Adult peroxisomal acyl-coenzyme A oxidase deficiency with cerebellar and brainstem atrophy

Published in:
Journal of Neurology, Neurosurgery and Psychiatry

DOI:
10.1136/jnnp.2009.176255

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Peroxisomal acyl-coenzyme A oxidase deficiency (MIM264470) is a disorder of peroxisomal fatty acid oxidation caused by a deficiency of straight-chain acyl-coenzyme A oxidase (SCOX). SCOX is the first enzyme of the peroxisomal β-oxidation system and is involved in the oxidation of various fatty acids. These include very-long-chain fatty acids (VLCFAs ≥C24:0), long-chain dicarboxylic acids and polyunsaturated fatty acids, but not branched-chain fatty acids such as pristanic acid and the C27:0 acid intermediates. Accumulation of VLCFAs is the only diagnostic marker for SCOX deficiency.

The first patients with SCOX deficiency, reported in 1988,1 were two siblings with neonatal hypotonia, seizures, apnoeic spells, delayed psychomotor development and neurological regression after the age of 2 years. Brain imaging showed progressive white-matter demyelination without cortical malformations. Following this report, a few additional cases have been described.2–6 Recently, the clinical, biochemical and mutational findings in a cohort of 22 patients have been published.7 All patients were children with a severe clinical presentation including psychomotor retardation, but they acquired limited skills such as sitting and standing without support. Almost all patients, however, showed a progressive loss of their motor achievements, and the mean age of regression was 28 months. The mean age of death was 5 years, with the oldest patient surviving until the age of 10.

Here we describe two SCOX-deficient siblings with a remarkable clinical presentation. The male proband was aged 52 when diagnosed as having SCOX deficiency. His early developmental milestones were normal. At age 10, he was noted to have scoliosis and a clumsy right hand. His gait showed progressive unsteadiness until the age of 28, when he became wheelchair-bound. He had some urinary and faecal urgency. On examination, at 52 years of age, he had mildly impaired cognitive function. His memory was poor, but he was well oriented and could give an adequate description of his present problems. The visual acuity in the right eye was restricted to hand movements; left eye 6/12. He had small lens opacities. Retinitis pigmentosa was observed in both fundi, more advanced in the right eye. There was no optic disc pallor. Gaze-evoked nystagmus on upgaze, downgaze and lateral gaze was present. He had a slurring dysarthric speech but near normal tongue movements. He had a jerky head tremor. There was some dystonic posturing of his arms, and ataxia was seen on finger–nose testing. There was spastic tone in the legs, which was not present in the arms. Reflexes were symmetrical but pathologically brisk throughout. Clonus was present in both ankles with impaired heel–shin testing. Plantar responses were extensor. Sensation was normal with all modalities.

Magnetic resonance brain imaging showed profound atrophy of the brainstem and cerebellum, particularly evident in the pons, and modest cerebral atrophy. No other abnormality was seen. Nerve-conduction studies were normal. ERG showed a virtually absent response from either eye.

The patient’s sister was 55 upon diagnosis. Her development was normal until 8 years of age when clumsiness and unsteady gait were noted. Examination, at age 55, showed cognitive impairment with disorientation in time and place. She had poor memory but could follow simple commands. She was confined to a wheelchair. She had bilateral cataracts, and fundi were not visible. She had limitation of eye movement in all directions, and gaze-evoked nystagmus in all directions. Her hearing was normal. She had slow tongue movements. There was preserved strength and normal tone in the arms but markedly impaired finger–nose testing. She was unable to move any muscle group in her legs, but reflexes were within normal limits. Plantar responses were extensor. There was normal sensation with all modalities.

The MRI scan of the sister also showed marked cerebellar and brainstem atrophy with modest atrophy of the cerebral hemispheres. There was no evidence of parenchymal signal abnormality (figure 1A–C).

