| Free recall total (3 trials) (T score) | 30 | 63 | 53 | 59 |
| Delayed free recall (T score) | <20 | 54 | 69 | 61 |
| Recognition memory (T score) | <20 | 61 | 61 | 61 |
| High-level support | | | | |
| **MECRT** | | | | |
| Immediate free recall (T score) | 42 | 51 | 70 | 70 |
| Semantic cue (raw score) | 7/9 | 9/9 | 3/3 | 3/3 |
| Delayed free recall (T score) | 44 | 48 | 57 | 62 |
| Semantic cue (raw score) | 6/8 | 9/9 | 5/5 | 4/4 |

In sharp contrast, the patient did not show learning deficits at baseline on the MECRT which provided high-level memory support. On this test, he recalled the items on the free recall trial when semantic cues were given, showing that he had encoded all the items.

He was treated with Cyanocobalamin 1000µg/ intramuscularly daily for five days followed by monthly injections. Follow-up neuropsychological assessments were performed at 2, 7, and 12 months after the initiation of treatment. Serum B12 level at 12 month follow up was within the normal range (510.7 pg/ml). Having fully recovered the patient has returned to work at the time of writing and continue to take regular B12 injections and when not available oral B12 supplements.

## Discussion

Our patient had clinical and haematological features characteristic of B12 deficiency with borderline low B12 levels. Ideally in such cases the raised levels of Methyl malonic acid (MMA) and homocysteine should be demonstrated. However we could not do these levels as patient could not afford. Together with clinical features, dramatic improvement with intramuscular B12 is strongly supportive of the diagnosis of B12 deficiency. He had neurological features known to be associated with Vitamin B12 deficiency like, tremor and an obsessive compulsive disorder. He showed a distinct pattern of memory abnormality due to Vitamin B12 deficiency. While the patient had great difficulty in learning an aurally-presented list of 12 items, he learned with relative ease a list of 16 items when they were presented through multiple modalities (e.g. visual and aural). This pattern of results stands in stark contrast to that seen in Alzheimer's disease with failure to encode new information despite receiving memory support[5]. It appears that attentional deficits and confusion cause disruption in learning in patients with B12 induced dementia. This finding is consistent with the observation that patients with B12 deficiency show a pattern of neuropsychological deficits similar to that seen in frontotemporal dementia[1].

### References

1. Osimani A, Berger A, Friedman J, Porat-Katz BS, Abarbanel JM. Neuropsychology of vitamin B12 deficiency in elderly dementia patients and control subjects. *Journal of Geriatric Psychiatry and Neurology* 2005; **18**(1): 33-8.
2. Lachner C, Steinle NI, Regenold WT. The neuropsychiatry of vitamin B12 deficiency in elderly patients. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2012; **24**(1): 5-15.
3. Solomon PR, Pendlebury WW. Recognition of Alzheimer's disease: the 7 Minute Screen. *Family Medicine* 1998; **30**(4): 265-71.
4. Bäckman L, Small BJ. Influences of cognitive support on episodic remembering: tracing the process of loss from normal aging to Alzheimer's disease. *Psychology and Aging* 1998; **13**(2): 267-76.
5. Salmon DP, Bondi MW. Neuropsychological assessment of dementia. *Annual Review of Psychology* 2009; **60**: 257-82.

Case report

# Acute ischaemic stroke as a rare complication of multiple wasp bites

**K U I S Gunathilake[1], M I M Rifath[2], S R Jayarathne[3], M Perera[3], Manjula C. Caldera[4]**

*Sri Lanka Journal of Neurology,* 2020, **7**, 20-21


## Abstract

Wasp bite can give rise to variety of clinical symptoms from local reactions to systemic effects such as anaphylaxis and vascular thrombosis. Neurological manifestations like strokes are rare in wasp bites. Pathophysiology of vascular involvement following wasp bite is yet not well known but presumed to be multifactorial.

A 40-year-old previously healthy woman presented with multiple wasp bites on face. On admission she was stable without any haemodynamic instability or neurological deficit. Next day she developed a left temporoparietal infarction. Screening for other contributory factors were negative.


## Introduction

Wasp bites are common encounters in general medical wards in especially in rural areas of Sri Lanka[1]. Wasps are categorised under the insect order Hymenoptera which comes under phylum Arthropoda. They are the third largest of all insect orders and useful as pollinators of wild and cultivated flowering plants[2]. Wasp sting though a minor injury may lead to serious medical complications. It can vary from simple local reactions to life threatening systemic complications including anaphylaxis and arterial thrombosis. Vascular thrombosis is a rare manifestation of wasp venom and only few cases have been reported in the literature[3]. The pathophysiology of vascular thrombosis may include vasoactive inflammatory and thrombogenic properties of venom as well as vasospasm caused by the venom.

## Case report

A 40-year-old previously healthy woman from Anuradhapura, Sri Lanka presented to accident and emergency department with multiple wasp bites on face. She was haemodynamically stable and clinical examination was unremarkable other than facial swelling secondary to wasp bites. She was later transferred to general medical ward for observation. Following morning, she was found to be confused. Neurological examination revealed left-right disorientation with hemi sensory and visual neglect. Her cranial nerves, motor examination of the limbs, and other system examination were normal. Urgent non contrast CT scan of the brain revealed an infarction in left temporo-parietal region. Her blood pressure, pulse rate, respiratory rate and oxygen saturation were within normal limits. She was started on antiplatelet drugs and statins.

Her full blood count, blood picture, liver and renal function tests, fasting blood sugar, lipid profile, electrocardiogram, transthoracic echocardiogram and transoesophageal echocardiogram with bubble contrast to exclude right to left shunts, carotid doppler, 24-hour Holter monitoring were normal. Thrombophilia screening tests including diluted russel viper venom test, kaolin clotting time, anticardiolipin antibodies, anti-beta-2 glycoprotein I antibodies, genetic thrombophilia screening tests (Factor V Leiden, Prothrombin 20210G>A, MTHFR 677C>T), Ham's test, serum homocysteine level did not reveal any abnormality. A CT angiogram of brain and neck vessels which was done on the third day of stroke was normal. She made a marked recovery in three months with mild deficits in episodic memory on cognitive assessment.

