ELSEVIER

THE CEYLON MEDICAL JOURNAL

Established 1887
The Official Publication of the Sri Lanka Medical Association
Volume 51, No. 1, March 2006
Quarterly ISSN 0009–0875

All communications should be addressed to **The Editors, CMJ**

Continued Overleaf

Hereditary spastic paraplegias

Molecular genetics may hold the key to precise diagnosis, including prenatal diagnosis and management

Disorders of the spinal cord can pose diagnostic and therapeutic challenges. The advent of new diagnostic tools such as magnetic resonance imaging (MRI) have improved diagnostic accuracy. Spinal imaging is essential in suspected spinal cord disease, as compressive lesions must be detected, and surgical intervention effected where appropriate. Imaging also enables accurate identification and localisation of non-compressive lesions.

The term 'non-compressive myelopathy' encompasses a diverse group of diseases, traditionally lumped together under a single label to establish the distinction from compressive cord lesions that may need surgical relief. Many infective (for example viral, tuberculosis, syphilis, tropical spastic paraparesis), inflammatory (post-viral, vasculitic), vascular (infarction), demyelinating (multiple sclerosis), degenerative (motor neurone disease) and metabolic (vitamin B_{12} deficiency) disorders are included under this generic term. It carries a risk of being a dustbin diagnosis, as a sense of therapeutic nihilism may preclude further investigation. A diligent search to establish the underlying cause is vital, as many are eminently treatable, and supportive care, prognostication and counselling are needed even where specific treatment is not available.

Hereditary spastic paraparesis (HSP, Strümpell-Lorrain syndrome) is one such disorder. Initial case descriptions by Seeligmüller, Strümpell and Lorrain in the late 19th century led to the recognition of HSP as a distinct clinical entity among the 'heredo-familial neuro-degenerative disorders'. Meticulous study of affected kindreds [1–3] has helped define the clinical features, the different types, and the patterns of inheritance.

Progressive spasticity of the lower limbs, as the name implies, is the clinical hallmark of HSP. Upper limb involvement is usually minimal, compared to severe spasticity of the legs. Weakness is usually mild, and difficulty in walking and the characteristic gait disturbance, sometimes leading to severe disability, are caused by spasticity. Hyper-reflexia and extensor plantar responses are cardinal features, and mild ataxia, pes cavus, loss of ankle jerks, mild sensory impairment and sphincter involvement are sometimes noted. Cranial nerve involvement and corticobulbar tract involvement are not seen [4,5].

The main clinical features can be explained by the pathological changes in HSP. Axonal degeneration of the corticospinal tracts (producing spasticity), posterior columns (sensory impairment, absent ankle jerks) and spinocerebellar tracts (ataxia) are the main pathological findings. This degeneration is a dying-back process starting in the terminal portions of the longest tracts in the spinal cord, thereby explaining the predominant lower

Zulfiqar Ahmed Bhutta FRCPCH, PhD
Karachi, Pakistan

Samiran Nundy FRCS, FRCP
New Delhi, India

N Medappa MD
New Delhi, India

Jane Smith BA, MSc
London, UK

Anita KM Zaidi MMBS, SM
Karachi, Pakistan

David Warrell MD, FRCP
Oxford, UK

Published by

Elsevier
A Division of Reed Elsevier India Pvt. Ltd.
17–A/1, Main Ring Road
Lajpat Nagar IV
New Delhi - 110024, India
Tel: +91–11–2644 7160–64
Fax: +91–11–2644 7156
Website: www.elsevier.com

Printed by

Ananda Press
Colombo, Sri Lanka

The Sri Lanka Medical Association
Wijerama House
6, Wijerama Mawatha
Colombo 7
SRI LANKA

Tel: +94 11 2693324

Fax: +94 11 2698802

Internet home page
http: //www.slmaonline.org/cmj

e-mail: SLMA@eureka.lk

This journal is indexed in BIOSIS, CAB International, EMBASE, and Index Medicus

limb involvement. Dorsal roots and ganglia, peripheral nerves and anterior horn cells are usually not involved [5, 6].

Over the years, many other neurological and non-neurological findings have been noted in association with HSP. This has led to the classification of HSP into 'pure' and 'complicated' HSP, depending on their absence or presence. These include optic atrophy, pigmentary retinopathy, dysarthria, amyotrophy, extrapyramidal disturbance, peripheral neuropathy, dementia, mental retardation, epilepsy, deafness, adrenal insufficiency and ichthyosis [4,5].

Inheritance of HSP can be autosomal dominant, recessive, or X-linked. Autosomal dominant HSP is the commonest, accounting for over 80% of cases [4,5,7]. Pure and complicated forms are seen with all modes of inheritance [4,5]. Age of onset can vary from infancy to the eighth decade, and seems to have an impact on the disease course and severity [3]. Early onset HSP (<35 years, type I) is relatively benign with slow progression, and many patients are asymptomatic, and have only spasticity on examination. Late onset HSP (>35 years, type II) is associated with more sensory symptoms, more sphincter involvement, more severe disability, and a more rapidly progressive disease course [3,5].

There is marked variation in the age of onset, clinical manifestations, disease severity and the clinical course between affected families, and even between members of the same family. This inter-familial and intra-familial clinical heterogeneity is seen in both pure and complicated forms, and irrespective of the age of onset and mode of inheritance [5,8].