Because of a clinical suspicion of a peroxisomal disorder, plasma VLCFAs were measured (table 1). The level of C26:0 was increased in plasma from both the brother (3.31 μmol/l) and the sister (1.59 μmol/l; control range 0.45–1.52 μmol/l). However, the C26:0/C22:0 and C24:0/C22:0 ratios
were only marginally increased in the brother and even normal in the sister. Interestingly, acylcarnitine analysis in plasma revealed the presence of trace amounts of C26-carnitine, C24-carnitine and C16-dicarboxylyl-carnitine. The level of the polyunsaturated fatty acids, including docosahexaenoic acid (C22:6 ω3), were normal in both plasma and erythrocytes of the siblings. Bile acid analysis in plasma as well as the analysis of pristanic and phytanic acid did not reveal any abnormalities. Organic acid profiling in urine showed increased excretion of sebacic acid (C10-dicarboxylic acid), 2-hydroxy-sebacic acid, 3-hydroxy-sebacic acid and suberic acid (C8-dicarboxylic acid). The prominent excretion of these dicarboxylic acids is characteristic for patients with a peroxisomal fatty acid oxidation disorder.

Subsequent investigations in cultured skin fibroblasts of the brother revealed a strongly reduced β-oxidation activity with C26:0 as substrate (590 pmol/(h.mg protein); control range 1025 to 2994 pmol/(h.mg protein)) (table 1). The activities of pristanic acid and C16:0 β-oxidation were completely normal. Immunofluorescence with antibodies against the peroxisomal matrix enzyme catalase and the peroxisomal membrane protein adrenoleucodystrophy protein (ALDP) revealed peroxisomes that were increased in size and reduced in number compared with control fibroblasts. These results prompted us to measure the activity of different β-oxidation enzymes in fibroblast homogenates. SCOX activity was clearly deficient (16 pmol/(min.mg protein); control range 49 to 151 pmol/(min.mg protein)) (not shown). To confirm the SCOX deficiency at the molecular level, we performed mutation analysis of the ACOX1 gene encoding SCOX. An apparent homozygous missense mutation, c.629G→A, was identified in DNA isolated from skin fibroblasts of the brother. The same apparent homozygous mutation was also identified in DNA isolated from lymphocytes of the sister. No material from the patients’ parents, who were first cousins, was available to confirm homozygosity. The mutation c.629G→A leads to the amino acid substitution p.R210H. Immunoblot analysis with antibodies against SCOX revealed the normal presence of the 72 kDa full-length protein and the 51 and 21 kDa bands, the products of the proteolytical cleavage of the full-length protein, in fibroblast homogenates of the brother.

Virtually all SCOX-deficient patients die early in childhood. Up to now, the oldest surviving patient with an SCOX deficiency described in the literature was a 19-year-old Japanese boy.

Table 1  Biochemical analyses in plasma and skin fibroblasts

<table>
<thead>
<tr>
<th></th>
<th>Brother</th>
<th>Sister</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C26:0 (µmol/l)</td>
<td>3.31</td>
<td>1.59</td>
<td>0.45 to 1.32</td>
</tr>
<tr>
<td>C24:0 (µmol/l)</td>
<td>100.3</td>
<td>86.1</td>
<td>33 to 82</td>
</tr>
<tr>
<td>C22:0 (µmol/l)</td>
<td>98.0</td>
<td>98.0</td>
<td>40 to 119</td>
</tr>
<tr>
<td>C26/C22 ratio</td>
<td>0.03</td>
<td>0.02</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>C24/C22 ratio</td>
<td>1.02</td>
<td>0.88</td>
<td>&lt;0.94</td>
</tr>
<tr>
<td>Phytanic acid (µmol/l)</td>
<td>3.8</td>
<td>3.4</td>
<td>0 to 9</td>
</tr>
<tr>
<td>Pristanic acid (µmol/l)</td>
<td>0.8</td>
<td>0.4</td>
<td>0 to 3.1</td>
</tr>
</tbody>
</table>

|                          |         |        |                  |
| Erythrocytes             |         |        |                  |
| DHA (pmol/10⁶ cells)     | 23.6    | 19.6   | 15.2 to 37.6     |
| Skin fibroblasts         |         |        |                  |
| SCOX activity (pmol/(min.mg protein)) | 16 | ND | 49 to 151 |
| C26:0 β-oxidation (pmol/(h.mg protein)) | 590 | ND | 1025 to 2994 |
| Pristanic acid β-oxidation (pmol/(h.mg protein)) | 1616 | ND | 691 to 2178 |
| C16:0 β-oxidation (pmol/(h.mg protein)) | 2964 | ND | 1729 to 5361 |

ND, not determined.

