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A new defect of peroxisomal function involving pristanic acid: a case report

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In general, peroxisomal disorders present either at birth with deficits resulting in severe hyponatraemia and craniofacial dysmorphism or as later onset psychomotor retardation, seizures, and hepatomegaly. There is, however, a considerable range of clinical problems within a disorder and overlap between disorders, so that some can only be differentiated on biochemical grounds.

We present a case of adult onset neurological disease the features of which were reminiscent of a peroxisomal disorder, but in a novel combination.

The biochemical defect has been recently elucidated, and has been shown to be due to a deficiency of 2-methylacyl-CoA racemase (AMACR) making our patient one of the first adults to be described with this condition.3

CASE REPORT

A 44 year old man presented with failing vision, having been suspected by his general practitioner of malingering.

He was born of non-consanguineous parents, one of six children, his brother and four sisters being in good health. He had left school at the age of 14. He had been a poor scholar with reading difficulties and after leaving had a succession of unskilled jobs from which he was invariably dismissed. At the age of 18 he presented with an encephalopathic illness characterised by 3 days of severe headache, nausea, and photophobia, with a single blackout followed by progressive confusion, irrational behaviour, and resulting in coma.

He developed focal seizures, with eye deviation to the left and jerking of the neck muscles, which on one occasion generalised. He had tonic deviation of his eyes to the right, sometimes with slow deviation, bilateral papilloedema, but no other focal neurological signs. He had a mild pyrexia and a neutrophil leucocytosis (13×10⁹/l). He underwent cerebral angiography and CSF analysis, including protein estimation, both of which were normal. An EEG showed gross disturbances with generalised slowing and loss of α activity. He required ventilation, but then underwent spontaneous recovery, whereupon he was found to be blind. This was initially suspected to be due to occipital lobe infarction, but pigmentary retinal changes were seen extensively in the periphery of both fundi, and a neuroretinitis was proposed. His EEG improved, but did not return to normal, remaining slowed. Vision slowly recovered, initially with perception of light, then colours, and finally acuity of N24 right N18 left. An encephalitis illness characterised by 3 days of severe headache, nausea, and photophobia, with a single blackout followed by progressive confusion, irrational behaviour, and resulting in coma.

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At the age of 22 he developed generalised seizures, only partially controlled with phenobarbital and phenytoin. An

Abbreviations: VLCFA, very long chain fatty acids; DHCA/THCA, dihydroxycholestanolic/trihydroxycholestanolic acid; AMACR, α-methylacyl-CoA racemase
EEG showed excessive slowing with a right temporal focus and a photoconvulsive response.

At the age of 25 he had an episode of status epilepticus, by which time his vision had declined to 6/36 right and 6/60 left uncorrected.

At the age of 34 he was involved in a road traffic accident and sustained a small right frontal extradural haematoma with confusion, not requiring surgery. After this he developed drop attacks and frequent headaches.

At the age of 41 he became aware of declining vision, and was found to have VA 1/18 L+R, constricted fields, and a generalised “retinopathy”.

When he presented at the age of 44, he was complaining of migrainous headaches daily from his accident, and a recent episode of amnesia with automatic behaviour. He had not had a previous episode of depression with an overdose, and he was known to have a low renal glucose threshold.

There was a family history of ischaemic heart disease, his father dying aged 67 of a heart attack. He was single without children, and taking only phenytoin and phenobarbital. There was a previous episode of depression with an overdose, and he was known to have a low renal glucose threshold.

His brain MRI did not show white matter abnormalities, as shown in Table 2. Table 2 lists the results of fatty acid and bile acid analyses in serum from the patient. The results show normal very long chain fatty acids, a slightly increased phytanic acid concentration, and profoundly increased pristanic acid concentration. Furthermore, both dihydroxycholestanoic acid and trihydroxycholestanoic acid are greatly increased.

These data pointed to a defect in the β-oxidation system which was supported by the finding of a reduced pristanic acid β-oxidation capacity (table 2). Subsequent studies showed that the primary defect in this patient was at the level of one of the β-oxidation enzymes themselves but rather in one of the auxiliary enzymes involved in β-oxidation called α-methyl-acetyl-CoA racemase.

**DISCUSSION**

Our patient had learning difficulties and his psychometric testing as an adult after his encephalitic illness suggested a longstanding premorbid problem with functional and language skills. Encephalitic illnesses have not been noted as a feature of peroxisomal disorders, although Goldman et al described a patient with Refsum’s disease who had an acute onset of ataxia after a viral illness—our patient was initially thought to have had a viral illness with pyrexia. Minor surgery may precipitate deterioration, so it could be postulated that oxidative stresses triggered decompensation or release of phytanic acid from fat stores as a result of catabolic stress. The association with encephalopathy we presume to be genuine, but coincidence cannot be excluded.

