Peroxisomal disorders

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Abstract

Peroxisomes are complex single-membrane cell organelles found in all cell types except erythrocytes. Peroxisomes have both catabolic and anabolic functions & these functions include the synthesis of plasmalogens, the formation of bile acids, polyunsaturated fatty acids, cholesterol & isoprenoids, & the degradation of very long-chain fatty acids (VLCFA's).

Peroxisomes multiply by division of existing peroxisomes & this complex process is regulated by both *PEX* & non-*PEX* genes. Peroxisomal disorders are broadly categorised into defects of peroxisomal biogenesis with deficiencies of multiple pathways e.g. Zellweger spectrum or defects affecting single enzymes such as D-bifunctional protein deficiency.

Peroxisomal disorders present with a wide spectrum of clinical disease ranging from the severe neonatal Zellweger syndrome with dysmorphic features, neurological abnormalities, hepatorenal and gastrointestinal dysfunction with death typically occurring within the first 6 months of life to adult onset X-linked adrenoleucodystrophy which can be confined only to adrenal insufficiency.

Keywords bile acids; peroxisomes; *PEX* genes; plasmalogens; VLCFA; X-linked ALD; Zellweger

Introduction

Peroxisomes are complex single-membrane cell organelles. They are found in all human cell types apart from red blood cells and have both catabolic and anabolic functions. These functions predominantly involve lipid metabolism. Peroxisomal functions include the synthesis of plasmalogens which are important constituents of cell membranes & myelin. They are also involved in the formation of bile acids, polyunsaturated fatty acids, cholesterol & isoprenoids. Peroxisomes β-oxidise very long-chain fatty acids (VLCFA's), α-oxidise phytanic acid and catabolise lysine via pipecolic acid and glyoxylate to glycine. Importantly they also contain catalase which converts the highly reactive oxygen species hydrogen peroxide into oxygen & water.

Peroxisomes multiply by division of existing peroxisomes. Peroxisomal membranes are assembled & peroxisomal matrix proteins are targeted from the cytosol & then imported into the organelle by a highly complex process dependent on specialised proteins termed peroxins which are encoded by *PEX* genes. As a consequence peroxisomal biogenesis involves the correct expression of multiple *PEX* genes of which 14 have been identified in humans. There are also a large number of single enzyme functions within the peroxisome encoded by non-*PEX* genes & defects in these result in a range of disorders with single enzyme deficiency.

Peroxisomal disorders are broadly categorised into defects of peroxisomal biogenesis with deficiencies of multiple pathways e.g. Zellweger spectrum or defects affecting single enzymes such as D-bifunctional protein deficiency. Most disorders are autosomal recessive, however the commonest peroxisomal disorder X-linked adrenoleucodystrophy has an X-linked mode of inheritance.

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Peroxisomal assembly

Peroxisomal biogenesis is complex and peroxisomes predominantly multiply by division of pre-existing peroxisomes but can arise de novo from pre-peroxisomal vesicles that originate from the endoplasmic reticulum. Peroxisomes do not contain any DNA themselves. All of the proteins required for assembly and function are encoded by nuclear genes and synthesised on free polyribosomes in the cytosol before post-translational import into the peroxisome. Transportation is highly selective and requires the presence of specific import sequences known as peroxisomal targeting sequences (PTS).

PTS's are recognised by receptors (PTS1 receptor and PTS2 receptor) which direct the peroxisomal proteins to the peroxisomal membrane. The target protein then enters the peroxisome by a sequential multi-step process involving recognition, docking, translocation across the peroxisomal membrane and recycling.

All proteins (peroxins) involved in peroxisomal biogenesis are encoded by *PEX* genes. To date 14 *PEX* genes have been identified as essential for human peroxisomal formation. *PEX5* encodes for the PTS1 receptor and *PEX7* encodes for the PTS2 receptor. Two isoforms of *PEX5* exist. The longer *PEX5L* encodes for the PTS1 receptor and additionally contains a *PEX7* binding domain required for directing PTS2 receptor to the peroxisomal membrane. PEX13 and PEX14 encode the peroxisomal membrane docking protein complex. *PEX1*, *PEX6* and *PEX26* are required for matrix protein import and encode proteins involved in the recycling of the PTS1 and PTS2 receptors. *PEX2*, *PEX10* and *PEX12* encode proteins involved in matrix protein import. *PEX3*, *PEX16* and *PEX19* encode proteins involved in the production of peroxisomal biogenesis proteins. *PEX11* encodes a peroxisomal protein involved in the proliferation of peroxisomes. Other genes including DLP1 are involved in the division of peroxisomes. In addition the peroxisome also contains over 50 matrix proteins and numerous membrane proteins.

Peroxisomal disorders

Peroxisomal disorders arise from either a defect in peroxisomal biogenesis (the peroxisomal biogenesis defects) or a defect in a single peroxisomal enzyme or protein (the single enzyme

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defects). The single enzyme defects include at least 10 distinct disorders.

Clinical presentation

The peroxisomal biogenesis defects include the Zellweger spectrum which accounts for approximately 80% of patients, while rhizomelic chondrodysplasia punctata (RCDP) accounts for the remaining patients with peroxisomal biogenesis disorders. RCDP is clinically and genetically distinct from the Zellweger spectrum.

