Clinical consequences of defects in peroxisomal \( \beta \)-oxidation

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Abstract

The disorders of peroxisomal \( \beta \)-oxidation, which have been well characterised at the molecular level, include defects of acyl-CoA oxidase, defects of the \( D \)-bifunctional protein (\( D \)-BP) (including specific defects of its enoyl-CoA hydratase and \( D \)-3-hydroxyacyl-CoA dehydrogenase components), defects of the very-long-chain fatty acid (VLCFA)-CoA importer [X-linked adrenoleukodystrophy (ALD)] and \( \alpha \)-methylacyl-CoA racemase deficiency. A survey of the clinical consequences of these defects indicates that defects in the acyl-CoA oxidase and \( D \)-BP can produce neonatal hypotonia, seizures in early infancy, retinopathy and progressive neurological dysfunction with leukodystrophy on imaging. Defects in the VLCFA-CoA importer and in the racemase do not produce disease until a long time after the neonatal period. However, again the clinical picture is dominated by neurological disease: impaired cognitive function with leukodystrophy in childhood X-linked ALD and retinopathy and neuropathy in racemase deficiency. It is difficult to escape the conclusion that defective peroxisomal \( \beta \)-oxidation has effects (such as impaired neuronal migration in the developing brain), which are more serious than those produced by the accumulation of substrates (VLCFAs, pristanic acid) alone.

Introduction

The \( \beta \)-oxidation pathway in the peroxisomes is uniquely capable of catalysing the oxidation of straight-chain fatty acids with 24 or more carbon atoms [very-long-chain fatty acids, (VLCFA)] and the oxidation of compounds with a branched (isoprenoid) carbon chain [1]. This latter group of compounds includes pristanoyl-CoA (derived from the \( \alpha \)-oxidation of phytanic acid in the diet) and \( C_{37} \) intermediates in bile acid synthesis, notably \( 3\alpha,7\alpha,12\alpha \)-trihydroxy-\( 5 \beta \)-cholestanoxy-CoA (THCA-CoA) and \( 3\alpha,7\alpha \)-dihydroxy-\( 5 \beta \)-cholestanoyl-CoA (DHCA-CoA). Measurement of VLCFA, pristanic acid and \( C_{37} \) bile acids in plasma provides a very important means of diagnosing a peroxisomal disorder and goes some way towards defining the exact type (Table 1). Our current view of the peroxisomal \( \beta \)-oxidation pathway is shown in Scheme 1. VLCFA need to be activated by conversion into the CoA esters and transported into the peroxisomes; the adrenoleukodystrophy (ALD) protein is thought to be

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involved in the transport process [2]. Pristanoyl-CoA derived from \( \alpha \)-oxidation of phytanic acid is a mixture of the \((2R)\) and \((2S)\) isomers and the \((2R)\) form needs to be converted into the \((2S)\) form by \( \alpha \)-methylacyl-CoA racemase before \( \beta \)-oxidation [3]. Similarly, in the synthesis of bile acids from cholesterol, the first steps produce the \((25R)\) isomer of \( \text{THCA-CoA} \) and the racemase is required to convert this into the \((25S)\) form before \( \beta \)-oxidation.

The major pathway for \( \beta \)-oxidation of VLCFA-CoA and other straight-chain substrates is thought to proceed via a straight-chain acyl-CoA oxidase (palmitoyl-CoA oxidase), via the \( \alpha \)-bifunctional protein (\( \alpha \)-BP) (which has enoyl-CoA hydratase and \( \alpha \)-3-hydroxyacyl-CoA dehydrogenase activities) and then via the 41 kDa 3-oxoacyl-CoA thiolase [1]. In contrast, \((22R)\)-pristanoyl-CoA and \((25S)\)-THCA-CoA are oxidized by a branched-chain acyl-CoA oxidase, the \( \alpha \)-BP and the sterol carrier protein \( \alpha \)-thiolase.