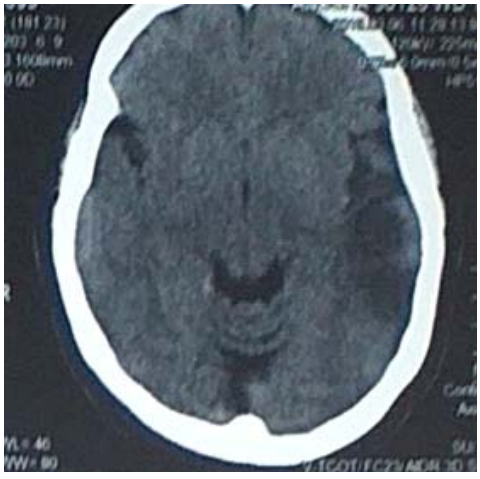


**Figure 1. Axial image of non- contrast CT scan of the brain showing infarction in left temporo-parietal region.**

[1] *Registrar in General Medicine,* [2]*Consultant Physician,* [3]*Senior House Officer,* [4]*Consultant Neurologist, Teaching Hospital Anuradhapura, Sri Lanka.* Correspondence: Manjula Caldera E-mail: calderamanjula@yahoo.com

With the temporal association of events in this previously healthy woman without other risk factors for ischaemic stroke, it was concluded that the stroke was associated with the wasp bites.

## Discussion

Wasp bites commonly cause simple allergic reactions whereas systemic complications including arterial thrombosis and anaphylaxis are rare[1,6]. Other reported systemic complications of wasp bite include myasthenia gravis, peripheral neuritis, Guillain-Barré syndrome, diffuse alveolar haemorrhage, acute renal failure, thrombocytopenic purpura and vasculitis[4].

Wasp venom contains mainly three categories of compounds.

A) High molecular weight proteins including phospholipases, hyaluronidase and antigen V. These molecules even in smaller amounts can cause allergic reactions and anaphylaxis.

B) Low-molecular-weight peptides including mastoparans, wasp kinin and chemotactic peptides which should present in larger quantities to cause complications such as anaphylaxis and other forms of systemic reactions.

C) Bioactive molecules including histamine, serotonin, catecholamines, acetylcholine and tyramine which cause vascular spasm, vascular inflammation and thrombosis[2].

Left middle cerebral artery territory infarction following multiple wasp bites[5], left cerebral infarction following three wasp bites[6] and cerebellar haemorrhagic infarction following multiple bee stings[7] have been reported. Few reports are available from Sri Lanka of cortical infarcts following multiple wasp and bee sting bites[8,9]. In our case we presume ischaemic stroke was potentiated by multiple wasp bites.

Exact pathophysiology of wasp venom induced arterial thrombosis is yet to be described. It may be multifactorial. Ischaemia due to hypotension following anaphylaxis is a possibility though we did not observe this in our case. Leukotrienes and thromboxane in venom can cause platelet aggregation and thrombosis whereas phospholipases trigger an IgE mediated reaction cascade leading to mast cell activation and synthesis of number of inflammatory mediators. Direct toxic effect of wasp venom compounds and vascular inflammation may also play a role[8] Vasospasm and blood cell aggregation followed by thrombosis is another possible mechanism[9]. It is most likely that cerebral infarction in this patient was a result of combined effects of above mentioned mechanisms.

## Conclusion

Physicians in rural medical practice encounter large number of wasp bites. Stroke is a rare but serious complication of hymenoptera envenomation. Awareness of these complications may prevent unnecessary investigations and delays in treatment.

### References

1. Clinico-epidemiology of arthropod stings and bites in primary hospitals of North Western province of Sri Lanka: Clinical Toxicology: Vol 56, No 10 [Internet]. [cited 2020 Apr 24]. Available from: https://www.tandfonline.com/doi/full/10.1080/15563650.2018.1447120

2. Dongol Y, Dhananjaya BL, Shrestha RK, Aryal G. Pharmacological and Immunological Properties of Wasp Venom. In: Pharmacology and Therapeutics. In Tech 2014.

3. Guzel M, Akar H, Erenler AK, Baydin A, Kayabas A. Acute ischemic stroke and severe multiorgan dysfunction due to multiple bee stings. *Turkish J Emerg Med.* 2016; **16**(3): 126-8.

4. Greif M, Pohl T, Oversohl N, Reithmann C, Steinbeck G, Becker A. Acute stent thrombosis in a sirolimus eluting stent after wasp sting causing acute myocardial infarction: A case report. *Cases J.* 2009; **2**(8).

5. Riggs JE, Ketonen LM, Bodensteiner JB, Benesch CG. Wasp sting-associated cerebral infarction: A role for cerebrovascular sympathetic innervation. *Clin Neuropharmacol* [Internet]. 1993 Aug [cited 2020; **16**(4): 362-5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8374916

6. Starr JC, Brasher GW. Wasp sting anaphylaxis with cerebral infarction. *Ann Allergy* [Internet]. 1977 Dec [cited 2020 Apr 24];39(6):431-3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/596679

7. Bhat R, Bhat KR, Shivashankar, Pais R. Bilateral haemorrhagic cerebellar infarction following honey bee sting. *J Assoc Physicians India* 2002; **50**(5): 721-2.

8. Varuni K, Sivansuthan S, Joseph Piratheepan G, Gajanthan R. A case report on unusual cause of young ischemic Cerebrovascular Accident: a rare complication of honey bee stings. *Jaffna Med J.* 2018; **30**(2): 32.

9. Dalugama C, Gawarammana IB. Ischemic stroke following a wasp sting – A rare complication: A case report. *J Med Case Rep.* 2018; **12**(1).

Point of view

# Is testosterone a potential agent for patients with delayed recovery from Guillain-Barre Syndrome?

**A S Vidanagamage[1], L Weeratunga[1], E L Asfir[1], I K Gooneratne[1], A Fernando[1]**

*Sri Lanka Journal of Neurology,* 2020, **7**, 22-27


## Abstract

***Background:*** Management of some of the patients with Guillain-Barre syndrome is challenging, requiring weeks to months of intensive care and prolonged institutional care.

***Case report:*** We report a 32-year-old male with acute inflammatory demyelinating polyneuropathy (AIDP) with markedly delayed recovery. He was ventilator dependent and multiple therapeutic interventions were attempted.

Other possible contributing factors for delayed recovery were looked into. Co-existing critical illness myopathy and polyneuropathy with low level of serum testosterone were detected. Following replacement of testosterone, he was weaned off from the ventilator within a short period of time after eleven weeks of ventilator dependency and slow recovery of neurological weakness had been achieved resulting in total independency and normal working capacity.