A comparison of his clinical features with those found in the other peroxisomal disorders shows a general similarity to those of late onset, particularly Refsum’s disease and in common with the single enzyme deficits, there are mild dysmorphic features, he has a seizure disorder with a peripheral neuropathy, no ataxia, a retinopathy and hypogonadism. His brain MRI did not show white matter abnormalities, as

**RESULTS**

Full blood count, differential count, urea, electrolytes, liver and bone profiles, thyroid function, glucose, B12 and folate, VDRL, TPHA, protein electrophoresis, and immunoglobulin concentrations were all normal or negative. Cholesterol was borderline low at 3.4 mmol/l (normal 3.5 – 5.2).

Testosterone was 3.2 nmol/l (normal 9–38), estradiol <30 pmol/l (normal 40–185 ), FSH 34.1 IU/l (normal 1.1–7.8), and LH 10.8 IU/l (1.1–9.4) confirming primary gonadal failure. Prolactin was normal.

Chromosomal analysis showed a normal male karyotype. Mitochondrial DNA analysis was negative for MELAS 3243, 3271, 8344 deletions.

The EEG showed occipital slowing with no seizure activity or photoconvulsive response. Visually evoked potentials were abnormal bilaterally with low amplitude disrupted wave forms. Brain stem auditory evoked potentials were normal with N1-N5 latencies of 3.3 ms left, 3.96 ms right. Brain MRI showed minor cerebral atrophy only with normal white matter. Chest radiography was normal. Nerve conduction studies shows a peripheral symmetric sensory motor axonal neuropathy.

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of fatty acid and bile acid analysis from serum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Value found</strong></td>
<td><strong>Normal</strong></td>
</tr>
<tr>
<td>VCLFA profile:</td>
<td></td>
</tr>
<tr>
<td>C26 (µmol/l)</td>
<td>0.53</td>
</tr>
<tr>
<td>C26/C22</td>
<td>0.008</td>
</tr>
<tr>
<td>C24/C22</td>
<td>0.58</td>
</tr>
<tr>
<td>Phytanic acid (µmol/l)</td>
<td>20</td>
</tr>
<tr>
<td>Pristanic acid (µmol/l)</td>
<td>105</td>
</tr>
<tr>
<td>Pristanic/phytanic</td>
<td>5.25</td>
</tr>
<tr>
<td>Bile acid profile (µmol/l):</td>
<td></td>
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<tr>
<td>Deoxycholic acid</td>
<td>0.02</td>
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<tr>
<td>Chenodeoxycholic acid</td>
<td>0.22</td>
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<td>Cholic acid</td>
<td>0.44</td>
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<tr>
<td>Ursodeoxycholic acid</td>
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</tr>
<tr>
<td>Hyocholic acid</td>
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<tr>
<td>Dihydroxycholestanoic acid</td>
<td>0.11</td>
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<tr>
<td>Trihydroxycholestanoic acid</td>
<td>2.90</td>
</tr>
<tr>
<td>Dihydroxycholestenolic acid</td>
<td>0.00</td>
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<tr>
<td>C29 dicarboxylic acid</td>
<td>0.01</td>
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</tbody>
</table>

<table>
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<tr>
<th>Table 2</th>
<th>Results from fibroblast studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>De novo plasmalogen biosynthesis:</td>
</tr>
<tr>
<td></td>
<td>DHAP-AT activity:</td>
</tr>
<tr>
<td></td>
<td>Pristanic acid β-oxidation activity*</td>
</tr>
<tr>
<td></td>
<td>AMACR activity†</td>
</tr>
<tr>
<td>Controls</td>
<td>Pristanic acid β-oxidation activity*</td>
</tr>
<tr>
<td></td>
<td>AMACR activity†</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>284</td>
</tr>
<tr>
<td></td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>1147 (SD 325) (n=30)</td>
</tr>
<tr>
<td></td>
<td>92 (SD 30) (n=11)</td>
</tr>
</tbody>
</table>

*pmol/h/mg protein; †pmol/min/mg protein.
ND, Not detectable; AMACR, α-methylacyl-CoA racemase.
For methods see Ferdinandusse et al.

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characterised as an absence of the missed, as peroxisomal disorders have always been assumed to
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abnormalities of pristanic acid metabolism were first associ-
ates), or loss of lipid functions “downstream”.
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are depending on the proportions of product accumu-
most be converted to their (fig 1) and abnormalities of pristanic acid metabolism were first associ-
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This currently described patient showed highly increased
pristanic acid concentrations and mildly raised phytanic acid,
and pristanic acid. Multiple enzymes are involved (fig 1) and
in tissues depending on the proportions of product accumu-
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why there should be this
distinction is uncertain, but there may be a differential effect
clinical syndromes highlight the import-
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their diet, but he
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no significant progression in his visual failure or neuropathy
over 2 years.
As biochemical and molecular biological techniques ad-
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J Allen, Department of Clinical Biochemistry, Southmead Hospital, Bristol BS10 5NB, UK
S Ferdinandusse, R J A Wanders, Laboratory of Genetic Metabolic Diseases, Emma Children’s Hospital AMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Correspondence to: Dr B N McLean, Department of Neurology, Royal Cornwall Hospital, Treliske, Truro, Cornwall TR1 3U, UK

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