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Paranodal pathology in Tangier disease with remitting-relapsing multifocal neuropathy

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Abstract

Pathological studies of a sural nerve biopsy in a man with Tangier disease presenting as a remitting-relapsing multifocal neuropathy showed abnormalities in the paranodal regions, including lipid deposition (65%) and redundant myelin foldings, with various degrees of myelin splitting and vesiculation (43%) forming small tomacula and abnormal myelin terminal loops (4%). The internodal regions were normal in the majority of myelinated fibres. Abnormal lipid storage was also present in the Schwann cells of the majority of unmyelinated fibres (67%). The evidence suggests that the noncompacted myelin region of the paranode is a preferential site for lipid storage in the myelinated Schwann cell, and that the space-occupying effects of the cholesterol esters leads to paranodal malfunction and tomacula formation as the pathological basis for the multifocal relapsing-remitting clinical course.

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1. Introduction

Tangier disease is characterised by the deficiency or absence of high-density lipoprotein (HDL) in plasma, and the accumulation of cholesterol esters in many tissues, including the tonsils, peripheral nerves, intestinal mucosa, spleen, liver, bone marrow, lymph nodes, thymus, skin and cornea. Severe HDL deficiency is due to mutation of a gene on human chromosome 9q31 encoding ATP cassette-binding transporter 1 (ABC1), which controls cellular apolipoprotein-mediated lipid removal. Mutations of the gene encoding ABC1 lead to a defect of cellular cholesterol removal and deposition of cholesterol esters throughout the body.[1–3] The finding of severe HDL deficiency and a low plasma cholesterol concentration accompanied by normal or elevated triglyceride levels in individuals with hyperplastic organ-yellow tonsil and adenoidal tissues is pathognomonic for the condition.[4]

Peripheral nerve dysfunction is the most frequent cause of presentation in adults with Tangier disease and more than one-third have symptoms of neuropathy.[4] Neuropathy in Tangier disease presents as one of two clinical patterns: a syringomyelia-like syndrome and remitting-relapsing multifocal neuropathy.[4,5] Axonal degeneration of small myelinated fibres, unmyelinated fibres and small dorsal root ganglion cells may be the pathological basis of the syringomyelia-like type of Tangier disease.[4,6] The mechanism for the remitting-relapsing pattern in the multifocal neuropathy, which accounts for 50% of neuropathies in Tangier disease,[4] remains unclear. Studies in the present case with Tangier disease and a relapsing multifocal neuropathy suggest that paranodal cholesterol ester storage leads to paranodal malfunction.

2. Case report

A 17-year-old male developed a painless left sciatic neuropathy over the course of 6 months, with progressive weakness of the left leg, foot drop and sensory disturbance. Electromyography revealed partial denervation in the left gluteus maximus and hamstring muscles. There were no voluntary motor units activated in the tibialis anterior or extensor digitorum brevis, but responses were elicited in these muscles following stimulation of the left peroneal nerve at the head of the fibula. Motor conduction velocity in the left popliteal nerve was 35 m/s, and sensory conduction velocity in the left sural nerve was 30 m/s (amplitude 10 μV). These findings indicated a proximal sciatic nerve lesion suggesting conduction block, but surgical exploration did not reveal any abnormality. The symptoms resolved over 6 months. Five years later, while carrying a backpack, weakness of left finger extension developed, consistent with a left posterior interosseous nerve palsy. After sleeping on the left arm during a long plane flight, the patient woke with widespread weakness and sensory change in the left arm. This gradually settled to residual signs of a left ulnar neuropathy. Ulnar motor nerve conduction velocity was 48 m/s (forearm) with preserved sensory nerve action potential (12 μV). Left median nerve motor (conduction velocity 63 m/s, distal latency 3.0 ms) and sensory conduction (latency 2.6 ms, amplitude 48 μV) were normal. F waves were difficult to elicit after stimulation of the left ulnar nerve in comparison with the left median nerve. The upper limb symptoms recovered over the next 6 months. Weakness of the left trapezius and sternomastoid, consistent with left accessory nerve palsy, and left forearm, consistent with a left posterior interosseous nerve palsy, then developed without any clear precipitant. These improved gradually. Three years later, the patient developed a left median nerve lesion. At this time, the tonsils were noted to be enlarged and yellow. Serum cholesterol was low, with absence of HDL and apolipoprotein A1.

3. Methods

Full-thickness left sural nerve biopsy was studied according to a standard protocol for teased nerve fibres, light and electron microscopy,[7] and quantitation of myelinated fibre (MF) population.[8] Paraffin and 1 μm plastic sections were immunostained as previously described[9] using a mouse monoclonal anti-myelin protein zero (P0) antibody (gift from J.J. Archelos), a mouse monoclonal anti-peripheral myelin protein 22 (PMP22) antibody (Chemicon, Temecula, CA), a rabbit polyclonal anti-myelin basic protein (MBP) antibody (Dako Cytomation, Glostrup, Denmark), and a mouse monoclonal anti-neurofilament protein-200 (NFP200) antibody (Sigma-Aldrich, St Louis, MO).

4. Results

Light microscopic examination of paraffin-embedded and frozen transverse sections stained with haematoxylin and eosin, trichrome, or Congo red did not reveal specific abnormalities, but 1 μm plastic sections stained with toluidine blue showed scattered MFs with disproportionately thin myelin sheaths relative to axonal diameters, indicative of remyelination. A characteristic feature was the presence of clear vacuoles in Schwann cells and fibroblasts. Electron microscopy showed that these vacuoles were non-membrane bound and were found in the cytoplasm of most non-myelinating Schwann cells (134/200) (Fig. 1A,B) and some fibroblasts (3/10; Fig. 1C). When examined longitudinally, such vacuoles were also found in the cytoplasm of