***Conclusion:*** Delayed recovery in GBS could be multifactorial. The effects of neuroendocrine changes in a critical illness could alter the expected recovery process. Thus, the role of testosterone in recovery from peripheral nerve injury, as well as in critical illness myopathy needs to be looked into.


**Key words:** Guillain-Barre syndrome, delayed recovery, critical illness myopathy, testosterone

## Case report

A 32-year-old male presented with bilateral upper and lower limb numbness followed by progressive ascending type weakness and a preceding history of recent diarrheal illness.

On examination there was bilateral symmetrical proximal predominant weakness with areflexia. His vital capacity (VC) declined from the 4th day of weakness and his blood pressure fluctuated with intermittent high values. On the 6$^{th}$ day of weakness, he was intubated.

The nerve conduction study showed an acute inflammatory demyelinating polyneuropathy (AIDP) pattern and the CSF showed cyto-protein dissociation compatible with Guillain-Barre syndrome. He was treated with IV immunoglobulin 0.4 g/kg for 5 days.

The recovery was very slow, and he underwent tracheostomy following prolonged intubation on the 12$^{th}$ day. He received a second cycle of IV immunoglobulin on 15$^{th}$ day of weakness. Due to poor recovery and dependency on a ventilator, in the absence of an alternative treatment strategy and with limited evidence in literature, therapeutic plasma exchange (PEX) was commenced on the 31st day of the illness. Only four out of five cycles could be performed as he developed gram negative septicemia. However, there was no clinical improvement. As he had a very long intensive care unit (ICU) stay with poor recovery, a second course of plasma exchange was commenced on the Day 51. In fact, his recovery was poor and was ventilator dependent.

The long illness was complicated with syndrome of inappropriate ADH release leading to hyponatremia (SIADH) which was managed successfully with fluid restriction. He suffered from a few episodes of febrile illnesses while in the ICU where there was culture positivity with gram negative bacteria on two occasions which were managed successfully with antibiotics. Repeat nerve conduction study on Day 71 showed absent sensory motor responses in the limbs indicating advanced secondary axonal loss following acute neuropathy. The Electromyogram (EMG) showed mixed neurogenic and myopathic changes suggestive of additional myopathic dysfunction secondary to prolonged critical illness. At the same time his serum testosterone level was low, although the serum dehydroepiandrosterone (DHEA) level was normal.

On anecdotal evidence it was decided to give him intra muscular testosterone 300 microgram weekly for three weeks, which was started on day 74 and completed on day 87. Within the first week, there was a marked increase in the vital capacity, and he was weaned off from the ventilator by day 83. The improvement of limb power was gradual and did not show such a dramatic response.

[1]*Institute of Neurology, National Hospital of Sri Lanka.*
Correspondence: Kishara Gooneratne E-mail: kishig@gmail.com

Repeat nerve conduction study and electromyography was done on day 101 and showed recovering neurogenic changes and absence of myopathic changes previously noted on day 71. Furthermore, sensory and motor responses were not yet evocable in the lower and upper limbs. This suggests established axonal degeneration following acute neuropathy. By day 180 the patient showed significant clinical recovery as he could walk without support and went back to his profession as a doctor by day 250 of the illness.

## Investigations

CSF – Protein 190 g/L, cells L- 5, RBC – 8 Polymorphs – nil, Glucose 5.4 mol/l, RBS – 9.3 mol/L

**First nerve conduction study on day 3**

| Nerve | Segment | Amplitude | Conduction Velocity [normal range] |
|---|---|---|---|
| **Motor nerve conduction** | | | |
| Right ulnar | Wrist<br>Wrist-elbow | 3.17 mV<br>2.99 mV (5.5 ± 2.0 (2.7)) | 50.8 m/S<br>[58.7 ± 5.1 (49)] |
| Left ulnar | ADM | 1.95 mV | |
| | Wrist-elbow | 1.88 mV (5.5 ± 2.0 (2.7)) | 45.2 m/S<br>[58.7 ± 5.1 (49)] |
| Left ulnar | FDI | 2.54 mV | |
| | Wrist-elbow | 1.33 mV<br>Conduction Block | 46.4 m/S<br>[58.7 ± 5.1 (49)] |
| Right peroneal | Ankle | 720 µV | |
| | Ankle-fibula | 720 µV [5.1 ± 2.3 (2.5)] | 38.3 m/S [48.3 ± 3.9 (40)] |
| Right tibial | Ankle | 2.55 mV [5.8 ± 1.9 (2.9)] | |
| Left peroneal | Ankle | 850 µV (5.1 ± 2.3 (2.5)) | |
| | Head of fibula | 739 µV | 40.3 m/S [48.3 ± 3.9 (40)] |
| Left tibial | Ankle | 5.42 mV (5.8 ± 1.9 (2.9)) | |
| **Sensory nerve conduction** | | | |
| Right ulnar | Wrist | 3 µV (35.0 ± 14.7 (18)) | |
| Left ulnar | Wrist | 3.5 µV (35.0 ± 14.7 (18)) | |
| Right sural | Sural | 35.3 µV (20.9 ± 8.0) | |
| Left sural | Sural | 38.8 µV (20.9 ± 8.0) | |
| EMG – Neurogenic changes only | | | |

**Second nerve conduction study on day 71**

| **Motor nerve conduction** | | | |
|---|---|---|---|
| Right Median | Wrist | NR | |
| | Wrist-elbow | | |
| | Elbow-axilla | | |
| Right Ulnar | Wrist | NR | |
| | Wrist-elbow | | |
| Right Peroneal | Ankle<br>Head of fibula | <br>NR | |
| **Sensory nerve conduction** | | | |
| Right Ulnar | | NR | |
| Right Sural | | NR | |
| Right Radial | | NR | |
| EMG – Mixed neurogenic and myopathic changes | | | |
| Left Biceps | Poor activation, small polyphasic unstable units | | |
| Right Biceps | Poor activation and small units | | |
| Right rectus femoris | No MUP activity | | |
| Right Extensor Digitorum | Fibrillation | | |
| | Positive Sharp Waves<br>Occasional small MUP | | |

