Peroxisomal Disorders

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Peroxisomes are large single membrane–bound organelles that are present in the cytoplasm of all cells. They are formed from the endoplasmic reticulum and replicate by division. As they have no DNA or ribosomes all proteins have to be imported into the organelle after synthesis in the nucleus and specific transport proteins exist on the membrane for different groups of proteins.
Peroxisomal Functions

Their name comes from their capacity to generate hydrogen peroxide as a by product of oxidative processes and a specific peroxisomal catalase exists to inactivate this potentially toxic compound.

They contain a mixture of enzymes for pathways for oxidation and biosynthesis of a wide variety of apparently disparate metabolites. These include:

1. Very long chain (>C24)fatty acid beta-oxidation by a pathway distinct from that in mitochondria.
2. Bile acid biosynthesis - the terminal steps use the peroxisomal beta oxidation pathway.
3. Ether lipid (plasmalogen) biosynthesis – these are components of the myelin sheath.
5. Pipecolic acid catabolism – a component of one of the pathways for lysine catabolism
6. An early step of cholesterol and isoprenoid biosynthesis – mevalonate kinase
7. Steps of oxalic acid catabolism.
Defects of Peroxisomal Function

Two main groups of defect are known:

1 Single Enzyme Defects due to defects in the gene for that enzyme.

2 Multiple Enzyme Defects. These can affect only two or three enzymes or can result in a complete loss of all peroxisomal functions. They are due to defects in proteins that transport these proteins into the peroxisome or into the membrane proteins of the peroxisome itself. In extreme circumstances all that is left are the “ghosts” of the peroxisomal membranes. Obviously these disorders are often clinically very severe and typically show multiple biochemical abnormalities which helps with their diagnosis.
X-linked Adrenoleucodystrophy is a disorder caused by a missing or defective protein called ALDP (X-ALD protein). ALDP is crucial for the transport of VLCFA from the cell into the peroxisome. This leads to the accumulation of very long chain fatty acids (VLCFA)(C24 & C26 chain length). These VLCFA are usually attached to gangliosides and cerebrosides so not surprisingly they accumulate most in the white matter of the brain and peripheral nerves and the adrenal cortex. As a result patients develop loss of myelin and adrenal dysfunction due to damage to the adrenal cortex.

However what is puzzling about this disorder is there is tremendous variability in the age of onset and pattern of symptoms not only between but also within families. Some patients develop neurological symptoms between 5-10 years of age with dementia and walking difficulties which progresses usually to an early death. Others do not develop mobility problems until adulthood whilst some only develop adrenal dysfunction (in fact it is important to exclude this condition in all male patients with unexplained Addison's Disease).

Whilst it is an X-linked condition and males are more severely affected female heterozygotes can show symptoms sometimes mistaken as multiple sclerosis.
Diagnosis is by quantitation of VLCFA in plasma by gas chromatography-mass spectrometry. Usually the concentrations of the VLCFA C24 and C26 fatty acids are expressed as a ratio to C22 fatty acids which are catabolised by the mitochondrial beta oxidation system. Males - show elevated ratios. However 10-20% of female heterozygotes may show normal values and diagnosis may require mutation screening of the ALDP gene. Phytanic and Pristanic acid can be quantitated on the same run. These are useful in diagnosing other peroxisomal disorders. Currently the main treatment options available are:-

1. Administration of a mixture of the glycerol esters of oleic and erucic acid (Lorenzo's Oil) to inhibit VLCFA synthesis. The value of this treatment in uncertain and is still being assessed.

2. Bone marrow transplantation - this needs to be done before overt clinical symptoms have developed as is under assessment as to its efficacy.
Typical GC-MS profiles of plasma VLCFA, phytanic acid and pristanic acid
Zellweger’s Syndrome

Zellweger’s syndrome patients usually present at birth with multiple abnormalities and develop dysmorphic features, hypotonia, seizures, deafness, progressive blindness, liver disease, psychomotor retardation and usually die in the first few months of life. Less severe forms do exist with a longer life span and show some but not all of the symptoms listed and were sometimes given different names such as Infantile Refsum’s Disease.

In line with the multiple clinical abnormalities they also usually show multiple biochemical abnormalities including:

1. Elevated plasma VLCFA
2. Elevated intermediates in plasma of the bile acid biosynthetic pathway and impaired bile acid synthesis.
3. Low plasma cholesterol
4. Elevated phytanic and pristanic acid—although this depends on diet.
5. No detectable membrane bound peroxisomal catalase.
6. A deficiency in cell membrane plasmalogen due to deficiencies in the peroxisomal enzymes responsible for their biosynthesis.

These gross abnormalities were found to be due to defects in genes coding for proteins involved in the import of groups of peroxisomal proteins or in membrane assembly.
Multiple Peroxisomal Disorders - Diagnosis

A few patients have now been described who clinically resemble a multiple peroxisomal disorder but only have a single biochemical abnormality. These had isolated defects in the peroxisomal fatty acid/bile acid beta oxidation pathway suggesting that a block in this pathway causes most of the more severe symptoms.

As a result it is important to measure more than one parameter to confirm the diagnosis. The most commonly tests are:

1. Plasma VLCFA
2. Plasma and urine bile acids looking for high levels of intermediates (not total bile acids) – this is done by gas chromatography-mass spectrometry.
3. Erythrocyte membrane plasmalogen quantitation by gas chromatography-mass spectrometry
4. Assay of platelet or leucocyte dihydroxyacetone phosphate:acylCoA transferase (DHAP-AT)

Once diagnosed further delineation of the type of peroxisomal disorder will usually require skin fibroblast studies in a more specialist laboratory.

Currently there is no treatment for this disorder and care is palliative.
Some Other Peroxisomal Disorders

**Single Peroxisomal Disorders**
Hyperoxaluria Type 1 - Renal failure. Diagnosis by plasma and urine oxalate quantitation.
Mevalonic Aciduria – cataracts, hepatosplenomegaly, intermittent elevated IgD and fever. Diagnosis - by urine organic acid gas chromatography-mass spectrometry
Adult Refsums Disease – Retinitis pigmentosa, hearing loss, ataxia, peripheral neuropathy. Diagnosis - by plasma phytanic acid quantitation. Treatable by dietary exclusion of phytols.

**Multiple Peroxisomal Disorders**
Rhizomelic Chondrodysplasia Punctata – short forearms, cataracts, mental retardation, dysmorphic features, stippling of the epiphyses on X-ray. Defects of plasmalogen biosynthesis and phytanic acid metabolism (VLCFA are normal). Can be single or multiple defects.
Self Assessment Questions

1. Plasma VLCFA is elevated in which of the following conditions:
   a) Adult Refsums Disease
   b) Infantile Refsums Disease
   c) Rhizomelic Chondrodysplasia Punctata
   d) X-linked adrenoleucodystrophy

2. X-linked adrenoleucodystrophy is associated with which of these symptoms:
   a) Cataracts
   b) Addison's Disease
   c) Dementia
   d) Enlarged Liver

3. Functions in which the peroxisome is involved include:
   a) Bile Acid Biosynthesis
   b) Medium Chain Fatty Acid Oxidation
   c) Oxalic Acid Metabolism
   d) Ester Phospholipid Biosynthesis
1. Plasma VLCFA is elevated in which of the following conditions:
   b) Infantile Refsums Disease
   c) d) X-linked adrenoleucodystrophy

2. X-linked adrenoleucodystrophy is associated with which of these symptoms:
   b) Addison's Disease
   c) Dementia

3. Functions in which the peroxisome is involved include:
   a) Bile Acid Biosynthesis
   c) Oxalic Acid Metabolism