### Oculography

Saccadic latency was increased to 322 ms in patient No 1 and to 289 ms in patient No 2 (normal 215 (17) ms). The horizontal saccades were hypometric with a mean accuracy of 71% in patient No 1 and 70% in patient No 2 (normal 93 (4)%). Horizontal saccades were slow with a mean velocity of 170°/s for 10° saccades in patient No 1 (normal >186°/s), whereas it was normal (193°/s) in patient No 2. In patient No 1, smooth pursuit was impaired with a gain of 0.4 for a peak target velocity of 10°/s and a frequency of 0.16 Hz (age matched normal 0.69 (0.11)). The gain of rightward smooth pursuit was 0.62 and that of leftward 0.49 in patient No 2 (normal 0.75 (0.07)).

### Caloric test, rotatory chair test and pure tone audiometry

Patient No 1 showed no responses during bithermal caloric irrigation of either ear (fig 1B-1). Sinusoidal rotation showed reduced gain and increased phase lead of the VOR. Time constants of pre- and post-rotatory nystagmus were reduced significantly (3.7 s, normal 14.6 (3.7) s). In patient No 2, the caloric responses were slightly decreased, and the gain and phase of the VOR were normal while time constants of pre- and post-rotatory nystagmus were moderately decreased (7.4 s). No patient showed hearing loss on pure tone audiometry.

### Head impulse tests

In patient No 1, the VOR gain of each lateral SCC during head impulse was greatly reduced whereas gains of the vertical SCCs were minimally reduced for only left anterior and right posterior SCCs (fig 1C). In patient No 2, head impulse VOR gain of each lateral SCC was significantly reduced while that of vertical SCC was normal. Patient No 1 had a follow-up evaluation 6 months later, and still showed memory dysfunction, GEN, subnormal gain and phase lead of the VOR during sinusoidal rotation, and decreased gain of the VOR during the head impulses in the lateral SCC planes even though the caloric responses improved markedly (fig 1B-2). Time constants of the VOR increased slightly compared with the initial ones.

## Discussion

Using the head impulse manoeuvre, we demonstrated differential susceptibility of the vestibular systems to thiamine deficiency. The VOR from the lateral SCCs was selectively or predominantly impaired and the vulnerability of the horizontal vestibular responses differed according to stimulation frequencies. According to previous histopathological studies, vestibular paresis in WE may be accounted for by lesions in the vestibular nucleus (VN).[1] Neuropathological examinations of patients with WE have revealed lesions in the VN, especially in the medial VN (MVN), nucleus prepositus hypoglossi, nodulus and uvula. MVN was most vulnerable to thiamine deprivation,[3] and histological abnormalities in the labyrinthine cristae and vestibular nerves were relatively minor in thiamine deficient pigeons.[4]

The vestibular neurons receiving different primary afferent input are distributed with some topographies across VN.[5] The neurons activated by the saccule, utricle, and anterior and posterior canals are located mainly in the lateral (LVN) and descending vestibular nuclei, while the neurons activated by the lateral canal were found mainly in MVN and LVN. Accordingly, we suggest that different susceptibility of the vestibular systems in our patients may result from selective vulnerability of the neurons in the MVN.

On follow-up evaluation, patient No 1 showed markedly improved caloric responses whereas the responses of rotatory chair and head impulse tests remained unchanged. In view of the selective deficit of high acceleration horizontal VOR during the acute phase in patient No 2, MVN neurons responsible for high acceleration horizontal VOR may be the most vulnerable to thiamine deficiency. A plausible explanation for this selective susceptibility may be high metabolic demands of the neurons responsible for the high acceleration VOR.

Alternatively, lesions of the abducens nucleus may impair conjugate horizontal saccadic, pursuit and vestibular eye movements in WE. However, no restriction in the horizontal ocular motor range, and selective deficit of high acceleration horizontal VOR and smooth pursuit in the presence of preserved saccadic velocities in patient No 2, do not support this assumption.