**Third nerve conduction study on day 102**

| **Motor nerve conduction** | | | |
|---|---|---|---|
| Right Median | | NR | |
| Right Ulnar | | NR | |
| Right Peroneal | | NR | |
| **Sensory nerve conduction** | | | |
| Right Ulnar | | NR | |
| Right Sural | | NR | |
| Right Radial | | 3 μV | |
| EMG | | | |
| Right Rectus Femoris | Poor activation<br>Bursts of large MUPs | | |
| Right Biceps | Large MUPs<br>Reduced interference | | |
| Previously noted myopathic changes are not seen and only recovering neurogenic changes are noted | | | |

**Other investigations**

| Day of illness | 6 | 59 | 87 | 94 |
|---|---|---|---|---|
| Hemoglobin – g/dl | 14.8 | 12 | 11 | 13.7 |
| S. Protein – g/L | 80 | 52 | 61 | |
| S. Albumin – g/L | 36 | 30 | 30 | |
| CRP | 12 | 95 | 48 | 13 |
| Testosterone | | 144 | 302 | |
| S. DHEA | | 5.8 | 5.9 | |

Normal values – S. DHEA – 3.8-13.1 µmol/L, Serum testosterone – 241-827 ng/dL

**Clinical progression of the disease with muscle power in MRC grading**

| Day of illness | VC/ Cc | Neck power | UL Proximal | UL distal | LL proximal | LL distal |
|---|---|---|---|---|---|---|
| 8 | 1000 | 2 | 2 | 3 | 2 | 2 |
| 15 - 2nd cycle of IV IG | | 2 | 0 | 0 | 0 | 0 |
| 27 | | 2 | 0 | 0 | 0 | 0 |
| 31 - PEX commenced | | | | | | |
| 51 - Second round of PEX | | | | | | |
| 58 | | 3 | 1 | 0 | 0 | 0 |
| 70 | | 3 | 2 | 1 | 0 | 0 |
| 74 (1st dose of Testosterone IM 300 mg | 350 | 3 | 2 | 1 | 0 | 0 |
| 76 | 850 | 4 | 2 | 1 | 0 | 0 |
| 78 | 1200 | | | | | |
| 80 | 1100 | | | | | |
| 83 off ventilator | | 4 | 2 | 2 | 2 | 0 |
| 85 | | 4 | 2 | 2 | 2 | 0 |
| 87 | | 4 | 3 | 2 | 3 | 0 |
| 91 | | 4+ | 4 | 4- | 3 | 3 |
| 107 | 1700 | 5 | 4 | 4 | 3 | 3 |
| Patient was transferred to ward | | | | | | |

Therapeutic plasma exchange (PEX), Intra venous immunoglobulin (IV IG)

## Discussion

This case highlights the management challenges in a patient with poor recovery in GBS on the background of limited evidence based treatment options. In fact, this has become a challenging situation worldwide, where some patients with poor recovery are kept in intensive care units for many months due to ventilator dependency, often being bed bound with a tracheostomy tube and permanent disability. About 50-70% recover without symptoms or with minor deficits that does not affect their day to day activities[1]. This patient did not show signs of recovery up to 8 weeks into the illness and he was ventilator dependent with remote expectations of recovery facing complications related to ICU stay.

### Factors affecting delayed recovery in GBS

There are several factors affecting delayed recovery in GBS. Old age, history of diarrhea preceding the weakness, and a low medical research council sum score (MRC-SS) at the time of hospital admission and after 1 week, were associated with inability to walk in the next few weeks to 6 months[2].

A significant proportion of GBS patients require intensive care support. Neuroendocrine changes during a long-lasting critical illness are different from changes during the acute phase. In the acute phase, the anterior pituitary actively secretes and there is peripheral inactivation of anabolic hormones. Whereas, prolonged critical illness is characterized by diminished neuroendocrine stimulation of the pituitary. Therefore, acute and prolonged critical illness are likely to be two different neuroendocrine paradigms. In acute stress, turning off the anabolic effects of adrenal androgens may be an appropriate response in order to redirect the utilization of energy. But, when a severe stressful condition last for a long time, hypogonadotropism can result[3].

This patient, who was a healthy young adult who was a father of a 5 months old child, was found to have a low level of serum testosterone (144 ng/dL) in the 8$^{th}$ week of illness. The normal range for his age is 241-827 ng/dL. His clinical course drastically changed following replacement of testosterone.

### Role of testosterone in nervous system

Testosterone act on several sites of the nervous system by several mechanisms. It could affect, the myelin sheath, the axons and the myocytes. In this patient, following the acute inflammatory demyelinating peripheral neuropathy, there was secondary axonal degeneration and coexisting critical illness myopathy. However, following therapy with testosterone his respiratory functions improved rapidly with slow recovery of limb power. Objectively the EMG study following therapy showed marked improvement of the myopathy with recovering neurogenic changes. However, on the nerve conduction study, the neurons were still not evocable as neurophysiological recovery lags markedly behind the clinical recovery.

The effects of testosterone on myelin had been demonstrated by several groups experimentally. Rashad Hussain et al demonstrated that treatment with testosterone could efficiently stimulate the formation of new myelin and could reverse the myelin damage in chronic demyelinating brain lesions caused by a toxin, cuprizone, which is toxic for oligodendrocytes. They also have identified the androgen receptor as a novel therapeutic target for myelin recovery[4]. This was reinforced by several other in vitro studies[5,6].

In peripheral nervous system, Schwan cell is responsible for myelination and Melcangi RC et al brings out experimental evidence of effects of testosterone and other sex steroids on gene expression on two peripheral myelin proteins, the glycoprotein Po and peripheral myelin protein 22 (PMP22) which play a vital role in the rebuilding of myelin. There is growing evidence of importance of androgen receptor with regard to its role in peripheral nervous system disorders and as a potential target for therapeutic intervention in demyelinating disorders of peripheral nervous system[7,8].

The role of testosterone in axonal regeneration of motor neurons and dendrites had been recognised. It plays an important role in the development of central nervous system. Androgens alter the morphology, survival and axonal regeneration of motor neurons. Androgen treatment enhances the ability of motor-neurons to recover from regressive changes and regenerate both axons and dendrites, restoring normal neuromuscular function through a variety of molecular pathways[9,10]. There are many important effects of testosterone on myocytes. Enhanced contractile protein synthesis is an important mechanism by which testosterone can enhance the size of muscle fibers. Testosterone induces the hypertrophy of both type I and type II muscle fibers. By several mechanisms it stimulates precursor cell proliferation and myogenic lineage in order to regenerate muscle cells[11,12].