In the September issue of the journal, Beligaswatte and colleagues [9] described a patient with complicated HSP that may well add to the clinical range of HSP. Although lack of electromyographic findings and pathological confirmation on nerve biopsy are limitations, their description of a demyelinating neuropathy further widens the variety of neurological features associated with HSP. Impairment of vibration and joint position sense and loss of ankle jerks are seen in pure HSP, but these are considered to be due to pathology of the posterior columns, rather than peripheral nerve involvement. Nerve conduction studies are usually normal in pure HSP [5,8]. Neuropathy is a well-recognised association in complicated HSP, but is commonly asymptomatic, usually sensory, and is largely limited to descriptions of axonal degeneration [4,5,10]. Distal sensorimotor neuropathy and mixed demyelinating-axonal changes on neurophysiological studies have been occasionally reported with complicated HSP [11,12].

The genetic basis of HSP is being slowly unravelled, and the associated chromosome loci are being discovered on a regular basis. The current classification of HSP is based on chromosome location (SPG 1 to SPG 27, SPG = spastic paraplegia gene). Several candidate genes and the proteins coded for by them have been identified (e.g., SPG4– spastin, SPG17– paraplegin, SPG3A– atlastin, SPG1– L1 cell adhesion molecule, SPG2– proteolipid protein, SPG20– Troyer syndrome–spartin) [4,5,7,13,14]. Many more are certain to be discovered.

The clinical heterogeneity in HSP is probably explained by the genetic heterogeneity. Autosomal dominant HSP, for example, is produced by changes in 10 different genetic loci (out of those discovered to date). Even within the same locus, inter-familial and intra-familial clinical variation is seen [5,13]. This may be due to different mutations occurring in the same locus, and a single mutation may produce a clinically homogeneous entity.

Molecular genetics may hold the key to precise diagnosis, including prenatal diagnosis, classification and treatment of HSP in the near future. Until such time, much can be done with symptomatic treatment, physical therapy, and appropriate counselling to minimise the disability and to relieve

the psychosocial problems associated with the diagnosis of a hereditary and degenerative disorder.

References

1. Bickerstaff ER. Hereditary spastic paraplegia. *Journal of Neurology, Neurosurgery and Psychiatry* 1950; **13:** 134–45.
2. Holmes GL, Shaywitz BA. Strümpell's pure familial spastic paraplegia; case study and review of the literature. *Journal of Neurology, Neurosurgery and Psychiatry* 1977; **40:** 1003–8.
3. Harding AE. Hereditary "pure" spastic paraplegia: a clinical and genetic study of 22 families. *Journal of Neurology, Neurosurgery and Psychiatry* 1981; **44:** 871–3.
4. Paik N-J, Lim J-Y. Hereditary spastic paraplegia. www.e-medicine.com. Accessed October 2005.
5. McDermott CJ, White K, Bushby K, Shaw PJ. Hereditary spastic paraparesis: a review of new developments. *Journal of Neurology, Neurosurgery and Psychiatry* 2000; **69:** 150–60.
6. Behan WMH, Maia M. Strümpell's familial spastic paraplegia; genetics and neuropathology. *Journal of Neurology, Neurosurgery and Psychiatry* 1974; **37:** 8–20.
7. Hedera P, Fenichel GM, Blair M, Haines JL. Novel mutation in the SPG3A gene in an African American family with an early onset of hereditary spastic paraplegia. *Archives of Neurology* 2004; **61:**1600–3.
8. Fink JK, Heiman-Patterson T for the Hereditary Spastic Paraplegia Working Group. Hereditary spastic paraplegia: advances in genetic research. *Neurology* 1996; **46:** 1507–14.
9. Beligaswatte AML, Bandusena S, Riffsy MTM, Gunasekara S, Wijesekera JC. A case of hereditary spastic paraplegia with demyelinating polyneuropathy. *Ceylon Medical Journal* 2005; **50:** 128–9.
10. Schady W, Smith CM. Sensory neuropathy in hereditary spastic paraplegia. *Journal of Neurology, Neurosurgery, and Psychiatry* 1994; **57:** 693–8.
11. Winner B, Uyanik G, Gross C, Lange M, Schulte-Mattler W, Schuierer G, Marienhagen J, Hehr U, Winkler J. Clinical progression and genetic analysis in hereditary spastic paraplegia with thin corpus callosum in spastic paraplegia gene 11 (SPG11). *Archives of Neurology* 2004; **61:** 117–21.
12. Windpassinger C, Wagner K, Petek E, Fischer R, Auer-Grumbach M. Refinement of the Silver syndrome locus on chromosome 11q12-q14 in four families and exclusion of eight candidate genes. *Human Genetics* 2003; **114:** 99–109.
13. Online Mendelian Inheritance in Man (OMIM). Hereditary spastic paraplegia. www.ncbi.nlm.gov. Accessed October 2005.
14. Proukakis C, Cross H, Patel H, Patton MA, Valentine A, Crosby AH. Troyer syndrome revisited. A clinical and radiological study of a complicated hereditary spastic paraplegia. *Journal of Neurology* 2004; **251:** 1105–10.

Udaya Ranawaka, *Neurologist, General Hospital (Teaching), Kurunegala, Sri Lanka.*
Correspondence: *E-mail : <udayaran@yahoo.com>. (Competing interests: none declared).*