What are peroxisomal disorders?

Peroxisomal disorders are rare congenital diseases characterized by the absence of peroxisomes in the cells of the body [1]. Since peroxisomes cannot be formed and all peroxisomal functions are defective, they are called *disorders of peroxisomal biogenesis* or *generalized peroxisomal disorders* [2]. Peroxisomes are small cell particles that carry out important biochemical reactions, most of them related to fat metabolism. These reactions are "promoted" by enzymes, which are specialized proteins that *catalize* or facilitate biochemical reactions by increasing their speed. Without enzymes, reactions would be so slow that they would be totally ineffective. If peroxisomes are absent or not functioning, reactions normally catalized by peroxisomal enzymes are defective. This is what happens in Zellweger's syndrome, the prototype of generalized peroxisomal disorders.

One of the most characteristic reactions that take place in the peroxisome is the breaking down (by β-oxidation) of very long chain fatty acids (VLCFA) with more than 22 carbon atoms (typically 24 and 26 carbon atoms). Peroxisomal β-oxidation shortens the chain length of the fatty acids until they can be further broken down in the mitochondria. If peroxisomes are absent this process is defective and the VLCFA increase in plasma and tissues. This is one of the hallmarks for the diagnosis of peroxisomal disease. Other characteristic abnormality is the decrease in plasmalogen levels. Plasmalogens are a special kind of phospholipids mainly localized in myelin (the fatty material that covers nerve fibers and forms white matter in the brain). Other typical lipid abnormalities are the increases in phytanic acid and in its α-oxidation product pristanic acid. Cholesterol and bile acid synthesis are also affected, which results in the low levels of these lipids found in peroxisomal diseases. Since their synthesis is blocked, some bile acid intermediates DHCA (dihydroxycholestenoic acid) and THCA (trihydroxycholestanoic acid) appear in blood and urine.

What is Zellweger's syndrome?

The cerebro-hepato-renal syndrome of Zellweger is the most severe peroxisomal disorder and a rapidly lethal disease [3]. The brain is profoundly affected in this disease, with neuronal and myelin abnormalities. Children with Zellweger's syndrome are very floppy, often have convulsions and become blind and die very early. They have a high forehead, widely open fontanels and a peculiar, flat face, with a small nose and often slanted eyes. The liver, kidneys, and adrenals are involved and there are characteristic X-ray abnormalities in the bones. Biochemically, patients with Zellweger Syndrome are also the most severe and plasmalogens are virtually absent in their red blood cells.

Infantile Refsum's disease:

A misnamed peroxisomal disorder

It must be noted that there is much confusion in the way peroxisomal disorders are named. Many doctors use the name *Zellweger's syndrome* to designate all generalized peroxisomal disorders. In the opposite extreme, more often doctors tend to diagnose all peroxisomal patients with *infantile Refsum's disease* (IRD), the less severe clinical form or phenotype. In the middle, there are patients with *neonatal adrenoleukodystrophy* (NALD), a peroxisomal disorder of intermediate severity and often undistinguished from infantile Refsum's disease. Quite often, even the word *infantile* is deleted and the patient's diagnosis is confused with Refsum's disease, an altogether different disorder of the adult. Refsum's disease is *not* a *generalized* peroxisomal disorder but an isolated enzyme defect. This is a confusion that should be avoided since it generates misunderstanding among doctors and parents. For the moment, it has not been found any clear

correlation between the gene defect (*genotype*) and the *phenotype*. So while we do not have a better genetic base to distinguish the different clinical pictures, it is better to simply call them classic Zellweger's syndrome (the most severe disease) and generalized peroxisomal disorders, without distinction between NALD and IRD. Indeed, some misnamed IRD patients who survive the first years of life will later develop signs characteristic of NALD, such as adrenal insufficiency and demyelination.

Symptoms of a peroxisomal disorder

It is often believed that a peroxisomal patient has a peculiar face. In particular, a small, flat face when looking from one side is quite characteristic. The eyes are slanted, with internal folds (*epicanthus*). The nose is small and the ears are low-set. However, these signs are not always clear and many diagnoses are lost for not detecting the facial signs described in books. A high forehead, with frontal bossing, and above all, a widely open anterior fontanel, are virtually constant and easy to find signs. More or less severe *hypotonia* (floppiness) is a constant sign. Mental and motor developments are always retarded. Vision and hearing are always deficient. So, if the pediatrician finds some of these signs and liver enlargement (hepatomegaly) at the examination there is enough reason to think of a peroxisomal disorder and do the screening for the disease.