This review will consider defects of palmitoyl-CoA oxidase, the \( \alpha \)-BP, the 41 kDa thiolase, the ALD transporter protein and \( \alpha \)-methylacyl-CoA racemase. The focus will be on patients whose defect has been established at the molecular level. Some comparisons will be made with children with defects of peroxisome biogenesis (e.g. cerebrohepatorenal syndrome of Zellweger, ZS) to illustrate the extent to which defective \( \beta \)-oxidation can produce the same clinical manifestations as a total absence or markedly decreased number of peroxisomes. Finally, reference will be made to unknown defects of peroxisomal \( \beta \)-oxidation. These are of two types: (1) patients with evidence of accumulation of VLCFA and/or pristanate and/or THCA/DHCA, in whom enzymology and molecular studies have not provided
a definitive explanation, and (2) enzymes that are known to have a specific function but for which no case of defective activity has been described, e.g. branched-chain acyl-CoA oxidase deficiency and t-bifunctional protein deficiency.

**Peroxisome biogenesis defects**

Infants with the most severe form of biogenesis defect, ZS, are abnormal at birth with characteristic dysmorphic features, severe muscular hypotonia and intractable seizures [4]. The head is usually of normal size but the infant has a tall sloping forehead and shallow supra-orbital ridges, giving the skull and face a distinctive appearance. Vision is impaired with a reduced electroretinogram; hearing is also affected with reduced brain stem auditory evoked responses. Adrenal function is impaired, with a decreased cortisol response to stimulation with corticotropin. The infants show severely delayed development, fail to thrive and have evidence of liver dysfunction, with cirrhosis on a liver biopsy. They can have punctate stippling of the cartilages around the knee, hip and other joints (chondrodysplasia punctata). Survival is seldom beyond 1 year of age. At post mortem the brain shows evidence of defective neuronal migration during development and the kidneys have small glomerular cysts. Defects in peroxisome biogenesis can also lead to neonatal ALD in which dysmorphic features, hypotonia and failure to thrive are not so severe but in which neurological deterioration occurs after a few months, concomitant with the appearance of white-matter changes on a computed tomography or magnetic resonance imaging (MRI) scan of the brain (leukodystrophy). In infantile Refsum disease, dysmorphic features are similar to ZS but more subtle; the hypotonia, delayed development, impaired vision and hearing and failure to thrive might not be apparent until 6 months to 1 year.

**Palmitoyl-CoA oxidase deficiency**

In 1998 Poll-The et al. described two siblings with ‘pseudo-neonatal ALD’ in whom immunoblotting showed an absence of the acyl-CoA oxidase [5]. This was later shown to be due to a deletion of more than 17 kb of the gene encoding palmitoyl-CoA oxidase, starting downstream of exon 2 and extending beyond the 3’ end of the gene [6]. These two siblings were not dysmorphic but they had severe muscular hypotonia, albeit with preserved tendon reflexes. Seizures started shortly after birth and became almost constant and uncontrolled by anticonvulsants. The infants showed severely retarded psychomotor development. In the third year of life, the older sibling had evidence of hearing loss and also of loss of vision manifesting first with nystagmus, followed by loss of the pupillary light reflex with optic atrophy on fundoscopy and a reduced electoretinogram and absent cortical visual evoked response. Progressive neurological deterioration was evident from 2½ years with hypertonia and hyper-reflexia in the limbs and additional dystonia in the arms. The clinical evidence of deterioration was associated with progression of abnormalities on the computed tomography scan of the brain, with development of extensive white-matter hypodensities and abnormal enhancement with contrast. Adrenal dysfunction was apparent from low plasma cortisol and raised plasma corticotropin concentrations. Plasma concentrations of VLCFA were elevated but the concentrations of phytanate and C37 bile acids were normal. Intact fibroblasts showed decreased oxidation of lignonerate (C26,0) and the liver peroxisomes were of variable size and shape. The second sibling showed very similar clinical abnormalities but additionally showed mild hepato-megaly in the neonatal period and tapetoretinal degeneration on fundoscopy at age 2 years.

