

Pearson Syndrome and Neuropathy, Ataxia and Retinitis Pigmentosa (NARP)

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Neurological syndromes are the most frequent clinical presentations of mitochondrial disorders, a group of human diseases characterized by defects of the mitochondrial energy output. Mitochondrial diseases are caused both by mutations, acquired or inherited, within mitochondrial DNA (mtDNA) and genetic inheritance. To date, more than 200 disease-causing point mutations to the mitochondrial genome have been reported.

Pearson syndrome

The disease typically begins in infancy or early childhood. It is characterized by refractory sideroblastic anemia, vacuolization of bone marrow precursors and exocrine pancreatic dysfunction. Both sexes are affected. Hematological signs begin in infancy, although a few neonatal cases have been described. These signs include macrocytic sideroblastic anemia, severe neutropenia or thrombocytopenia. The presence of vacuolization in granulous and erythroblastic progenitors, visible on the myelogram, is highly suggestive of the syndrome. Besides the hematological deficiency, patients present with fibrotic exocrine pancreatic dysfunction with malabsorption and diarrhea, or a defect in oxidative phosphorylation resulting in lactic acidemia and an increased lactate/pyruvate ratio. Other organs can be affected, either simultaneously or during the course of the disease: frequent renal involvement with tubulopathy and aminoaciduria is observed, as well as hepatic involvement with hepatomegaly, cytolysis and cholestasis, endocrine gland disturbances, neuromuscular disorders, cardiac involvement and splenic atrophy.

Although maternal transmission has been described, it is typically sporadic mitochondrial cytopathy caused by mtDNA deletions. These deletions lead to a deficiency in mitochondrial respiratory chain function. The heteroplasmy, explains the high variability in clinical expression observed both between patients and between the various organs of an affected subject. Indeed, pathological manifestations occur when some level of mutated DNA has accumulated in a given tissue.

Pearson's syndrome is diagnosed by the presence of a single large scale rearrangement of mtDNA, as observed in Southern blot hybridization analysis of blood DNA. Management is symptomatic and includes treatment of infectious episodes and of metabolic accidents, transfusion in case of severe anemia (sometimes with erythropoietin therapy), pancreatic extracts and management of endocrine disorders. Death often occurs before the age of three years, due to septic risks, metabolic crisis with lactic acidosis or hepatocellular failure. Patients who survive early infancy typically undergo phenotypic evolution: hematological manifestations spontaneously resolve,

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whereas neurological and myopathic signs either appear or worsen. Some patients develop typical Kearns Sayre syndrome with ophthalmoplegia, ataxia, pigmentary retinitis, conduction defects and myopathy.

Neuropathy, ataxia, and retinitis pigmentosa (NARP)

NARP is characterized by developmental delay, seizures, proximal neurogenic muscle weakness, ataxia, dementia, sensory neuropathy, and retinitis pigmentosa.

This is a maternally transmitted multisystem disorder of young adult life which is associated with a T8993G mutation (mutation resulting in the replacement of a leucine by arginine) in the ATPase 6 gene. The mutation is heteroplasmic, the clinical severity of the disease being dependent on the proportion of mutant mtDNA. A T8993C mutation (mutation resulting in the replacement of leucine by proline) and T9176C mutation alter the ATPase 6 gene were associated with a less severe clinical course of NARP. These mutations are invariably heteroplasmic and result in a broad range of clinical manifestations from mild peripheral retinitis pigmentosa to severe neurological disease, depending on the percentage of mutant mtDNAs. When the percentage of mutant mtDNA is >95%, patients show the clinical, neuroradiological and neuropathological findings of maternally inherited Leigh's syndrome (MILS). MILS is a multisystem degenerative encephalopathy with onset in infancy, characterized by hypotonia, myoclonus, brainstem dysfunction, peripheral neuropathy, developmental delay, psychomotor regression, ataxia, seizures, and optic atrophy. NARP and MILS may co-exist in the same family.

Brain MRI examination of NARP patients has revealed the presence of moderate, diffuse cerebral and cerebellar atrophy, and, in the most severely affected patients, symmetric lesions of the basal ganglia. In muscle biopsy, RRF are absent. Muscle fibers are COX positive, but a subset of fibers may be either negative or deficient for mitochondrial ATPase. The diagnosis can be confirmed by the characteristic pathological findings in brain MRI. In addition, retinitis pigmentosa, present in about half of MILS patients, is a distinguishing

clinical feature.

Keywords: Mitochondria; DNA; Disorders; Pearson syndrome; NARP