Figure 1  Axial T2 weighted images at the level of the middle cerebellar peduncles (A) and the lateral ventricles (B), and midline sagittal T1 weighted image (C). There is marked atrophy of the cerebellum, middle cerebellar peduncles and brainstem, with modest atrophy of the cerebrum. No parenchymal signal abnormality is seen.
who manifested psychomotor retardation and regression during
the late infantile period and who required respiration and tube
feeding since the age of 11.5 10 The siblings described in this
report have a remarkably mild presentation of SCOX deficiency
and are alive at 52 and 55 years of age. The brain imaging
contrasts with reported findings in the literature which describe
changes occurring in early childhood: initially there is signal
abnormality in cerebellar white matter, the middle cerebellar
decussation and brainstem tracts, with vermian atrophy; later,
abnormal signal appears in the pyramidal tracts more superiorly
in the brainstem, and in the posterior limb of the internal
capsule; the parieto-occipital periventricular white matter and
spleenium of corpus callosum are then involved with later spread
to frontal white matter.3—5

In agreement with the relatively mild clinical presentation,
the biochemical parameters in skin fibroblasts of the brother
were only mildly abnormal. The residual C26:0 β-oxidation
activity was one of the highest of a cohort of 20 SCOX-deficient
skin fibroblasts available in our laboratory (590 compared with
a patient range of 161—598 pmol/(h.mg protein)). This suggests
that the SCOX protein displays some residual activity. This is
difficult to ascertain in skin fibroblasts because the other peroxis-
osomal acyl-coenzyme A oxidase, which primarily handles
branched-chain substrates, has been shown also to display a low
activity towards straight-chain fatty acids.11 However, the
amino acid substitution identified in the siblings does not affect
the catalytic unit or the co-factor (FAD) binding site when
analysing the crystal structure of rat SCOX,12 in contrast to
almost all the other amino acid substitutions described in SCOX-
deficient patients.

In conclusion, we present the first adult patients with
peroxisomal acyl-coenzyme A oxidase deficiency. This diagnosis
should be considered even when imaging findings are not typical
of a peroxisomal disorder, and may also be suggested by
abnormal VLCFAs in patients clinically atypical of the adreno-
leucodystrophy/myeloneuropathy spectrum.

Acknowledgements We thank PAW Mooyer, C Dekker, H Rusch, S Denis, W Smit
and EM Hogenhout for technical assistance. We thank G Warner for referring the
patient to us. We would like to thank Dr Jeremy Quiney for his kind help in analysis
and despatch of samples.

Funding This work was supported by The Netherlands Organisation for Scientific
Research (NWO, grant number 916.46.109) and the F6 European Union Project
‘Peroxisomes’ (grant number LSHG-CT-2004512016).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

peroxisomes and a specific deficiency of acyl-CoA oxidase (pseudo-neonatal
2. Watkins PA, McGuinness MC, Raymond GV, et al. Distinction between
peroxisomal bifunctional enzyme and acyl-CoA oxidase deficiencies. Ann Neurol
presenting with dysmorphism, neurodevelopmental autistic-type regression and
7. Ferdinandusse S, Denis S, Hogenhout EM, et al. Clinical, biochemical, and
mutational spectrum of peroxisomal acyl-CoA oxidase deficiency. Hum Mutat
defects of peroxisome biogenesis: a novel tool for screening diagnosis using tandem
9. Korman SH, Mandel H, Gutman A. Characteristic urine organic acid profile in
branched chain fatty acids and of the bile acid intermediates di- and
trihydroxyxysterogens are oxidized by one single peroxisomal branched chain
flavoenzyme acyl-CoA oxidase-II from rat liver, the peroxisomal counterpart of

312 J Neurol Neurosurg Psychiatry 2010; 81:310—312. doi:10.1136/jnnp.2009.176255