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## References

1 **Furman JM**, Becker JT. Vestibular responses in Wernicke's encephalopathy. *Ann Neurol* 1989;**26**:669–74.
2 **Ghez C**. Vestibular paresis: a clinical feature of Wernicke's disease. *J Neurol Neurosurg Psychiatry* 1969;**32**:134–9.
3 **Witt ED**, Goldmann-Rakic PS. Intermittent thiamine deficiency in the rhesus monkey. I. Progression of neurological signs and neuroanatomical lesions. *Ann Neurol* 1983;**13**:376–95.
4 **Dreyfus PM**, Victor M. Effects of thiamine deficiency on the central nervous system. *Am J Clin Nutr* 1961;**9**:414–25.
5 **Brettler SC**, Baker JF. Directional sensitivity of anterior, posterior, and horizontal canal vestibulo-ocular neurons in the cat. *Exp Brain Res* 2001;**140**:432–42.

# Neurofibromatosis type 1 with involvement of the enteric nerves

Gastrointestinal symptoms in neurofibromatosis type 1 (NF1) is increasingly recognised, usually associated with gastrointestinal stromal tumours (GIST). We describe a patient with NF1 who presented with recurrent bowel symptoms and pseudo-obstruction. At laparotomy, a segment of distended transverse colon was resected and histological examination revealed extensive dysplasia of the enteric nervous system different from GIST. These findings indicate that diffuse abnormalities of the gastrointestinal nerves may be symptomatic in patients with NF1 and should be considered as a possible cause of ''functional bowel problems'' in these patients. We suggest that the autonomic nervous system (eg, in the gastrointestinal system) can be involved similar to other peripheral nerves in NF1.

The patient, aged 73 years, had a NF1 diagnosed according to established consensus criteria.[1] She had multiple small cutaneous neurofibromata, axillary freckling and café au lait spots. One large neurofibroma was removed at age 12 years. There was no evidence of skeletal abnormalities, optic gliomas, plexiform neurofibromata or malignant peripheral nerve sheath tumours. There was no family history of neurofibromata. Neurological tests, including examination of ability to sweat, was normal except for slight right-sided clumsiness and facial weakness, as a result of a previous stroke. Remarkably, some years ago she presented with a picture of intermittent abdominal pain, bloating and diarrhoea. CT and coloscopy showed a dilated segment of the distal transverse colon, in keeping with the diagnosis of chronic intestinal pseudo-obstruction. Because of the severity of her symptoms, she was referred for surgery.

At laparotomy, she underwent a transverse colectomy with resection of 21 cm of grossly distended colon. Centrally, the colonic circumference measured 36 cm. This led to some symptomatic improvement. However, she remains with considerable bowels symptoms, including gastroparesis and neurogenic bowel incontinence, confirmed by manometry and pudendus nerve stimulation, showing bilateral pathology. Additionally, she suffered from urinary stress incontinence and reduced bladder capacity, as shown by urodynamic measurements. MRI of the lumbar spine was normal.

Pathological examination of the resected colon showed that in the mesentery and on the serosal surface there were small neurofibromata, measuring up to 0.5 cm in diameter and appearing largely fibrotic on histology. Sections from the resection ends did not show any significant histological abnormality. However, in much of the central area of the colon there was hyperplasia and tortuosity of the nerves, particularly within the myenteric plexus (fig 1A), and also to a lesser extent within the submucosa. These changes were multifocal and associated with Schwann cell proliferation. These areas of hyperplasia were CD34 negative. Within affected areas there was a loss of ganglion cells from the myenteric plexus and the presence of scattered neurons within the inner and outer muscle layers, some of which were binucleate (fig 1B, C). Ganglion cell hyperplasia was not seen in the areas sampled. There was patchy fibrosis and chronic inflammation of the muscularis layers, but no convincing muscle hyperplasia.