Wanders et al. [7] described a further case of palmitoyl-CoA oxidase deficiency, diagnosed by immunoblot analysis. Suzuki et al. [8] added two further cases and Watkins et al. [9] a further five cases, all diagnosed by lack of complementation with the fibroblasts from the patients of Poll-The et al. These ten cases confirmed that dysmorphic features are unusual, although the two siblings described by Suzuki et al. had hypertelorism, epicanthic folds, a low nasal bridge, low-set ears and polydactyly. All patients had marked hypotonia (but sometimes with preserved reflexes) and seizures (but onset of seizures was often between 2 and 4 months and could sometimes be controlled with medication). All showed psychomotor delay but almost all acquired some gross and fine motor skills. Most subsequently showed regression and/or the appearance of a leukodystrophy on imaging. Adrenal insufficiency was common but liver involvement was mild, with slight hepato-megaly and hepatic fibrosis being described. The average age of death was approx. 4 years.

**n-BP deficiency**

The first description of a patient with bifunctional protein deficiency was from Watkins et al. [10].
Although, on the basis of immunoblot data, this patient was originally thought to have a deficiency of the \( L \)-bifunctional protein, reinvestigation by Grunsven et al. [11] showed that the disease-causing mutation (present on both alleles) was a deletion of 2 bp at positions 422 and 423 of the \( D \)-BP cDNA. This resulted in the production of a truncated \( D \)-BP. Two other patients with inactivity of the whole \( D \)-BP were described by Suzuki et al. [12]. One had a 52 bp deletion, and the other a 237 bp deletion, in the gene encoding \( D \)-BP. These three patients were all abnormal at birth, with dysmorphic features that included a large head, large fontanelles, frontal bossing, a high arch palate, micrognathia, pectus excavatum and talipes equinovarus. Studies of the brain in \( D \)-BP deficiency have shown evidence of abnormal brain development with polymicrogyria and ectopic neurons in the white matter. The newborn with \( D \)-BP deficiency shows marked hypotonia and intractable seizures. Hepatomegaly and hepatic dysfunction (low clotting factors) can be present but progression to cirrhosis has not been described (in contrast to ZS). Bleeding arising from vitamin K deficiency has been documented, as has osteoporosis leading to pathological fractures. One infant had the punctate calcific stippling of the shoulder and knee joints similar to that seen in ZS. In contrast with patients with palmitoyl-CoA oxidase deficiency, patients with \( D \)-BP deficiency have shown little or no developmental progress. However, in both disorders, definite regression has been described. The patients with a total absence of \( D \)-BP died between the ages of 6 months and 2 years.

Further cases of \( D \)-BP deficiency have been identified by the failure of their fibroblasts to complement fibroblasts from the patient of Watkins et al. [10]. Some of these patients could have a defect in only one component of the \( D \)-BP (see below) but the clinical features of the patients were broadly similar to those described for total \( D \)-BP deficiency [9]. Dysmorphic features were present in 14 of 15, with macrocephaly in 10 of 12, a prominent forehead, flat nasal bridge and micrognathia. All had profound neonatal hypotonia, 14 of 15 had neonatal seizures and 13 of 15 had seizures after the neonatal period. All showed no developmental progress, scans showed leukodystrophy in 6 of 8 and there was evidence of a neuronal migration defect in 7 of 8. Liver abnormalities were mild; several had osteoporosis. Mean age at death was 9 months.

**Deficiency of the hydroxyacyl-CoA dehydrogenase component of the \( D \)-BP**

Among patients identified by a lack of complementation with the \( D \)-BP-deficient patient of Watkins et al. [10], there were patients who did complement one another: 'intragenic complementation'. In one group, the main bile acid in plasma was varanic acid ([24\( \xi \),25\( \xi \)]-[3\( \alpha \],7\( \alpha \],12\( \alpha \],24-tetrahydroxy-5\( \beta \)-cholestanolic acid); this suggested that the defect was likely to be in the hydroxyacyl-CoA dehydrogenase component of the bifunctional protein. The first patient shown to have a defect of this type by both molecular and enzymic studies was described by van Grunsven et al. [13]. The patient was homozygous for a substitution of serine for glycine at residue 16. This is predicted to affect the NAD\(^+\)-binding site. This patient was abnormal at birth, with a high forehead and frontal bossing, a large fontanelle and low-set ears. He also had hypospadias. He was hypotonic with muscle wasting and had seizures. Mild hepatomegaly was documented. An MRI scan showed dysmyelination.

