SHORT REPORT

Congenital insensitivity to pain: a 20 year follow up

Andrew J Larner, Jill Moss, Marco L Rossi, Milne Anderson

Abstract

The exact nosological status of "congenital insensitivity to pain" remains in doubt. Possible pathological correlates of this clinical syndrome include sensory neuropathy, central lesions at the level of the reticular formation or dorsal horn of the spinal cord, or a central indifference to, or asymbolia for, pain. The reassessment of two members of a kindred previously reported more than 20 years ago as having congenital insensitivity to pain indicated that they in fact had an inherited sensory and autonomic neuropathy. Prolonged follow up and morphometric analysis of sequential nerve biopsies may be necessary to definitively establish this diagnosis.

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In 1973, Thrush reported four siblings with numerous painless injuries, bone fractures, Charcot joints, and autonomic dysfunction.[1 2] The absence of any relevant lesion demonstrable in peripheral nerve biopsies led him to suppose that the neural defect in these children was to be found centrally, in the reticular formation and/or dorsal horn of the spinal cord. Hence these children were said to have a congenital insensitivity to pain.[1] Subsequent reports and reviews of similar patients have emphasised peripheral nerve changes, particularly the loss of small myelinated fibres, and hence envisage this condition as a hereditary sensory neuropathy with or without autonomic neuropathy, of which there are a number of variants.[3 4] The opportunity to reassess two members of the kindred reported by Thrush allowed us to consider some of these differences of opinion.

Nerve conduction studies

		Case 1	Case 2
Right ulnar nerve:			
Motor conduction velocity:	forearm	52 m/s	57 m/s
	around elbow	53 m/s	58 m/s
	terminal latency	3·1 ms	2·5 ms
	F wave	Absent	—
Sensory potential at wrist:	amplitude	2 μV	—
	velocity	42 m/s	—
Left ulnar nerve:			
Sensory potential at wrist:	amplitude	NR	—
	velocity	NR	—
Right radial nerve:			
Sensory action potential:	amplitude	3μV	—
	velocity	45 m/s	—
Right median nerve:			
Motor conduction velocity:	forearm	53 m/s	—
	terminal latency	5 ms	—
	F wave	absent	—
Sensory potential at wrist:	amplitude	2 μV	7 μV*
	velocity	45 m/s	44 m/s
Left median nerve:			
Sensory potential at wrist:	amplitude	NR	—
	velocity	NR	—
Right sural nerve:			
Sensory action potential:	amplitude	NR	6 μV*
	velocity	NR	46 m/s
Left sural nerve:			
Sensory action potential:	amplitude	NR	—
	velocity	NR	—

* lower limit of normal 5 μV. NR = not recordable; — = not performed.

Case reports

CASE 1

This case (case III.6 from Thrush[1]) developed a mutilating acropathy, especially in the lower limbs, in childhood.[1] He presented again at age 30 with a year's history of increasing difficulty with his walking. He felt off balance and that his legs were stiff, necessitating the use of two sticks to walk. Salient findings on clinical examination included bilateral Charcot ankle joints. Upper limbs were normal in appearance with preserved sensation and reflexes but in the legs there was distal impairment of light touch sensation, loss of vibration sense to the knees, and impaired proprioception distally. Although he could discriminate between sharp and blunt, there was global insensitivity to pain. Ankle jerks were absent; plantar responses were flexor.

Electrophysiological testing (table) failed to record sensory action potentials in both sural nerves, left median nerve, and left ulnar nerve. Motor nerve conduction velocities were normal throughout, and EMG showed normal motor unit potentials and interference patterns. Hence there was evidence for a generalised sensory neuropathy of axonal type.

Sural nerve biopsy showed moderately severe loss of large and medium sized myelinated fibres with evidence of axonal degeneration on light microscopy. Electron microscopy showed segmental demyelination in some fibres and numerous thinly myelinated axons indicating remyelination. Occasional onion bulb whorls, suggesting repeated episodes of demyelination and remyelination, were seen. Unmyelinated fibres were morphologically normal. Morphometric analysis showed the density of myelinated and unmyelinated nerve fibres to be 3800/mm^2 and 18 000/mm^2 respectively; Jacobs and Love[5] found that the densities of myelinated and unmyelinated axons in normal subjects remained fairly constant between the ages of 10 and 60 at

Midland Centre for Neurosurgery and Neurology, Holly Lane, Smethwick, Warley, West Midlands B67 7JX, UK
A J Larner
Milne Anderson

Charing Cross Hospital, London W6 8RF, UK

Department of Histopathology
J Moss

Department of Forensic Medicine
M L Rossi

Correspondence to:
Dr A J Larner, Department of Anatomy, Downing Street, Cambridge, CB2 3DY, UK.