On the other hand, when considering the effect of androgen deprivation, for instance in patients with prostate carcinoma, who were treated with androgen deprivation therapy (ADT), several neuromuscular effects could be observed. Those include decreased neuromuscular performance due to reduced motor unit recruitment, reduced fiber innervation and reduced acetylcholine release. Reduced androgens in serum also inhibit the motor growth and repair in muscle and cause atrophy of muscles[13]. All these suggest an important role for androgens and androgen receptor on nervous system.

## Conclusion

Delayed recovery in Guillain-Barre syndrome could be multifactorial. The unnoticeable neuroendocrine changes that take place in critical illness could alter the expected recovery process. Testosterone as an androgen has a wide spectrum of action on central and peripheral nervous system. There was significant objective improvement following replacement of testosterone in this patient. The therapeutic role of testosterone and the androgen receptor in recovery from nerve injury and critical illness myopathy need to be looked into.

### References


1. Ranawaka UK. Guillain-Barre syndrome – a Sri Lankan profile. *Journal of the Ceylon College of Physicians* 2014; **45**: 6-15.
2. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. *Neurology* 2011; **76**(11): 968-75. doi: 10.1212/WNL.0b013e3182104407
3. Berghe GVD, Zegher FD, Bouillon R. Acute and Prolonged Critical Illness as Different Neuroendocrine Paradigms. *The Journal of Clinical Endocrinology & Metabolism* 1998; **83**(6): 1827-34. https://doi.org/10.1210/jcem.83.6.4763
4. Hussain R, Ghoumari AM, Bielecki B. The neural androgen receptor: a therapeutic target for myelin repair in chronic demyelination. *Brain* 2013; **136**(Pt 1): 132-46. doi: 10.1093/brain/aws284
5. Bielecki B, Matterm C, Ghoumari AM, et al. Unexpected central role of the androgen receptor in the spontaneous regeneration of myelin. *Neuroscience* 2016; **113**(51): 14829-34. doi: 10.1073/pnas.1614826113
6. Bianchi V, Marbini A. Neuroregenerative Effect of Oxandrolone: A Case Report. *American Journal Case Reports* 2015; **16**: 763-7.
7. Melcangi R C, Magnaghi V, Galbiati M, Ghelarducci B, Sebastiani L, et al. The action of steroid hormones on peripheral myelin proteins: a possible new tool for the rebuilding of myelin?. *J Neurocytol* 2000; **29**(5-6): 327-39. doi: 10.1023/a:1007105121765
8. Magnaghi V, Cavarretta I, Galbiati M, Martini L, Melcangi RC. Neuroactive steroids and peripheral myelin proteins. *Brain Res Brain Res Rev.* 2001; **37**(1-3): 360-71. doi: 10.1016/s0165-0173(01)00140-0.
9. Biatek M, Zaremba P, Borowicz KK, Czuczwar SJ. Neuroprotective role of testosterone in the nervous system. *Pol J Pharmacol* 2004; **56**(5): 509-18.
10. Keith N. Fargo, Eileen M. Foecking, Kathryn J. Jones, and Dale R. Sengelaub. Neuroprotective actions of androgens on motoneurons. *Front Neuroendocrinol* 2009; **30**(2): 130-41. doi: 10.1016/j.yfrne.2009.04.005
11. Anstey M, Desai S, Torre L, Wibrow B, et al. Anabolic Steroid Use for Weight and Strength Gain in Critically Ill Patients: A Case Series and Review of the Literature. *Case Rep Crit Care* 2018; doi: 10.1155/2018/4545623
12. F Kadi. Cellular and molecular mechanisms responsible for the action of testosterone on human skeletal muscle. A basis for illegal performance enhancement. *J Pharmacol* 2008; **154**(3): 522-8. doi: 10.1038/bjp.2008.118
13. Oliver K. Glass, Sundhar Ramalingam, Michael R. Harrison. Resistance Exercise Training in Patients with Genitourinary Cancers to Mitigate Treatment-Related Skeletal Muscle Loss. *Clinical Advances in Hematology & Oncology* Volume 14, Issue 6, June 2016.

# Ophelia syndrome

**Saman B. Gunatilake**

*Sri Lanka Journal of Neurology,* 2020, **7**, 28-29

***Alexandre Cabanel's Ophelia***

*Alexandre Cabanel (French; 28 September 1823 – 23 January 1889) was a French painter. He painted historical, classical and religious subjects in the academic style. Cabanel shows Ophelia slipping very gracefully from the broken limb of a crooked willow. She doesn't seem too perturbed by the fact that she is about to land in the water. Cabanel has given his Ophelia the look of a medieval princess. She is very blonde and pretty, and her flowers have already dropped into the brook.*

Ophelia syndrome is the association of Hodgkin lymphoma (HL) with an autoimmune limbic encephalitis. This syndrome is named after Ophelia, the tragic heroine of Shakespeare's play Hamlet. In contrast to Gertrude (Hamlet's mother), who is a psychologically nuanced and fleshed out character, Ophelia is considered by many to be rather one dimensional. She is, more or less, a tool to be exploited by her father (Polonius), brother (Laertes), and lover (Hamlet). As the play progresses, she transforms from a dutiful daughter to a bawdy seducer until finally, she can no longer tolerate the cognitive dissonance within her and descends into madness and ultimately dies as a result of drowning. It was first described by Dr. Ian Carr whose daughter, at the age of 15, developed progressive loss of memory, depression, hallucinations, and bizarre behaviour (*Lancet* 1982). These symptoms aptly describe Ophelia's deluded and obsessional attraction to the equally deluded and murderous Hamlet. Ophelia syndrome is a relatively mild disease without the Shakespearean tragic ending because it has a good outcome if recognised and treated.

Ophelia syndrome is the association of Hodgkin lymphoma (HL) with an autoimmune limbic encephalitis (LE), as a result of anti-metabotropic glutamate receptor 5 antibodies (mGluR5), which are found on post-

synaptic terminals of neurons and microglia and is expressed primarily in the hippocampus and amygdala. The syndrome frequently resolves following treatment of the underlying lymphoma. It is supposed that mGluR5 antibodies are pathogenic and that reduction in tumor burden leads to reduction in their circulating level.