Gastrointestinal involvement in NF1 is increasingly recognised and its frequency is estimated at 11–25%.[2] However, the vast majority of these cases are caused by GISTs,[3] which usually occur in the small bowel and frequently present with gastrointestinal bleeding. Although GISTs, as well as ganglioneuromas, are reported in NF1, they were not present in our case, and the areas of hyperplasia were CD 34 negative (in contrast with GISTs). Neurofibromata may also rarely occur in the gastrointestinal nerves but are usually asymptomatic; those present in our case were unlikely to be sufficient to cause the symptoms. The histopathological features in our case most closely resembled those described by Fuller and Williams[3] and Feinstat and colleagues,[4] although the focal ganglion cell hyperplasia in the submucosa was not noted in our case, and are best described as neuronal intestinal dysplasia. Similar lesions have also been described in cases of multiple endocrine neoplasia, type 2b,[5] indicating that separate genetic pathways can lead to this condition.

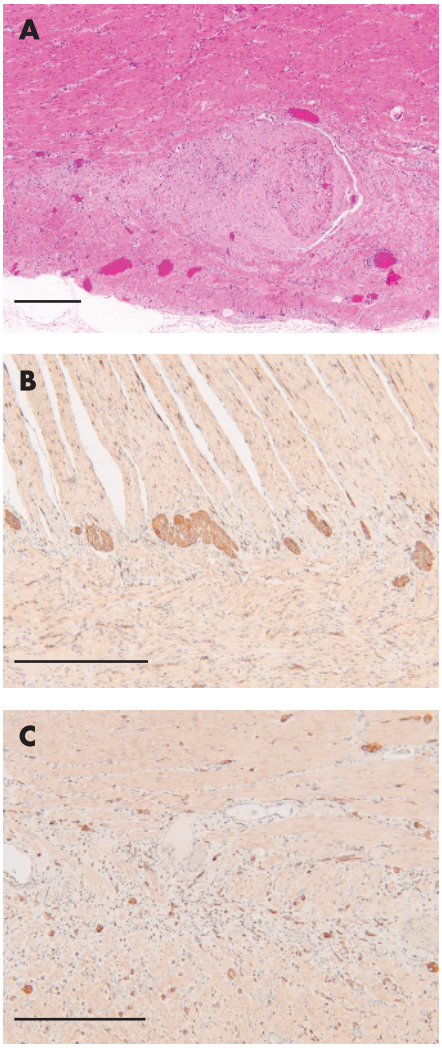


**Figure 1** (A) Haematoxylin and eosin stained section showing hyperplastic nerves within the myenteric plexus. (B, C) Immunocytochemistry with an antibody to neuron specific enolase. (B) Ganglion cells can be seen distributed between the inner and outer layers of the muscularis externa at the resection margin. (C) Within the distended section of colon, there is loss of ganglion cells from the myenteric plexus, together with neurons scattered throughout the muscularis externa. Scale bar is 500 μm.

The persistent symptoms and electrophysiological abnormalities in our patient suggests more widespread involvement of the enteric nervous system. We suggest that diffuse abnormalities of the gastrointestinal autonomic nervous system may occur, in a similar way to other peripheral nerves,[6] in NF1, and this possibility should be considered when patients present with what appears to be ''functional bowel problems''.

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## References

1 **Gutmann DH**, Aylsworth A, Carey JC, *et al*. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997;**278**:51–7.
2 **Pinsk I**, Dukhno O, Ovnat A, *et al*. Gastrointestinal complications of von Recklinghausen's disease: two case reports and a review of the literature. *Scand J Gastroenterol* 2003;**38**:1275–8.
3 **Fuller CE**, Williams GT. Gastrointestinal manifestations of type 1 neurofibromatosis (von Recklinghausen's disease). *Histopathology* 1991;**19**:1–11.
4 **Feinstat T**, Tesluk H, Schuffler MD, *et al*. Megacolon and neurofibromatosis: a neuronal intestinal dysplasia. Case report and review of the literature. *Gastroenterology* 1984;**86**:1573–9.
5 **Carney JA**, Go VL, Sizemore GW, *et al*. Alimentary-tract ganglioneuromatosis. A major component of the syndrome of multiple endocrine neoplasia, type 2b. *N Engl J Med* 1976;**295**:1287–91.
6 **Ferner RE**, Hughes RA, Hall SM, *et al*. Neurofibromatous neuropathy in neurofibromatosis 1 (NF1). *J Med Genet* 2004;**41**:837–41.