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7500–10 000/mm² and 30 000–40 000/mm² respectively.

An evoked potential series (visual, somatosensory, brainstem auditory) produced normal results. Autonomic testing of the pupil produced dilatation with 4% cocaine, no effect with 0·1% adrenaline, and an exaggerated response to 2·5% methacholine, results indicating partial parasympathetic and sympathetic denervation of the pupil, the last being central rather than peripheral. Cardiac autonomic function tests (R-R variation, carotid massage, tilt table, Valsalva's manoeuvre) were all entirely normal. MRI of the complete neuraxis showed no focal lesion, atrophy, or change in signal intensity.

CASE 2

Case 2 (case III.5 from Thrush[1]), an elder brother of case 1, presented again at the age of 31 complaining of right leg weakness, unpleasant sensations in the right leg, urinary urgency, and erectile impotence. Clinically he had a Charcot joint at the left ankle. The arms showed pronounced scarring due to repeated trauma and burns but, aside from the insensitivity to pain, were neurologically intact. Leg musculature was wasted and there was reduced appreciation of pinprick, light touch, and vibration from the knees down, but proprioception was preserved. Upper limb reflexes were normal, but in the lower limbs only the left knee jerk was present. Nerve conduction studies were within normal limits (table). Cardiac autonomic function tests were also normal. Cerebrospinal fluid analysis showed a raised protein concentration (0·85 g/l) and electrophoresis showed the presence of oligoclonal bands. MRI of the complete neuraxis showed no abnormal signal change. The patient declined a further cutaneous nerve biopsy.

Discussion

A comparison of these histories with those of 20 years ago[1] showed that there has been unequivocal progression of the clinical signs in these patients: both have developed distal sensory loss to several modalities and have lost tendon reflexes. In case 1, electrophysiological evidence of a sensory axonal neuropathy has developed. Pupillary autonomic testing is qualitatively unchanged. Although direct comparison of the two nerve biopsies from case 1 is difficult, as morphometric analysis of the original biopsy was not performed, both show preferential loss of large myelinated fibres with relative preservation of unmyelinated fibres. Hence, we believe that these patients have a hereditary sensory and autonomic neuropathy (HSAN).

The mode of inheritance in this family is uncertain,[1] but its occurrence in four siblings, the offspring of normal, non-consanguinous parents, suggests autosomal recessive inheritance.[4] Of the autosomal recessive variants of HSAN (types II, III, and IV[3 4]), our cases most resemble type II in which all types of sensation are affected, tendon jerks are lost, sensory action potentials may not be present, and there is minor autonomic involvement (impotence, bladder disturbance).

There has been debate as to whether clinical progression occurs in recessively inherited sensory neuropathy, or whether the disease is static.[6] Nukada *et al*[7] have presented clinical evidence of slow progression of HSAN type II, but with a relatively accelerated course over the first one or two decades. Sural nerve biopsies in this variant typically show profound or even complete loss of the largest myelinated fibres, with some reduction of unmyelinated fibres[3 7]; evidence of increasing fibre loss with time relative to controls has been presented.[7] Contrary to our observations, Nukada *et al*[7] saw no evidence of onion bulb formation in surviving myelinated fibres. In patients with autosomal recessive hereditary sensory neuropathy and neurotrophic keratitis, Donaghy *et al*[4] saw occasional regenerative clusters in sural nerve biopsies indicating that some degeneration and subsequent regeneration of myelinated fibres had occurred, implying progression of the neuropathy but without any clinical indication thereof.

Thrush reported normal sensory nerve conduction velocities, and motor nerve conduction velocities at the lower limit of normal, in the original report.[1] The present investigations showed an unequivocal sensory axonal neuropathy in case 1, but normal studies once again in case 2. It has been pointed out by several authors that normal electrophysiological studies do not rule out a neuropathy as sensory action potentials reflect conduction in large myelinated fibres which may be preserved. Similarly, retention of tendon reflexes may be seen in "small fibre" neuropathy.[3 4]

Considerable clinical and genetic heterogeneity in the inherited sensory and autonomic neuropathies seems likely. The loss of myelinated fibres in the biopsies from case 1 was very much less severe than reported in other cases, and it is therefore possible that, contrary to previous reports,[7] there is variability in nerve biopsy morphology in HSAN type II. Prolonged follow up and detailed analysis of sequential nerve biopsies may be necessary to definitively establish the diagnosis of HSAN, and to differentiate it from "congenital insensitivity to pain".

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