Lewis-Sumner Syndrome and Tangier Disease

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Objective: To report unusual electrophysiologic data in a patient with Tangier disease in an effort to better understand the pathophysiologic features of the peripheral nerve lesions in this disease.

Design: Case report.

Patient: A 15-year-old girl had subacute onset of asymmetric neuropathy with persistent conduction block, resembling Lewis-Sumner syndrome.

Main Outcome Measures: Electrophysiologic data in Tangier disease.

Results: After initially unsuccessful treatment with intravenously administered immunoglobulins, the finding of an abnormal lipid profile led to the diagnosis of Tangier disease due to the R587W mutation in the adenotriphosphate-binding cassette transporter-1 gene (ABCA1) (OMIM 9q22-q31). Conduction block, which is the electrophysiologic hallmark of focal demyelination, can be present in Tangier disease. It could be induced by focal nerve ischemia or by preferential lipid deposition in the paranodal regions of myelinated Schwann cells. The presence of a conduction block in Tangier disease may lead to a misdiagnosis of dysimmune neuropathy.

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TANGIER DISEASE IS A RARE AUTOSOMAL RECESSIVE DISORDER CAUSED BY MUTATIONS IN THE ADENOTRIPHOSPHATE-BINDING CASSETTE TRANSPORTER-1 GENE (ABCA1).

REPORT OF A CASE

A 15-year-old girl was examined because of progressive weakness of the left hand with paresthesia in the fourth and fifth fingers. Her parents were French natives and were not consanguineous. The patient and her family (her father, paternal grandfather, and a paternal uncle) had neither medical or familial history of peripheral neuropathy or cardiovascular disease; however, 3 members of her family (her father, paternal grandfather, and a paternal uncle) had pes cavus. She had a healthy younger brother. Findings from the neurologic examination showed global muscular atrophy in the left hand and pes cavus in both feet. The left abductor pollicis brevis, interossei, and extensor carpi radialis muscles were weak. Tactile, pain, and temperature sensations were diminished in the left ulnar area. Bicipital and knee deep-tendon reflexes were decreased, and tricipital, wrist, and ankle deep-tendon reflexes were absent. The patient had neither hepatosplenomegaly nor enlarged, yellow tonsils. All arterial peripheral pulses were present, and an electrocardiogram was normal.

A motor nerve conduction study disclosed a definite conduction block of 81% in the elbow-to-wrist segment of the left median nerve, with increased distal motor latency. Compound muscle action potential amplitude of the left ulnar nerve was...
severely decreased, with marked homogeneous slowdown conduction velocity. Sensory nerve action potential amplitude was decreased in the left median nerve and more markedly in the ulnar nerve, without any slowing of sensory conduction (Table). Compound muscle action potential and sensory nerve action potential amplitude and conduction velocity of the other nerves of both upper and lower limbs were normal. Needle electromyography of the first left dorsal interosseous muscle and the left abductor pollicis brevis muscle showed fibrillation activity at rest, with reduction of motor unit potential recruitment. The other upper limb muscles were normal. Cerebral magnetic resonance imaging and analysis of cerebrospinal fluid yielded normal findings. Doppler ultrasonography showed no abnormalities in the cervical and lower limb arteries. Electromyographic examination of the patient’s father yielded normal findings. A diagnosis of sensorimotor multifocal neuropathy was made. Because the patient’s symptoms resembled those of Lewis-Sumner syndrome, intravenous immunoglobulin therapy was administered (Tegeline [Laboratoire Francais du Fractionnement et des Biotechnologies, Les Ulis, France], 2 g/kg; 1 course every 6 weeks for a total of 6 courses), which resulted in poor functional improvement and only minor changes in electrophysiologic data.

