

Mitochondrial DNA Depletion Syndrome: An Overview

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Mitochondrial diseases can be caused by genetic defects in either the mitochondrial or the nuclear genome.

The mitochondrial DNA depletion syndrome (MDS) is a clinically heterogeneous group of mitochondrial diseases characterized by a marked reduction number of copies of mtDNA in affected tissues and organs. The change is quantitative. Is an autosomal recessive disorder.

Recent studies have shown that 11% of children younger than 2 years old who are referred to as muscle weakness, hypotonia and developmental delay have MDS.

There are 3 types of presentation: myopathic - symptoms appear in the first year of life with food intolerance, growth delay, hypotonia, muscular weakness and renal dysfunction (Toni-Fanconi syndrome). The creatine kinase is high. Death occurs in most cases in the first years of life due to pulmonary insufficiency and infections. These patients rarely survive until adolescence.

Other type is hepatocerebral. Is the most common form, with symptoms that appears between birth to 6 months of life: persistent vomiting, growth delay, hypotonia and hypoglycemia. Hepatic biopsy showed lipid steatosis, proliferation of the bile ducts and fibrosis. These children died in the first year of life due to hepatic failure, seizures and global neurological deterioration. Sodium valproate should not be used to control seizures by precipitating acute hepatic failure. There is a peculiar presentation of the hepatocerebral form, the so-called Alpers-Huttenlocher syndrome, characterized by hepatic failure, seizures progressing to continuous partial epilepsy and neurological global deterioration, that can be fatal. Liver dysfunction is usually progressive with proliferation of bile ducts for cirrhosis and chronic liver failure. The DGUOK and MPV17 genes are the ones with the highest number of mutations described in this type. Mutations in genes POLG, C10orf2, TK2 and SUCLG1 may also be associated with this form of clinical presentation.

The last type is encephalomyopathic form: the onset of symptoms occurs in childhood, with hypotonia, severe psychomotor retardation, deafness, loss of movement, external ophthalmoplegia, generalized seizures and renal tubular dysfunction. The lactate is high and the magnetic resonance imaging in the brain, showed lesions in the basal ganglia suggestive of Leigh disease. Mutations in the RRM2B, SUCLA2 and SUCLG1 genes are associated with this type.

The diagnosis of MDS can be done by muscle biopsy using PCR or southern- blot. Study by PCR seems better than southern-blot, because the result came in hours, have less risk of contamination and also showed more specificity and sensibility.

We can also use mitochondrial nuclear test by next generation sequencing (NGS) for the detection of the genes involved in MDS.

Is considered MDS when a reduction in the number of copies of mtDNA is greater than 65% in relation to the control subject. In severe cases, this reduction can go to 80-90%.

The treatment consist of transplantation of the affected organ. Liver transplantation may be beneficial for patients with hepatic involvement caused by mutations DGUOK, MPV17 and POLG genes, but only if they not developed neurological symptoms. Gene therapy

that stimulates nucleotide biosynthesis may delay the development of symptoms. Some patients respond to Coenzyme Q10, but in most situations, the prognosis is poor.

We only offer prenatal diagnosis and genetic counseling in cases where the mutation is identified.

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