# BOOK REVIEWS

## An introduction to the life and work of John Hughlings Jackson with a catalogue raisonné of his writings

George York, David Steinberg. London: The Wellcome Trust Centre for the History of Medicine, 2006, £35.00, pp 139. ISBN 0 95484 1 9 1

The name Hughlings Jackson still has considerable currency with neurologists of all interests, but his name is also widely known within psychiatry. This may be because he was perhaps one of the first neuropsychiatrists, someone who tried to understand the development of symptoms following cerebral lesions, but the symptoms also included abnormal mental states.

This little book gives a very succinct account of his life, but also of his neurological model. It is one of the clearer descriptions of Hughlings Jackson's principles this reviewer has read, and they only take up the first 30 pages of the text. Following that there is a catalogue of all of the known writings of Hughlings Jackson from 1861 through to 1909, and then appendices of some published work, essentially pamphlets, some of which were circulated privately, and also unpublished documents which reside in the Rockefeller Medical Library of the National Hospital for Neurology and Neurosurgery.

This is a most useful and nicely produced book for anybody who would like an introduction to Hughlings Jackson's works, but is essential for Jacksonian Scholars.

This reviewer would merely cavil with the failure in the discussion of Hughlings Jackson's work to appreciate his interest in mental phenomena, with overemphasis on a view that Hughlings Jackson only considered the nervous system as a sensory–motor machine. Although it is known that Jackson favoured a psychophysical parallelism (the doctrine of concomitance) and avoided metaphysical explanations for scientific phenomena, rejecting unconscious mental states, his interest in psychiatry was considerable. This was stimulated by Daniel Hake Tuke and Thomas Laycock, and when he was at the National Hospital he visited the Bethlem Hospital and did ward rounds with Thomas Savage. Furthermore, he closely collaborated with James Crichton Browne at the West Riding Lunatic Asylum.

An outline of his thinking, still so important for neurology and psychiatry, can be gleaned from this useful book. As his obituarist Golla remarked ''(Hughlings Jackson's) fundamental conception of the real significance of symptoms as the evidence of release of control is never lost sight of, and provides the clue to much that has been hopelessly entangled by the irrational attribution of positive symptoms to nervous matter that has undergone destruction''.

**M R Trimble**

## The human brain and its disorders

Edited by D Richards, T Clark, C Clarke. Oxford: Oxford University Press, 2007, pp 379. ISBN 978 0 19 929984 3

This is an introductory textbook of neurological and psychiatric disorders with essential information about the structure and function of the normal brain. It has 379 pages divided into 16 chapters, 12 of which deal with clinical categories, including cerebrovascular diseases, epilepsy, Alzheimer's disease and related disorders, other neurodegenerative conditions, brain infections, multiple sclerosis, headache and chronic pain, neurosurgery, anxiety and related disorders, mood disorders, schizophrenia and related psychoses, psychoactive substance and addiction.

The first four chapters are devoted to basic aspects of neuroscience: structure, function, genomics of brain diseases and basic psychiatric concepts. Although each chapter is very concise, it contains fairly new topics, for example, vaccination therapy for Alzheimer's disease. There are many contrivances such as emboldened, coloured key words with definitions provided in the glossary. Each chapter starts with an introduction, highlighted by key points, self-check questions, case studies, extension boxes and followed by summary and further reading. The chapters are extensively cross referenced. Descriptions are concise, and figures and schema are suitably placed, which help readers to understand the book. In addition, there is a very kind explanation on how to use the book in the preface.

One of its features is the heads of the sections in the chapters written in interrogative sentences, which makes the book very familiar to readers, and provides the feeling that the reader has got the answers after having read that section or chapter. The only shortcoming is that the plate section is inserted in the middle of the chapter on multiple sclerosis. It should be at the end of the book.

Finally, this is a very user friendly introductory textbook of neuroscience. I recommend this book, particularly to non-MD junior neuroscientists, because most chapters are devoted to neurological and psychiatric disorders. The book may also be very useful to first or second year medical students who are interested in neuroscience.

**Hidehiro Mizusawa**