**Deficiency of the enoyl-CoA hydratase component of the \( D \)-BP**

One subgroup of patients with \( D \)-BP deficiency complemented the patients with hydroxyacyl-CoA dehydrogenase deficiency and had no varanic acid (or other bile acid intermediates) in plasma. The complementation studies suggested the possibility of deficiency of the enoyl-CoA hydratase component of the \( D \)-BP. This was confirmed enzymically by Grunsven et al. [14] and they went on to show that two patients in the group were homozygous for an Asn\(^{417} \rightarrow \)Tyr mutation in the enoyl-CoA hydratase coding region of the \( D \)-BP gene. These first patients with proven enoyl-CoA hydratase deficiency were abnormal from birth with hypotonia, refractory seizures, severe psychomotor delay and possibly impaired vision and/or hearing (they failed to respond to auditory or visual stimuli and to fix and follow with their eyes). Dysmorphic features were subtle in one infant (shallow supra-orbital ridges only) but the other had macrocephaly and a typical Zellweger facies. Both developed hydrocephalus, one at 3 months and one at 8 months. One died at 4 months and the other at 1 year.

**Deficiency in 41 kDa thiolase**

Only one patient with deficiency of the 41 kDa thiolase has been described so far; this patient was
diagnosed on the basis of immunoblotting of the peroxisomal β-oxidation proteins in the liver (absence of thiolase) [15,16]. A molecular defect has not been confirmed. The infant was abnormal from birth with profound hypotonia (and absent tendon reflexes), intractable seizures and subtle dysmorphic features (high arch palate, flattened chest with flared ribs). She made no developmental progress and had reduced visual evoked responses from the occipital cortex. She had a ventricular septal defect and developed cardiac failure. She died at 11 months. Mild hepatic fibrosis was present at post-mortem.

**X-linked ALD (X-ALD)**

Much has been written on the clinical manifestations of X-ALD, which is the consequence of mutations in the ALD protein, an ATP-binding cassette protein that is probably necessary for import of VLCFA-CoA into the peroxisomes [17]. This review will contain a brief summary, focusing on the commonest type, childhood ALD. In contrast with the patients described so far, boys with ALD are entirely normal at birth. They have no dysmorphic features, a normal muscle tone, no seizures and a normal early psychomotor development. Onset of symptoms is usually at approx. 7.2 years (range 2.75–10 years) with changes in behaviour (emotional lability, withdrawal or hyperactive behaviour). At the same time there can be perceptive or intellectual difficulties (specifically difficulty understanding speech, attention deficit, astereognosis and graphaesthesia). These problems often progress to expressive and motor difficulties (apraxia, dysarthria and dysphasia followed by a spastic gait or hemiparesis with hyper-reflexia). Visual disturbance is common with, initially, reduced visual fields and acuity, but later strabismus and optic atrophy. Focal or generalized seizures occur as a late feature of the disease. Symptoms and signs of adrenal insufficiency include weakness and tiredness, anorexia, vomiting and diarrhoea/constipation, pigmentation (including involvement of the mucous membranes) and crises with abdominal pain, vomiting and dehydration. MRI images of the brain in boys with ALD characteristically show abnormalities of the occipital white matter with a surrounding area that enhances with contrast.

Other manifestations of mutations in the ALD protein include adrenomyeloneuropathy in which the spinal cord and peripheral nerves are principally affected. Similar pathology can occur in female carriers of mutations in the ALD gene. A pattern of neurological disease similar to that seen in childhood ALD affecting principally the cerebral white matter can occur in adolescents and adults. Males with mutations in the ALD gene can also present with isolated adrenal insufficiency or be asymptomatic (or presymptomatic).