During follow-up, an abnormal lipid profile was discovered that showed an elevated triglyceride level (166.37 mg/dL; normal range, 33.63-132.74 mg/dL [to convert to millimoles per liter, multiply by 0.0113]), a decreased total plasma cholesterol concentration (126.64 mg/dL; normal range, 158.30-235.52 [to convert to millimoles per liter, multiply by 0.0259]), and a nearly absent plasma concentration of high-density lipoprotein cholesterol (5.79 mg/dL; normal range, 50.19-77.22 mg/dL [to convert to millimoles per liter, multiply by 0.0113]). Further analyses revealed an almost undetectable level of ApoA-I and lipoprotein A-I and very low concentrations of ApoA-II but without any obvious molecular abnormality of ApoA-I and ApoA-II. The normal cholesterol esterification ratio excluded a lecithin-cholesterol acyltransferase deficiency. On the basis of these results, Tangier disease was suspected. A sequencing of the 50 exons of ABCA1 led to the identification of a homozygous substitution in exon 14 (c.1759C>T), R587W, which has already been reported in a family with Tangier disease. Both parents of the patient were heterozygous for this mutation. They refused consent to screen their son for the disease. The patient was given a low-fat diet. Six months later (2 years after the first evaluation), clear improvement in muscle strength was noted in the left hand, with regression of the atrophy and partial recovery of the hypoesthesia. Another electromyographic examination was performed, which showed substantial improvement in compound muscle action potential amplitude of the left median and left ulnar nerves (Table). However, the conduction block first noted in the forearm segment of the left median nerve persisted, as well as the reduced motor conduction velocities in various segments of the left ulnar nerve. Moreover, a new conduction block with conduction slowing was recorded in the right ulnar nerve at the level of the elbow. The sensory nerve action potential amplitude had improved in the left ulnar nerve but decreased in the left median nerve (Table).

Table. Amplitudes of CMAP and SNAP in Successive Electromyographic Examinationsa

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Nerveb</th>
<th>Distal Motor latency, ms</th>
<th>Distal CMAP Amplitude, mV</th>
<th>Velocity, m/s</th>
<th>CMAP Amplitude Variation, %</th>
<th>SNAP Velocity, m/s</th>
<th>SNAP Amplitude, µV</th>
</tr>
</thead>
<tbody>
<tr>
<td>First, 6 mo after illness onset</td>
<td>Median</td>
<td>45</td>
<td>84</td>
<td>21</td>
<td>45</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>Ulnar</td>
<td>64</td>
<td>17</td>
<td>7</td>
<td>46</td>
<td>56</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>21</td>
<td>6</td>
<td>56</td>
<td>68</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>Last, 30 mo after illness onset</td>
<td>Median</td>
<td>24</td>
<td>33</td>
<td>49</td>
<td>49</td>
<td>49</td>
<td>81</td>
</tr>
<tr>
<td>Ulnar</td>
<td>24</td>
<td>26</td>
<td>11</td>
<td>24</td>
<td>23</td>
<td>23</td>
<td>81</td>
</tr>
<tr>
<td>Normal values</td>
<td>Median</td>
<td>&lt;3.7</td>
<td>&gt;6</td>
<td>&gt;48</td>
<td>&lt;-20</td>
<td>&gt;45</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Ulnar</td>
<td>&lt;3.2</td>
<td>&gt;6</td>
<td>&gt;48</td>
<td>&lt;-20</td>
<td>&gt;45</td>
<td>&gt;15</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Abbreviations: CMAP, compound muscle action potential; SNAP, sensory nerve action potential.

a Abnormal values are boldfaced.
b The median nerve is stimulated at the wrist and elbow; the ulnar nerve is stimulated at the wrist, under the elbow, above the elbow, and in the armpit.

COMMENT

We report a case of asymmetric sensorimotor multifocal neuropathy with conduction block in the upper limbs, suggestive of Lewis-Sumner syndrome, even though the age at onset was unusually young. Lewis-Sumner syndrome usually develops in the fifth decade of life. Intravenous immunoglobulin therapy was ineffective. The existence of pes cavus supported the hypothesis of a hereditary neuropathy. The localization of the nerve conduction block outside the common entrapment sites, together with the normality of the sensory nerve action potential of the lower limbs, ruled out a diagnosis of hereditary neuropathy.
reditary neuropathy with liability to pressure palsies. The abnormal lipoprotein profile led to the diagnosis of Tangier disease and identification of the R587W homozygous mutation in exon 14 of ABCA1. Tangier disease has been diagnosed in about 70 patients from 60 different families worldwide. Juvenile cases are usually identified on the basis of enlarged yellow tonsils. Neuropathy is the first symptom of the disease in one-third of adult patients with a phenotype of a multifocal remitting-relapsing neuropathy. The symptoms are related to either asymmetric polyneuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy. The literature reports only 1 case, in a 17-year-old patient with neuropathy or multiple mononeuropathy.

