Annotations

Inherited peroxisomal disorders involving the nervous system

For genetic reasons peroxisomes may be absent or lack one or more of their enzymes. The result may be subtle and long delayed, but is often catastrophic and immediately recognisable as a serious disorder at birth. The trouble for the clinician is that it is often not possible to make a diagnosis unless the right tests are thought of: these tests are not part of routine ‘metabolic screens.’ It is first necessary to frame the question ‘could this be a peroxisomopathy?’ The object of this annotation is to help with when and how to answer this question.

Peroxisomes

Peroxisomes are subcellular organelles with a single membrane which occur in every cell apart from the mature erythrocyte. They are seen best by appropriate preparation of a biopsied liver specimen where they are about 0-5 μ in diameter and round on section. A high concentration is inferred in other tissues including proximal renal tubules, adrenal cortex, brown fat (particularly in cold adaptation), and myelin forming glia. Peroxisomes, in addition to the peroxidation from which the name derives, are involved in numerous metabolic processes. For clinical diagnostic purposes the most important enzymatic actions to be aware of are the β oxidation of very long chain fatty acids (VLCFA), the synthesis of bile acids, and the synthesis of ether glycerolipids (plasmalogens), the latter involving the enzyme acyl CoA:diacylglycerol transferase which is commonly known as DHAP-AT. Although not conclusively proved at the time of writing, the location of the phytanic acid oxidase which is deficient in Refsum disease must also be in the peroxisome.

Classification of inherited peroxisomal disorders

Inherited peroxisomal disorders are classified into three groups. In group 1 are conditions in which peroxisomes are absent or greatly diminished, with a generalised impairment of peroxisomal functions. In group 2 peroxisomes are present but there is an impairment of some but not all peroxisomal functions. In group 3 only a single peroxisomal function is defective. Because of the great importance of the peroxisomal enzymes involved in the β oxidation of VLCFA and the use of measurements of VLCFA in diagnosis, this group is itself subdivided. Group 3A includes those conditions in which VLCFA oxidation is impaired and thus VLCFA accumulates, and group 3B those in which the single enzyme defect is of another sort.

Generalised peroxisomal disorders (group 1)
The now classical example is the cerebro-hepato-renal syndrome of Zellweger.1 2 The typical neonate is more dysmorphic than a baby with Down’s syndrome with high forehead and huge fontanelle with metopic extension. Inactivity is even greater than in the Prader-Willi syndrome and hypotonia especially of the muscles of the neck is profound. Epileptic seizures commonly begin in the neonatal period. Because of general unresponsiveness it is difficult to tell that the infant is blind and deaf, but the electroretinogram (ERG) and brainstem auditory evoked responses (BAER) are both flat. The liver is firm and the renal cortex is echogenic. Calcification of the patellae and other cartilages may overshadow the considerable retardation of the bone age. Malformations of the heart or gut may be present and dominate the clinical picture. After early death, general pathology shows hepatic fibrosis, renal cysts, and small adrenals with striated inclusions (the striations representing VLCFA). The brain shows both malformation and degeneration. All the features of Zellweger syndrome appear to stem from a virtual lack of peroxisomes and their functions.

More difficult to recognise in group 1 are the milder variants of Zellweger syndrome. Complementation studies suggest that mild Zellweger syndrome, infantile Refsum disease, and hyperpiperolicacidaemia may be the same disorder.3 Four recent publications include photographs of the faces of these children up to age 13 and the similarities are considerable.4-7 Characteristically the lobule of the ear is unformed and the palate high arched. Presentation may not be with neurological problems but rather with failure to thrive and steatorrhoea, and low plasma cholesterol and vitamin E concentrations. Clues to the peroxisomal aetiology come from the
palpable liver, the retarded bone development, and
the defects of vision (retinal) and hearing (sensori-
nearl) which become apparent. Dots of pigment on
the retina are characteristic. With time, development
ceases and although these children may be mobile
they show considerable mental handicap perhaps
with autistic features. Originally some of these
children were regarded as having a variant of
Refsum disease (see below) but it is now clear that
when there is a generalised peroxisomal deficiency
phytanic acid from the diet accumulates with age.8

The last of the current members of group 1 goes
by the title of neonatal adrenoleukodystrophy
(NALD). It got this name because of its patho-
logical resemblance to X linked adrenoleuko-
dystrophy the first member of group 3A. Compli-
mentation studies indicate that it is genetically
distinct from the others. A Affected infants may be
hypotonic and have neonatal seizures but early
disorder of development may be mild. Dysmorphic
features are also slight—facial photographs are
included in three recent reports.9–11 Retinal blind-
ness may be the over-riding early feature so that the
infant is regarded as having Leber’s amaurosis.12
Later, neuropathy is common.9,10 The most charac-
teristic part of the history, however, is that after
even a few years of progress there is regression,
only abrupty after a febrile illness, with loss of
skills and neurological functions and fatal outcome.

IMPAIRMENT OF SOME PEROXISOMAL FUNCTIONS
(GROUP 2)
Rhizomelic chondrodysplasia punctata (RCDP) is
the only certain disorder having a defect in a
selected number of peroxisomal functions,14 but it
may be that the Conradi-Hünermann form15 will
also become included. Infants with RCDP should be
easily recognisable by the proximal shortening of
their limbs and epiphyseal calcifications, cataracts,
and (if survival is sufficiently long) evidence of
mental handicap.