The fairly well-recognised 'conventional' antibodies are those against VGKC (Caspr 2 and LGI1), NMDA, and AMPA. There is however an almost endless list of less familiar antibodies such as those against glycine, adenylate kinase 5, thyroid, GABA-A receptors, α-enolase, neurexin-3α, dipeptidyl-peptidase-like protein 6 (DPPX), and myelin oligodendrocyte glycoprotein (MOG). The group of disorders caused by antibodies to metabotropic receptors are another exciting area in autoimmune encephalopathies. The main antibody in this group targets the metabotropic glutamate receptor 5 (mGluR5) and at least five autoantibodies have been reported in patients with Ophelia's syndrome: anti-mGluR56-8; anti-Hu9, 10; anti-NMDAr11; anti-SOX1 and anti-PCA212, however in many other reports autoantibodies have been absent.

There is another constellation of signs and symptoms named after Ophelia, known as the Ophelia complex (and not Ophelia syndrome), in psychiatry. It is characterized by low self esteem, anxiety, inability to take decisions and increased risk for depression – especially in young females in the peripubertal period.

# Neurology quiz

*Sri Lanka Journal of Neurology,* 2020, **7**, 30-32

***(Compiled by Saman B. Gunatilake)***

**1. In which stroke syndrome is the heart sign seen in DW and FLAIR MRI?**

a) Lateral medullary syndrome

b) Anterior spinal artery thrombosis

c) Bilateral medial medullary syndrome

d) Top of the basilar syndrome

e) Artery of percheron thrombosis

**2. Neurological worsening after a stroke in sleep apnoea**

a) Reversed Robin Hood syndrome

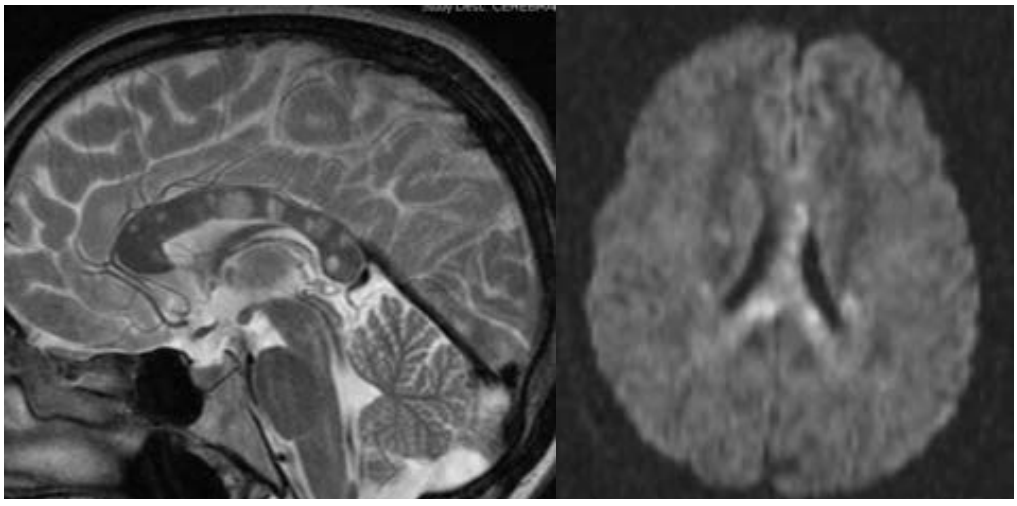
b) Pickwickian syndrome

c) Capgras syndrome

d) Moya Moya disease

e) Takayasu disease

**3. A 26 year-old female presents with ataxia, diplopia and headache**



What is the diagnosis?

