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.

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/mm² and 18 000/mm² respectively; Jacobs and Love1 found that the densities of myelinated and unmyelinated axons in normal subjects remained fairly constant between the ages of 10 and 60 at

Nerve conduction studies

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td><strong>Right ulnar nerve:</strong></td>
<td><strong>Right ulnar nerve:</strong></td>
</tr>
<tr>
<td>Motor conduction velocity: forearm</td>
<td>52 m/s</td>
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<tr>
<td>Motor conduction velocity: terminal elbow</td>
<td>53 m/s</td>
</tr>
<tr>
<td>Sensory potential at wrist: amplitude</td>
<td>2 μV</td>
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<tr>
<td><strong>Left ulnar nerve:</strong></td>
<td><strong>Right median nerve:</strong></td>
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<tr>
<td>Sensory potential at wrist: amplitude</td>
<td>NR</td>
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<tr>
<td><strong>Right median nerve:</strong></td>
<td><strong>Right median nerve:</strong></td>
</tr>
<tr>
<td>Sensory potential at wrist: amplitude</td>
<td>3 m/s</td>
</tr>
<tr>
<td><strong>Left median nerve:</strong></td>
<td><strong>Left median nerve:</strong></td>
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<tr>
<td>Sensory potential at wrist: amplitude</td>
<td>NR</td>
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<td><strong>Right sural nerve:</strong></td>
<td><strong>Right sural nerve:</strong></td>
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<tr>
<td>Sensory potential at wrist: amplitude</td>
<td>NR</td>
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<tr>
<td><strong>Left sural nerve:</strong></td>
<td><strong>Left sural nerve:</strong></td>
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<tr>
<td>Sensory potential at wrist: amplitude</td>
<td>NR</td>
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</tbody>
</table>

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

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There has been debate as to whether clinical progression occurs in recessively inherited sensory neuropathy, or whether the disease is static.4 Nukada et al4 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 fibres5; evidence of increasing fibre loss with time relative to controls has been presented.7 Contrary to our observations, Nukada et al7 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 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.1,4

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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Discussion

A comparison of these histories with those of 20 years ago1 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. Papillary 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. Of the autosomal recessive variants of HSAN (types II, III, and IV+), 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).
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