This patient further developed recurrent truncular palsies. Previously published electrophysiologic data in Tangier disease show reduced motor or sensory conduction velocities and prolonged distal latency, suggestive of demyelination. The major pathologic findings in peripheral nerve biopsy specimens are demyelination and remyelination, neuronal loss, and lipid accumulation in Schwann cells. In 1999, a mutation in ABCA1 was identified in Tangier disease. ABCA1 is a transporter that participates in the transfer of high-density lipoprotein cholesterol from cells to plasma. Lack of ABCA1 could contribute to a growth of engorged Schwann cells because of their inability to export lipids acquired from scavenged dead neurons. These abnormal Schwann cells could be responsible for a focal myelin dysfunction, electrophysiologically revealed by a conduction block, which reflects the failure of propagation of a nerve impulse along a structurally intact axon. According to this hypothesis, a recent neuropathologic study in a patient with Tangier disease with relapsing and remitting mononeuropathy revealed a preferential lipid deposition in the paranodal regions of myelinated Schwann cells and focal myelin swellings (small tomacula) in the teased fiber preparations. The authors conclude that these abnormalities are responsible for paranodal dysfunction with slowing of nerve conduction or conduction block. Another hypothesis is that focal nerve ischemia secondary to lipid accumulation within the vasa nervorum could initiate conduction block by disrupting myelin. Electrophysiologic features interpreted as a conduction block have previously been reported in neuropathy secondary to necrotizing vasculitis. A conduction block observed in such neuropathies may be secondary to focal axonal failure presumably related to infarctive axonal injury. Some authors suggest that electrophysiologic abnormalities are then transient and that the term conduction block should be used in necrotizing vasculitis only if serial studies produce findings consistent with this electrophysiologic diagnosis. In our patient, the conduction block in the left median nerve persisted after 2 years without any sign of wallerian degeneration (increased compound muscle action potential amplitude at last examination), which could confirm the hypothesis of a myelin ischemic lesion.

The R587W homozygous mutation in exon 14 of ABCA1 has been reported in only 1 Italian family. The proband had severe premature coronary heart disease and a mild clinical phenotype of Tangier disease without neuropathy and with a normal triglyceride level. From this case, Bertolini et al suggest that the R587W mutation might affect the function of ABCA1, specifically in the intima of the arterial wall, and have a much lower effect on ABCA1 function in other locations such as the peripheral nerves. Our case does not confirm this hypothesis.

The pathophysiology of Tangier disease remains unclear. Progress in genetic studies and electrophysiologic data will likely enable better understanding of this disease. The presence of conduction block in Tangier disease may lead to a misdiagnosis of dysimmune neuropathy.

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Author Contributions: Dr Theaudin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Theaudin, Couvert, Fournier, Bruckert, Carrie, and Le Forestier. Acquisition of data: Theaudin, Couvert, Fournier, Bougie, Bruckert, Perrotte, Valsalde, Maisonneuve, and Bonnefont-Rousselot. Analysis and interpretation of data: Theaudin, Couvert, Fournier, Maisonneuve, and Bonnefont-Rousselot. Drafting of the manuscript: Theaudin and Fournier. Critical revision of the manuscript for important intellectual content: Theaudin, Couvert, Fournier, Bougie, Bruckert, Perrotte, Valsalde, Maisonneuve, Bonnefont-Rousselot, Carrié, and Le Forestier. Administrative, technical, and material support: Bougie and Le Forestier. Study supervision: Theaudin, Fournier, Carrié, and Le Forestier.

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REFERENCES