a) Cogan's syndrome

b) Vogt-Koyanagi-Harada syndrome

c) Susac syndrome

d) Sarcoidosis

e) Multiple sclerosis

**4. In Fabry's disease all of the following are true except**

a) Decreased serum a-galactosidase A (GLA) activity

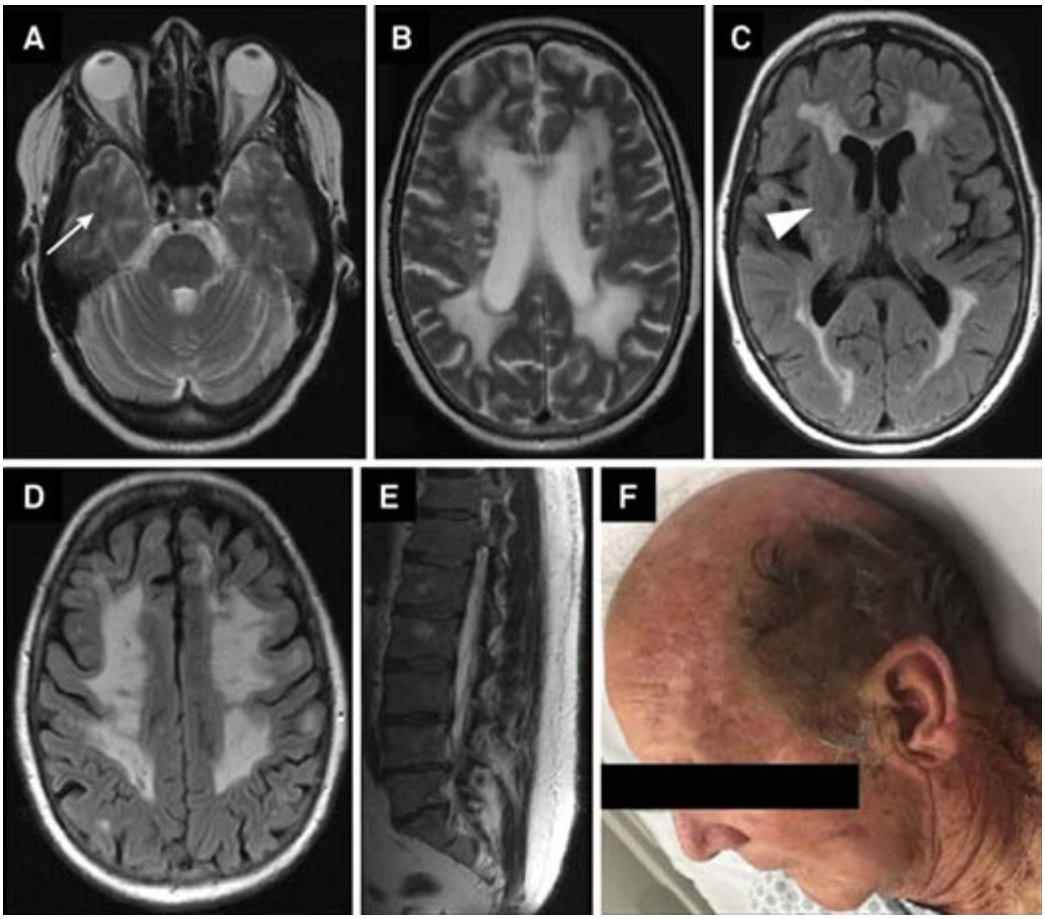
b) Vertebrobasilar dolichoectasia

c) Angiokeratoma

d) Pulvinar hyperintensities in MRI

e) Autosomal recessive

**5. What is the diagnosis?**




a) MELAS

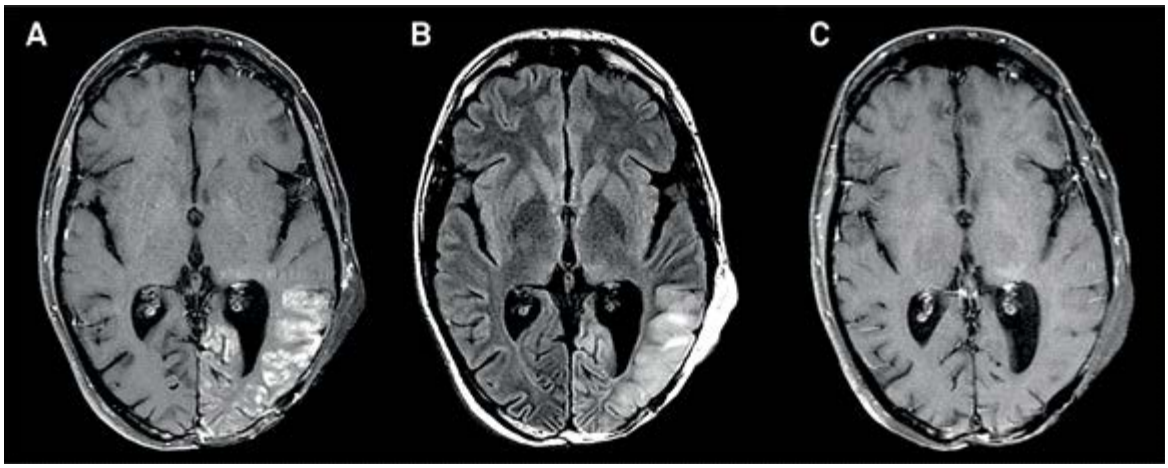
b) CARASIL

c) Cerebro retinal vasculopathy (RVCL)

d) Hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS)

e) CADASIL

**6.** A 33-year-old, right-handed male with a left occipital hemangiopericytoma treated with resection/radiation (60 Gy) with resultant focal epilepsy, presented with severe left-sided headache, expressive aphasia/right homonymous hemianopsia and right-sided hemisensory deficits. The EEG was unremarkable. Initial MRI brain scans are shown in *Figures A and B*. He improved with analgesics and returned to his baseline in two weeks. The MRI was repeated after 16 days *(Figure C)*.




What is the diagnosis?

a) MELAS

b) Tumour recurrence

c) SMART syndrome

d) Sturge Weber syndrome

e) PRES

*(Answers on page 36)*

# Guidelines to authors

*Sri Lanka Journal of Neurology,* 2020, **7**, 33-35

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.

Submissions to be emailed to the editor Prof Saman Gunatilake. 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, in 11pt (Calibri font preferable), on 216 × 279 mm (8 × 11 in), or A4 (212 × 297 mm) size paper in Microsoft Word Software. 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.

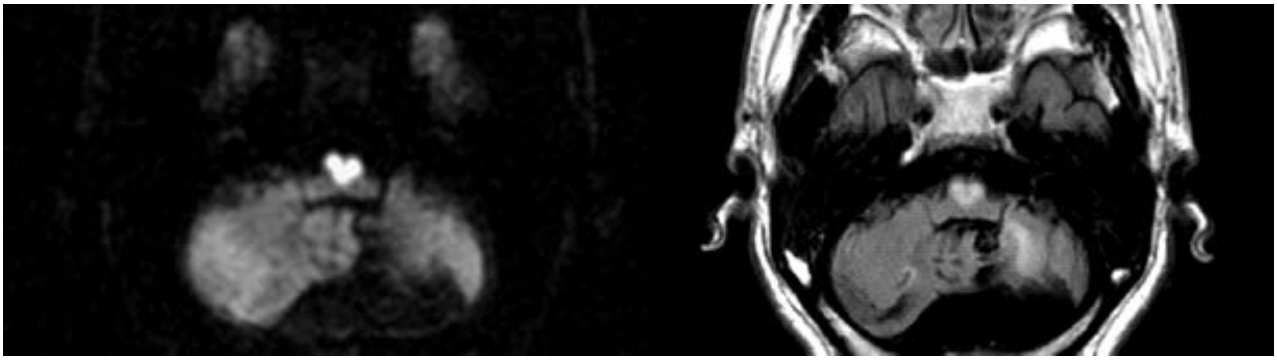
# Answers to neurology quiz

*Sri Lanka Journal of Neurology,* 2020, **7**, 36-38

***Answer 1***

**C) Bilateral medial medullary syndrome**

**Heart shaped sign**



Bilateral medial medullary infarction (bilateral MMI) is an extremely rare cerebrovascular accident presenting with quadriplegia as the initial symptom and resulting in poor functional prognosis. Diagnosis of bilateral MMI has become possible based on brain MRI findings. In the early stage, bilateral MMI is sometimes misdiagnosed as Guillain-Barré syndrome. The medulla oblongata is divided into anterior-medial territory, anterior-lateral territory, lateral territory, and posterior territory, according to vascular supply. It is considered that blood is supplied to these areas by the vertebral artery and the anterior spinal artery, but it is often difficult to identify the occluded blood vessel because of the vastly complex network formed by these blood vessels. The “heart appearance” sign is considered to appear when the infarct occurs in the former two regions (anteriormedial territory, anterior-lateral territory). For an early diagnosis of bilateral MMI, it is essential to bear in mind that characteristic findings may be obtained by diffusion-weighted MRI.

***Answer 2***

**a) Reversed Robin Hood syndrome**

Reversed Robin Hood syndrome (RRHS) has recently been identified as one of the mechanisms of early neurologic deterioration in acute ischemic stroke (AIS) patients related to arterial blood flow steal from ischemic to nonaffected brain.