DEFECTS OF A SINGLE PEROXISOMAL ENZYME (GROUP 3)
Our knowledge of disorders of a single peroxisomal
function (group 3) is expanding at a great rate. This
is primarily so in group 3A which now contains four
conditions having a primary defect in VLCFA
metabolism. The identity of the respective enzyme
deficiencies has been established in little over a
year.

Disorders with accumulation of VLCFA (group 3A)
Adrenoleukodystrophy (ALD) presents in boys as
either school failure due to central demyelination
(visual on a computed tomogram) or as adrenal
insufficiency, hence the old name Addison-Schilder
disease. A remarkable feature of this X linked
disorder is extreme variability within pedigrees,16 so
that later onset adrenomyeloneuropathy (presenting
with spastic paraparesis) or adult onset ALD may
coeexist. People with the gene defect may even be
asymptomatic beyond middle age. The similarity of
the neuropathology to aggressive multiple sclerosis
and the presence of oligoclonal bands in the cere-
brosplinal fluid has supported the idea that for
childhood ALD to occur an autoimmune mechanism
is necessary in addition to the genetic defect in
VLCFA metabolism. That defect has now been
identified as of a specific peroxisomal acyl-CoA
synthetase.17 The site of the gene on Xq28 is
adjacent to the genes for red and green colour
blindness which may be simultaneously deleted.18

Defects of β oxidation: ‘pseudo-Zellweger syndrome’,
‘pseudo-NALD’, etc
In normal VLCFA metabolism the acyl-CoA syn-
thetase by the enzyme deficient in ALD is oxidised
by three peroxisomal enzymes in sequence: acyl-
CoA oxidase (‘oxidase’), bifunctional protein, and
3-oxoacyl-CoA thiolase (‘thiolase’).

The first disorder now known to lack one of these
enzymes was originally labelled ‘pseudo-Zellweger
syndrome’19; it was later discovered that the child in
question lacked only the protein of the thiolase
enzyme.20 The clinical and pathological features
resembled Zellweger syndrome except that dys-
morphic features were not so appreciable and there
was no calcific stippling. A further family has been
described21 in which although the thiolase protein
was present as shown by immunoblot, the duodenal
bile acid pattern indicated thiolase deficiency and
was identical to that of the infant with pseudo-
Zellweger syndrome (PT Clayton, personal com-
unication). Except for the huge fontanelle (in
keeping with a severely delayed bone age), dys-
morphic signs were slight in this family (figure). In
a further child with evidence of thiolase inactivity,
calcific stippling of the patellae was present
(MD King, personal communication). All of these
infants had neonatal onset seizures and profound
hypotonia (figure).

Isolated deficiency of the oxidase protein leads to a
clinical course like NALD, entitled pseudo-
NALD.22 Pseudo-NALD was also the name given
to the condition of a similar patient in whom the
pathology also resembled NALD.23 Later, the
oxidase protein was found to be present,24 but
presumably it is present in an inactive form.

The last of the three selective β oxidation dis-
orders, bifunctional protein deficiency, has now
been discovered (HW Moser, personal communica-
tion) in a patient with ‘clinical clues’ (see below).
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Refsum disease (group 3B)
The only reasonably established group 3B disorder affecting the nervous system is Refsum disease which with retinitis pigmentosa, neuropathy, and deafness may present in mid childhood. Here the isolated defect is of (presumed) peroxisomal phytanic oxidase.

Clinical clues to a possible peroxisomopathy

Pointers to one or other peroxisomal disorder include: large fontanelle, absent ear lobules, neck hypotonia, early seizures, developmental standstill delay or arrest, pigmentary retinopathy (with a low ERG), sensorineural deafness (with low BAER), hepatomegaly (with or without fibrosis), unexplained hypocholesterololaemia or hypovitaminosis E, and calcific stippling of epiphyses.

Tests in suspect patients

Measurement of the enzyme DHAP-AT in fibroblasts or thrombocytes should detect all the generalised peroxisomal disorders (group 1), and those in group 2. The concentration of VLCFA is raised in plasma and fibroblasts in all the generalised peroxisomopathies (group 1) and in all those in group 3A. Abnormal bile acids in urine, plasma, and bile should be detected (at any rate in the young patient) in all of group 1; in those with absent or defective thiolase the pattern is different and may be specific. Bile acids are normal in ALD and in oxidase deficiency; the situation in bifunctional protein deficiency is not yet known. A properly prepared liver biopsy specimen in group 1 will show absent or grossly deficient peroxisomes, whereas in group 3A many of the peroxisomes are large (up to 1 μ), and they may be odd shaped. Phytanic acid is of course raised in the plasma in Refsum disease, but after infancy it will be raised in all the ('mild') group 1 disorders and in RCDP.

Treatment

Specific therapeutic possibilities are at present limited except in Refsum disease where low phytanic acid diet with or without plasmapheresis and low fat diet has proved effective. Low phytanic acid diet has also been used in two children with mild group 1 disorder ('infantile Refsum'). The neurological improvement reported, including possible arrest of progressive neuropathy, needs confirmation by further studies. However, as in all chronic disorders affecting the nervous system, non-specific treatment (for example, phenytoin for seizures) may help. More specifically, vitamin E supplementation is reasonable in those older children with a secondary deficiency. Attempts to abort ALD by the rigorous low VLCFA diet, oleate and erucate supplements, and plasmapheresis have not yet shown convincing benefit. When there is an affected family member, prevention is possible in all the group 1, 2, and 3A disorders, in that early prenatal diagnosis can be made by DHAP-AT analysis in groups 1 and 2 and by VLCFA measurements in groups 1 and 3A.

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References


*Contains 129 references up to 1985.

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