The clinical phenotype of Zellweger spectrum, also known as cerebrohepatorenal syndrome, consists of three overlapping phenotypes. The most severe phenotype being Zellweger syndrome (ZS) followed by an intermediate form, neonatal adrenoleucodystrophy (NALD), which is not to be confused with X-linked ALD, and the mildest form infantile Refsum disease (IRD). The overall frequency of ZS is approximately 1:50,000. ZS classically presents with characteristic craniofacial features including large anterior fontanelle, full forehead, shallow orbital ridges, epicanthal folds, high arched palate, broad nasal bridge and small nose with anteverted nares. Ocular abnormalities such as cataracts, glaucoma and corneal clouding are common. In addition there is encephalopathy, seizures, severe hypotonia, hepatorenal abnormalities including renal cysts and skeletal abnormalities. Patients usually succumb to the disorder within the first few months of life and survival is extremely rare beyond a year. Patients with the milder forms of the Zellweger spectrum have similar but less severe symptoms to ZS and survival varies from four months to several decades. For example, virtually all IRD patients have moderate dysmorphic features and sensorineural hearing loss with pigmentary retinopathy. Early hypotonia and deranged liver function are common. However most IRD patients learn to walk, although their gait is frequently ataxic and their mental function is usually in the severely retarded range as compared to profound retardation in NALD and ZS. Rarely much milder phenotypes have been described.

RCDP is clinically distinct from the Zellweger spectrum and also has severe classical presentations and milder phenotypes. Clinically, RCDP symptoms include characteristic proximal shortening of the limbs (rhizomelia), cataracts, facial dysmorphism, microcephaly, small stature, and psychomotor retardation.

For all of the peroxisomal biogenesis disorders treatment is largely symptomatic and supportive.

Single enzyme defects

The single enzyme defects result in the loss of a single protein and subsequently the loss of a single peroxisomal function. Although over 50 peroxisomal matrix and numerous membrane proteins have been identified only about 10 disorders associated with single enzyme defects have been described, indicating that there are many more unrecognised disorders. The known single peroxisomal enzyme/protein defects are summarised in Table 1, the more common/frequently encountered defects are summarised below.

The most common single enzyme defect is X-linked adrenoleucodystrophy. The inheritance is X-linked with approximately 20% of female carriers eventually presenting with clinical symptoms. The clinical phenotypes vary from the severe childhood cerebral presentation through to a mild adult form. There is also an Addison disease only presentation. Severe childhood disease takes the form of a progressive demyelination of the cerebral neurones and adrenal insufficiency. This early onset male disease usually starts between 3 and 10 years of age with behavioural abnormalities. Initial referral is often to a psychiatrist or psychologist. There is further progression to dementia, speech difficulty with loss of hearing & vision and finally relentless progression to decorticate spastic quadriparesis, with pigmentation of the skin secondary to adrenal insufficiency. The most effective treatment is haematopoietic stem cell transplantation which is only effective if carried out in pre-symptomatic or early symptomatic patients. There is also late onset adolescent and adult cerebral forms of X-ALD which follow a similar but delayed course. The milder adult onset X-ALD which presents with peripheral neuropathy and Addison disease (adrenomyeloneuropathy), with or without cognitive decline, may affect both males and female carriers. A small cohort of X-ALD patients will present with isolated adrenal insufficiency (Addison only X-ALD).

Summary of the single peroxisomal protein/enzyme defects

Defective peroxisomal function	Disorder
β-oxidation of very long-chain fatty acids	X-linked adrenoleukodystrophy
	Acyl-CoA oxidase deficiency
	Bifunctional protein deficiency
	Sterol carrier protein deficiency
	α-methyl-acyl-CoA-racemase deficiency
α-oxidation of phytanic acid	Refsum disease
Hydrogen peroxide metabolism	Catalase deficiency
Glyoxylate metabolism	Hyperoxaluria type I
Etherphospholipid biosynthesis	DHAP-AT deficiency
	Alkyl-DHAP synthase deficiency

Table 1

Refsum disease, which should not be confused with Infantile Refsum disease, is also a single enzyme defect and is due to defective phytanoyl-CoA hydroxylase. The enzyme is required for the α-oxidation of phytanic acid to pristanic acid. Patients with Refsum disease accumulate large amounts of phytanic acid in plasma and tissues. The clinical features include; pigmentary degeneration, peripheral neuropathy and cerebellar ataxia usually presenting before the second decade of life. However, the age of onset and clinical severity varies according to the degree of residual enzyme activity. Effective treatment can be achieved by strict avoidance of dietary phytanic acid and plasmaphoresis.

Bifunctional enzyme deficiency is a single enzyme defect due to defective bifunctional enzyme which is required for peroxisomal β-oxidation. Bifunctional enzyme deficiency is rare and classically presents with neonatal hypotonia, dysmorphic features, seizures, hepatomegaly and developmental delay. The degree of severity is however highly variable.

Diagnostic approach

As described in the clinical section, peroxisomal disorders can be grouped into two broad subgroups; the single enzyme defects