One of the mechanisms related to infarct expansion, leading to neurologic deterioration in the setting of acute cerebral ischemia, is an intracranial arterial blood flow steal phenomenon in patients with proximal arterial occlusions. Auto regulation of blood vessels is lost in the infarcted area and as result vasodilatation that occurs normally with hypercapnia does not occur. More specifically, with hypercapnia, flow velocities paradoxically decrease in the vessels supplying ischemic tissues at the time of velocity increase in the normal arteries, which are able to respond to the carbon dioxide stimulus with a more effective vasodilation. This results in an intracranial steal phenomenon. If this steal phenomenon leads to neurologic deterioration, the reversed Robin Hood syndrome (RRHS) is diagnosed. Robin Hood is known to have robbed the rich to give the poor, but as seen here when blood is robbed from the ischaemic region the term reversed Robin Hood syndrome is used.

***Answer 3***

**c) Susac syndrome**

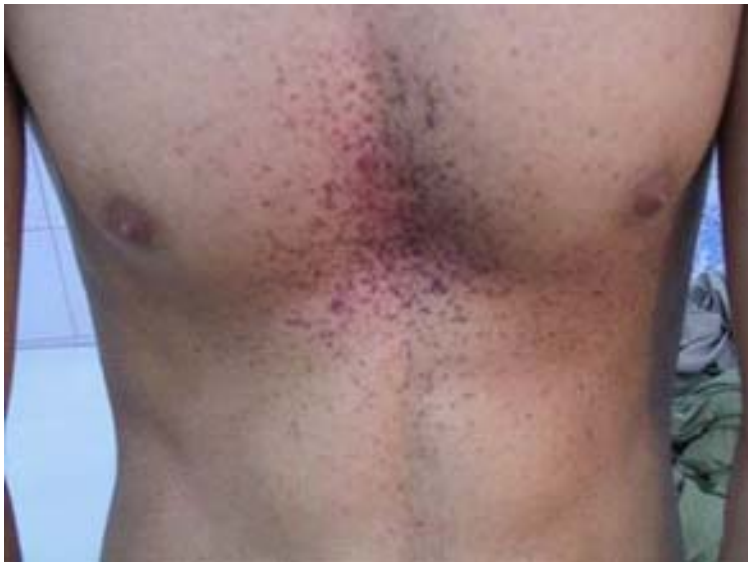
Susac syndrome (SS), also known as SICRET syndrome (small infarctions of cochlear, retinal and encephalic tissue), is a rare syndrome typically affecting young to middle-age women that is clinically characterized by the triad of acute or subacute encephalopathy, bilateral sensorineural hearing loss, and branch retinal arterial occlusions. Symptoms include episodes with headache, encephalopathic symptoms, focal neurologic deficits, sudden hearing loss for middle and low frequencies, and scintillating scotomata. Individuals with an encephalopathic course experience acute or subacute episodes of cognitive deficits, vigilance or mood changes, psychiatric symptoms (eg, psychosis or depression), fatigue, focal neurologic deficits, and, less frequently, seizures.

Characteristic MRI features are present even if all components of the clinical triad have not yet manifested. There tend to be multiple, small white matter lesions which have a predilection for the corpus callosum. Callosal lesions are considered almost pathognomonic and have many important characteristic features: typically involve the central fibers of the callosal body and splenium without abutting the callosal undersurface (with relative sparing of the periphery) – black holes in T1.

***Answer 4***

**e) Autosomal recessive**

Fabry's disease is a rare X linked recessive inherited lysosomal storage disorder. In young adult stroke Fabry's is the cause of stroke in about 5% of males and 3% of females labelled as 'cryptogenic stroke' [Fellgiebel A et al 2006]. Both males and females should be screened for this XLR inherited disease when investigating young adult cryptogenic stroke. Peripheral neuropathy: Patients complain of neuropathic pain with burning pains in the limbs "acroparaesthesia" which starts in adolescence or before aggravated by exercise. Skin: Cutaneous purplish angiokeratomas on the abdomen, umbilicus and genital areas Eyes: Corneal dystrophy. Corneal verticillata detectable by slit lamp examination. Cardiac: LV hypertrophy and conduction abnormalities. Hypertrophic cardiomyopathy may be seen. Renal: Progressive renal disease and eventual chronic kidney disease. CNS: small vessel stroke disease is significant.



*Answer 5*

**b) CARASIL**

CADASIL and CARASIL are hereditary small vessel diseases leading to vascular dementia. CADASIL commonly begins with migraine followed by minor strokes in mid-adulthood. Dominantly inherited CADASIL is caused by mutations (n > 230) in NOTCH3 gene, which encodes Notch3 receptor expressed in vascular smooth muscle cells (VSMC).

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), is disease of the arteries in the brain, which causes tissue loss in the subcortical region of the brain and the destruction of myelin in the CNS. CARASIL is characterized by symptoms such as gait disturbances, hair loss, low back pain, dementia, and stroke. In rare, recessively inherited CARASIL the clinical picture and white matter changes are similar as in CADASIL, but cognitive decline begins earlier. In addition, gait disturbance, low back pain and alopecia are characteristic features. Individuals with CARASIL may experience spondylosis and alopecia beginning in their teens, although alopecia is not seen in all patients.

T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities involving the white matter of the anterior temporal poles (the O'Sullivan sign) seen in 90% of patients of CADASIL is not seen in CARASIL.

*Answer 6*

**c) SMART syndrome**

Stroke-like migraine attacks after radiation therapy (SMART) syndrome is a rare condition that involves complex migraines with focal neurologic findings in patients following cranial irradiation for central nervous system malignancies. Patients usually present years after radiation therapy (6-30 years in a case series) with seizures and subacute stroke-like episodes with symptoms such as hemiplegia, aphasia, and hemianopia. These episodes have been associated with headaches and are often preceded by a migraine-like aura. The hallmark of SMART syndrome is prominent unilateral gyral enhancement with mild mass effect, usually in an area included in the radiation ports. It is also observed as cortical thickening (hyperintense in T2 and FLAIR) with or without diffusion restriction. Typically, the condition is self-limiting and gradually resolves over the course of several weeks. Little is known about the mechanisms behind the disorder, making successful treatment challenging.

Differential diagnosis includes tumor recurrence, leptomeningeal carcinomatosis, infection, vascular disorders, mitochondrial encephalomyopathy with lactic acidosis and stroke, hemiplegic migraine, posterior reversible encephalopathy and post-ictal MRI changes.