Familial spinocerebellar degeneration as an expression of adrenoleukodystrophy

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SUMMARY A family with adrenoleukodystrophy and clinical manifestations of spinocerebellar degeneration was studied. Two adult male first cousins showed progressive limb and truncal ataxia, slurred speech and spasticity of the extremities. Brain CT scans demonstrated atrophy of the pons and cerebellum, in both cases. Very long chain fatty acids in plasma and erythrocyte membranes were elevated in the affected patients and intermittently increased in an aunt and the mother of one patient, thereby indicating homozygotes and carriers of adrenoleukodystrophy, respectively. This unusual type of adrenoleukodystrophy seems to be transmitted as an X-linked recessive trait.

Adrenoleukodystrophy and adrenomyeloneuropathy are X-linked recessive disorders characterised by adrenal insufficiency and demyelination in the central and peripheral nervous systems.1–3 Biochemically, very long chain fatty acids (VLCFA) accumulate in the tissues and body fluids.4 5 We describe here a family with adrenoleukodystrophy and clinical manifestations of spinocerebellar degeneration, attributed to an X-linked recessive inheritance, based on an analysis of VLCFA.

Case reports (pedigree fig)

Case 1 (III-9) A Japanese man had been well until age 27 years, and physical and mental developments were normal. At age 27, he noticed dysarthria and unsteadiness in walking, and these symptoms were progressive. On admission, he was alert and oriented. Recent and remote memory seemed intact. He would calculate well, but sometimes could not understand simple questions. Total IQ measured by Wechsler Adult Intelligence Scale was 65. There was dark pigmentation on his skin, gums and lower half of the sclera. Visual and hearing acuities were normal. Ocular movements were smooth, without nystagmus. His speech was markedly slurred. Extremities were dysmetric on finger-nose and knee-heel tests. Bilateral lower extremities were moderately spastic and deep tendon reflexes were exaggerated with positive bilateral Babinski’s sign. His gait was markedly ataxic and somewhat spastic. He could hardly walk without support, yet sensory impairment was not demonstrated.

The plasma ACTH level was 20–25 pg/ml (normal 10–100). Plasma cortisold level responded well to ACTH stimulation (6-3 to 27-4 μg/dl, 30 min after 0-25 mg of intravenous ACTH injection; (normal response > double of basal level). Plasma FSH, aldosterone and testosterone levels were normal. An EEG revealed findings of occasional theta waves among the background activities. Motor nerve conduction velocity was 34.4 m/s in the right peroneal nerve (normal 45–53) and sensory nerve conduction velocity was 28 m/s in right sural nerve (normal 46–60). Brain CT scans demonstrated atrophy of the pons and cerebellum, but the cerebrum seemed to be intact.

Case 2 (III-2, a first cousin of case 1) A man who first noticed an unsteady gait at age 22
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Six members in the family (II-5, II-6, III-4, III-5, III-8 and III-10) proved to be neurologically normal.

VLCFA levels
VLCFA levels in the sphingomyelin of the plasma and erythrocyte membranes were measured, using high-performance liquid chromatography. Increased levels of VLCFA in both plasma and erythrocyte membranes were observed in cases 1 and 2 (Table). II-5 and II-6 showed intermediate increase in VLCFA. Other members of the family were normal.

Discussion
While adrenomyeloneuropathy is a well-known variant of adrenoleukodystrophy, rarer forms have been reported; adrenoleukodystrophy with symptoms of Kluver-Bucy syndrome and adrenoleukodystrophy resembling brain tumour of the left hemisphere. Marsden et al. reported an adrenoleukodystrophy patient presenting as spinocerebellar degeneration. They did not report the VLCFA levels but the patient did have a positive family history of adrenoleukodystrophy. The patient had cerebellar signs as well as dementia, incontinence, epileptic seizures, optic atrophy and hypeaesthesia in the legs with stocking-type distribution. Recently Ohno et al. also reported a sporadic case of adrenoleukodystrophy presenting as olivopontocerebellar atrophy.

