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

B N McLean, J Allen, S Ferdinandusse, R J A Wanders

Peroxisomes are subcellular organelles found in all mammalian cell types, and are particularly abundant in fibroblasts and liver cells, where they account for 40% of organelles. They are involved in various metabolic pathways, including the oxidation of fatty acids, the synthesis of sterols, and the degradation of xenobiotics.

The first well-defined disorder described in 1946 was a peroxisomal disorder, Zellweger syndrome, characterized by severe neurological and systemic features. In general, peroxisomal disorders present either at birth with deficits resulting in severe hypotonia 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 α-methylacyl-CoA racemase (AMACR) making our patient one of the first adults to be described with this condition.

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 encephalitic 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, making our patient one of the first adults to be described with this condition.

AN adult onset novel disorder of peroxisomal function is described, characterised by retinitis pigmentosa resulting in progressive visual failure, learning difficulties, a peripheral neuropathy, and hypogonadism. The defect results in accumulation of pristanic acid, and the bile acid intermediates, dihydroxycholestanolic acid and trihydroxycholestanolic acid, and is due to a deficiency of α-methylacyl-CoA racemase, making this the first fully characterised description of this defect. Screening of patients with retinitis pigmentosa should be extended to include pristanic acid and/or bile acid intermediate concentrations, as dietary measures offer a potential treatment for the disorder.

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 been employed since his encephalopathy.

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 had been a comparison of his clinical features with those found in the other peroxisomal disorders, although Goldman et al17 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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of fatty acid and bile acid analysis from serum</th>
</tr>
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<tbody>
<tr>
<td><strong>VCLFA profile:</strong></td>
<td><strong>Value found</strong></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><strong>Phytanic acid (µmol/l):</strong></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><strong>Bile acid profile (µmol/l):</strong></td>
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</tr>
<tr>
<td>Deoxycholic acid</td>
<td>0.02</td>
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<tr>
<td>Chenodeoxycholic acid</td>
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<tr>
<td>Cholic acid</td>
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<tr>
<td>Ursodeoxycholic acid</td>
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<tr>
<td>Hyocholic acid</td>
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<tr>
<td>Dihydroxycholanoic acid</td>
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<td>Trihydroxycholanoic acid</td>
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<tr>
<td>Dihydroxycholestenonic acid</td>
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<tr>
<td>C29 dicarboxylic acid</td>
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<tr>
<th>Table 2</th>
<th>Results from fibroblast studies</th>
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<tr>
<td>Patient</td>
<td>De novo plasmalogen biosynthesis:</td>
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<tr>
<td></td>
<td>DHAP-AT activity:</td>
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<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>
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</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 Ferdinandusse16. |

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. Encephalitis have not been noted as a feature of peroxisomal disorders, although Goldman et al17 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
Pristanic acid abnormalities of pristanic acid metabolism were first associated with VLCFAs, DHCA/THCA, and pristanic acid. Multiple enzymes are involved (Fig 1) and so far identified are those relating to VLCFAs, DHCA/THCA, and pristanic acid. Analysis of both enzymes is required to establish the precise defect.

This currently described patient showed highly increased pristanic acid concentrations before degradation by peroxisomal β-oxidation, although in the second R and S stereoisomers accumulate, and in racemase deficiency only R stereoisomers accumulate. Analysis of both enzymes is required to establish the precise defect.

He therefore has a unique combination of features, distinct from the other peroxisomal disorders, but with many features in common, particularly with Refsum’s disease. His disease course has been relatively benign.

Preumably this is autosomal recessive as are most of the other peroxisomal disorders, but his family have refused blood testing and skin biopsy. The presence of hypogonadism does make the possibility of an X-linked disorder, but we have been made aware of a woman with the condition (personal communication), so this seems unlikely.

Given that Refsum’s disease responds to dietary elimination of phytanic acid, therapy for this disorder was attempted using a pristanic acid and phytanic acid depleted diet, but he would not tolerate the dietary change. His seizures have remained controlled on phenytoin alone, and there has been no significant progression in his visual failure or neuropathy over 2 years.

As biochemical and molecular biological techniques advance, further peroxisomal disorders are likely to emerge.

These overlapping clinical syndromes highlight the importance of wider screening of biochemical function using plasma and fibroblasts. We recommend that any patient presenting with retinal pigmentation resulting in visual failure, and neurological disturbances, particularly seizures and a peripheral neuropathy, be screened not only for VLCFA/C26 ratio, but also pristanic acid concentrations and mildly raised phytanic acid concentrations. Had the pristanic acid concentrations not been measured, the condition would have been missed, as peroxisomal disorders have always been assumed to cause abnormalities of VLCFA or phytanic acid.

The biochemical defect causing Refsum’s disease lies “upstream”, yet the clinical phenotype of the disorders differ, although with considerable overlap. Why there should be this distinction is uncertain, but there may be a differential effect on tissues depending on the proportions of product accumulation (phytanic and pristanic acid and bile acid intermediates), or loss of lipid functions “downstream”.

In humans, the only peroxisomal disorders of β-oxidation so far identified are those relating to VLCFAs, DHCA/THCA, and pristanic acid. Multiple enzymes are involved (fig 1) and abnormalities of pristanic acid metabolism were first associated with generalised peroxisomal disorders.

This currently described patient showed highly increased pristanic acid concentrations and mildly raised phytanic acid and VLCFA concentrations. Had the pristanic acid concentrations not been measured, the condition would have been missed, as peroxisomal disorders have always been assumed to cause abnormalities of VLCFA or phytanic acid.

The biochemical defect in this case has only recently been characterised as an absence of the α-methylacyl-CoA racemase. There is stereoselectivity of the α-methyl branched acyl CoA esters and the bile acid intermediates, and these must be converted to their S forms before degradation by peroxisomal β-oxidation. Absence of the racemase has the same consequences as a deficiency of the branched chain acyl-CoA oxidase, although in the second R and S stereoisomers accumulate, and in racemase deficiency only R isomers accumulate. Analysis of both enzymes is required to establish the precise defect.

He therefore has a unique combination of features, distinct from the other peroxisomal disorders, but with many features in common, particularly with Refsum’s disease. His disease course has been relatively benign.

Figure 1. The peroxisomal β-oxidation pathway, showing the steps involved in the oxidation of pristanic acid and THCA/DHCA. The site of activity of AMACR, where the defect occurs in this disorder, is indicated.

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**Authors’ Affiliations**

B N McLean, Department of Neurology, Royal Cornwall Hospital, Treliske, Truro, Cornwall TR1 3LJ, UK
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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 3JU, UK

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