**α-Methylacyl-CoA racemase deficiency**

The first cases of α-methylacyl-CoA racemase deficiency were described by Ferdinandusse et al. [3]. One case was a 50-year-old woman who complained that her legs felt heavy on exercise and that she was dragging her feet on walking. She had difficulty getting out of a chair and walking upstairs. Examination revealed a spastic paraparesis; nerve conduction studies showed that she also had a demyelinating polyneuropathy. An MRI scan showed non-specific changes (prominent areas of signal in the thalami in T2 weighted scans with low signal in T1 mode). Plasma VLCFA levels were normal, phytanic acid concentrations varied from normal to mildly elevated, and pristanic acid, DHCA and THCA levels were markedly elevated. Dietary restriction of phytanic acid led to a decrease in pristanate levels; after this treatment she was stronger and was, for example, able to walk upstairs. A second patient with racemase deficiency, a man in his thirties, had had mild learning difficulties during childhood. He had developed an encephalitic illness at 18 years that had led to a loss of vision, which was followed by partial recovery then loss of acuity again with restriction of visual fields and evidence of pigmentary retinopathy on fundoscopy. Further neurological assessment showed signs of a sensory motor neuropathy affecting the arms more than then legs; nerve conduction studies suggested an axonal neuropathy. The patient also suffered from epilepsy and primary hypogonadism. A further case of racemase deficiency has been diagnosed in an adult female with sensory motor neuropathy and pigmentary retinopathy and increased plasma concentrations of phytanate and pristanate. Our conclusion at present must be that the major clinical manifestations of racemase deficiency must be adult-onset sensory motor neuropathy and pigmentary retinopathy.

**Conclusions**

A comparison of the clinical consequences of specific defects of peroxisomal β-oxidation is shown in Table 2. It is clear that defects in palmitoyl-CoA oxidase and in the d-BP can cause

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## Table 2
Comparison of the clinical manifestations in different defects of peroxisomal β-oxidation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Childhood X-ALD</th>
<th>Racemase</th>
<th>Palmitoyl-CoA oxidase</th>
<th>α-BP</th>
<th>OH-Acyl-CoA DH</th>
<th>Enoyl-CoA hydratase</th>
<th>Biogenesis (ZS)</th>
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<tr>
<td>Neonatal hypotonia</td>
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<td>+++</td>
<td>+++</td>
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<td>Liver dysfunction/fibrosis</td>
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<tr>
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<td>Leukodystrophy/regression</td>
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<td>++</td>
<td>++</td>
<td>†</td>
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<td>†/+</td>
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<td>Age at death</td>
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<td>4 years</td>
<td>9 months</td>
<td>16 months</td>
<td>8 months</td>
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</tr>
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</table>

*See in infantile Refsum disease.
†No developmental progress.
neonatal hypotonia and seizures in early infancy, progressive neurological dysfunction with leukodystrophy on imaging, retinopathy, mild hepatomegaly with steatosis and mild fibrosis, adrenal dysfunction and osteoporosis. Defects in the n-BP can cause mild dysmorphism (ZS-like or macrocephaly). Defects in the enoyl-CoA hydratase component of the n-BP can cause hydrocephalus. Only defects of peroxisome biogenesis regularly produce cirrhosis, chondrodysplasia punctata and major dysmorphism. Head size at birth is increased in n-BP defects; it is decreased in disorders that affect plasmalogen biosynthesis (e.g. rhizomelic chondrodysplasia punctata or isolated dihydroxyacetonephosphate acyltransferase deficiency) and normal in peroxisome biogenesis defects. In the latter patients there might be competing influences of decreased peroxisome β-oxidation and decreased plasmalogen synthesis. Defects in VLCFA-CoA transport and in racemase do not produce disease until long after the neonatal period. The clinical picture is dominated by neurological disease: cognitive function in X-ALD, retinopathy and neuropathy in racemase deficiency. Adrenal failure can produce symptoms in X-ALD. Although defects of peroxisomal β-oxidation can produce an accumulation of substrates that is greater than that seen in X-ALD, it is difficult to escape the conclusion that defective peroxisomal β-oxidation has effects (such as neuronal migration defects) that are more serious than those produced by the accumulation of substrates alone.