From the clinical picture of slowly progressive limb and truncal ataxia and brain CT scans showing atrophy of the brainstem and cerebellum, the diagnosis of spinocerebellar degeneration was made in our patients. The case 1 patient was considered to have peripheral neuropathy, determined from studies on conduction velocity. In an analysis of VLCFA of the patients and their family members, the patients were considered to have adrenoleukodystrophy and their aunt and the mother of case 1, as the carriers. This seems to be the first report of a family of adre-

Table  Very long chain fatty acids of sphingomyelin in plasma and erythrocyte membranes

<table>
<thead>
<tr>
<th>Plasma</th>
<th>C24:0</th>
<th>C25:0</th>
<th>C26:0</th>
<th>Erythrocyte membranes</th>
<th>C24:0</th>
<th>C25:0</th>
<th>C26:0</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-5</td>
<td>1.29</td>
<td>0.044</td>
<td>0.020</td>
<td>2.98</td>
<td>0.097</td>
<td>0.179</td>
<td></td>
</tr>
<tr>
<td>II-6</td>
<td>0.96</td>
<td>0.028</td>
<td>0.011</td>
<td>2.32</td>
<td>0.058</td>
<td>0.134</td>
<td></td>
</tr>
<tr>
<td>III-2</td>
<td>1.25</td>
<td>0.034</td>
<td>0.020</td>
<td>3.18</td>
<td>0.092</td>
<td>0.207</td>
<td></td>
</tr>
<tr>
<td>III-4</td>
<td>0.57</td>
<td>0.011</td>
<td>0.004</td>
<td>2.42</td>
<td>0.050</td>
<td>0.091</td>
<td></td>
</tr>
<tr>
<td>III-5</td>
<td>0.71</td>
<td>0.011</td>
<td>0.013</td>
<td>2.40</td>
<td>0.043</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td>III-8</td>
<td>0.76</td>
<td>0.013</td>
<td>0.011</td>
<td>2.33</td>
<td>0.038</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>III-9</td>
<td>1.56</td>
<td>0.053</td>
<td>0.025</td>
<td>3.27</td>
<td>0.127</td>
<td>0.250</td>
<td></td>
</tr>
<tr>
<td>III-10</td>
<td>0.58</td>
<td>0.012</td>
<td>0.006</td>
<td>2.56</td>
<td>0.066</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.70</td>
<td>0.012</td>
<td>0.010</td>
<td>2.45</td>
<td>0.060</td>
<td>0.100</td>
<td></td>
</tr>
<tr>
<td>(n = 18)</td>
<td>±0.06</td>
<td>±0.003</td>
<td>±0.002</td>
<td>±0.21</td>
<td>±0.012</td>
<td>±0.015</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed on the basis of C22:0. Control values are expressed as mean ± SD.
noleukodystrophy presenting as spinocerebellar degeneration. VLCFA analyses indicated that transmission was through an X-linked recessive trait, the same as in cases of classical adrenoleukodystrophy and adrenomyeloneuropathy.

Necropsy data on two patients with adrenoleukodystrophy and cerebellar lesions have been reported.\textsuperscript{12} 13 In both, there was demyelination of the white matter in the cerebellum and in the pons. Tateishi \textit{et al}.\textsuperscript{13} detected lesions in the cerebellar cortex, inferior olive and pontine nucleus, lesions which closely resembled typical ones seen in cases of olivopontocerebellar atrophy. The case 2 patient had no clinical signs of adrenal insufficiency and adrenal function tests were normal, in both cases. Some biochemically-confirmed adrenoleukodystrophy patients did have a normal adrenal function.\textsuperscript{5} Therefore, adrenoleukodystrophy should not be ruled out and VLCFA should be measured in patients with spinocerebellar degeneration, even in the absence of adrenal insufficiency, because treatment for the adrenoleukodystrophy may be feasible.\textsuperscript{14} – 17

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