**Unknown defects of peroxisomal β-oxidation**

A variety of patients have been described who have evidence of defective peroxisomal β-oxidation but whose precise defect has not been determined. One clinical syndrome is the onset of ataxia in a 4–5-year-old child with elevated pristanate and C₂₇ bile acid levels but normal VLCFA concentrations. Fibroblasts show normal oxidation of branched-chain substrates and racemase activity is normal [18,19]. In another scenario, we are currently studying two Turkish families with two affected children in each family. The clinical picture is one of progressive spastic paraparesis during the preschool and school years with ataxia and neuropathy but preserved cognitive functioning. MRI scans show dysmyelination; plasma concentrations of VLCFA and pristanate (but not C₂₇ bile acids) are elevated. It is clear that continuing studies of patients with peroxisomal disorders will contribute to our understanding of the biochemistry of the peroxisome.

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**References**

Peroxisome-proliferator-activated receptors as physiological sensors of fatty acid metabolism: molecular regulation in peroxisomes

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Abstract

The enzymes required for the β-oxidation of fatty acyl-CoA are present in peroxisomes and mitochondria. Administration of hypolipidaemic compounds such as clofibrate to rodents leads to an increase in the volume and density of peroxisomes in liver cells. These proliferators also induce simultaneously the expression of genes encoding acyl-CoA oxidase, enoyl-CoA hydratase-hydroxyacyl-CoA dehydrogenase (multifunctional enzyme) and thiolase (3-ketoacyl-CoA thiolase). All these enzymes are responsible for long-chain and very-long-chain fatty acid β-oxidation in peroxisomes. Similar results were observed when rat hepatocytes, or liver-derived cell lines, were cultured with a peroxisome proliferator. The increased expression of these genes is due to the stimulation of their transcription rate. These results show that the peroxisome proliferators act on the hepatic cells and regulate the transcription through various cellular components and pathways, including peroxisome-proliferator-activated receptor α (PPARα). After activation by specific ligands, either fibrates or fatty acid derivatives, PPARα binds to a DNA response element: peroxisome-proliferator-responsive element (PPRE), which is a direct repeat of the following consensus sequence: TGACCTXTG-ACCT, found in the promoter region of the target genes. PPARα is expressed mainly in liver, intestine and kidney. PPARα is a transcriptional factor, which requires other nuclear proteins for function including retinoic acid X receptor (RXRα) and other regulatory proteins. From our results and others we suggest the role of PPARα in the regulation of the peroxisomal fatty acid β-oxidation. In this regard, we showed that although PPARα binds to thiolase B gene promoter at -681 to -669, a better response is observed with hepatic nuclear factor 4 (‘HNf-4’). Moreover, rat liver PPARα regulatory activity is dependent on its phosphorylated state. In contrast, a protein-kinase-C-mediated signal transduction pathway seems to be modified by peroxisome proliferators, leading to an increase in the phosphorylation level of specific proteins, some of which have been shown to be involved in the phosphoinositide metabolism.

Introduction

Fatty acid β-oxidation, together with that of glucose, is an important pathway to provide cellular energy (in the ATP form) by producing reducing equivalents (NADH) and also to release large amount of acetyl-CoA, a precursor for several important pathways including cholesterol synthesis, farnesyl pyrophosphate and geranylgeranyl pyrophosphate precursors needed for Ras protein–membrane anchoring, and dolichol for glycosylation. Moreover, very-long-chain fatty acid β-oxidation in peroxisomes is considered to regulate the level of arachidonic acid indirectly as a precursor of eicosanoids. Peroxisomes are ubiquitous organelles originally discovered by Rhodin in 1954 [1] and first isolated and characterized by De Duve’s group in 1965 [2]. They appear as membrane-bound vesicles (Figure 1) and contain numerous catabolic and anabolic