Neuropathy, ataxia and retinitis pigmentosa (NARP) syndrome

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Creation Date: April 2004

Scientific Editor: Doctor Enrico Bertini

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Abstract
The syndrome of Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP) is clinically heterogeneous but it is often characterized by a combination of sensory-motor neuropathy, cerebellar ataxia, and night blindness. Its prevalence is approximately estimated at 1:12 000. NARP usually presents in young adults. Clinical presentation includes a combination of the following symptoms: early salt and pepper retinopathy; retinitis pigmentosa; sluggish pupils; nystagmus; blindness; proximal muscle weakness; developmental delay; corticospinal tract atrophy; dementia; hearing loss; seizures; ataxia; sensory neuropathy; proximal neurogenic muscle weakness. A maternally inherited condition, the NARP syndrome is associated with the 8993T>G mutation in the mtDNA gene, MTATP6, coding for the subunit ATPase 6. The 8993T>G mutation results in an amino acid change from a highly conserved leucine 156 to arginine (L156R) and leads to a severe impairment of the synthesis of mitochondrial ATP, reducing cellular energy and cell death, particularly in tissues highly dependent upon the oxidative phosphorylation metabolism, such as brain and retina. This mutation is also retrieved in 8-10% of Leigh disease, which in this case is conventionally defined with the acronym MILS (maternally-inherited Leigh syndrome). Thus, MILS represents the most severe phenotypic presentation of the NARP syndrome and it usually manifests in subsequent affected generations resembling pseudo-anticipation. Treatment is only supportive. Antioxidants have been recently proposed as helpful on the basis of experimental “in vitro” evidences.

Keywords
NARP, Neuropathy, Ataxia, and Retinitis Pigmentosa, MLIS, mtDNA; MTATP6 gene; 8993T>G transversion mutation.

Disease name and synonyms
Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP)

Diagnostic criteria/definition
The NARP syndrome is clinically heterogeneous but it is often characterized by a combination of sensory-motor neuropathy, cerebellar ataxia, and night blindness. Laboratory investigations in skeletal muscle are often negative. A maternally
inherited condition, the NARP syndrome is associated with a point mutation at nucleotide 8993 in the mitochondrial (mt)DNA gene coding for ATPase 6 of mtDNA.

**Differential diagnosis**
Approximately 10-20% of patients with Leigh syndrome carry either the T8993G or T8993C MTATP6 mutation. In such cases, patients are better defined as having maternally-inherited Leigh (MILS) syndrome and differ from typical NARP patients by the presentation of a more aggressive and lethal neurodegenerative disorder.

In sporadic cases, differential diagnosis should consider the rare autosomal recessive Refsum's disease, which is usually ruled out by the failure to demonstrate elevated serum phytanic acid levels. Cockayne's syndrome is a condition that should be easily recognisable because of microcephaly, dwarfism, and a distinctive physiognomy. In addition, death often occurs in childhood.

The neurological features of Bassen-Kornzweig usually do not include deafness. Acanthocytosis in blood and the absence of betalipoproteins are other distinctive manifestations. Usher's syndrome is a genetically heterogeneous disorder usually characterized by congenital deafness, but cases with a more progressive evolution have been described. Retinitis pigmentosa, deafness, ataxia, and mental retardation may also occur in rare cases of spinocerebellar disorder, in Hallgren's syndrome, or in neurological complication of lipidosis. However, presence of a congenital and usually profound deafness or evidence for myoclonus epilepsy are commonly found.

**Etiology**
The NARP syndrome is maternally transmitted and is associated with a T-to-G point mutation at nucleotide 8993 in the mtDNA gene, MTATP6, coding for the subunit ATPase 6. The 8993T>G mutation results in an amino acid change from a highly conserved leucine 156 to arginine (L156R) and leads to a severe impairment of the synthesis of mitochondrial ATP, reducing cellular energy and cell death, particularly in tissues highly dependent upon the oxidative phosphorylation metabolism, such as brain and retina. The 8993T>G transversion is retrieved in about 75% of patients. Two other MTATP6 mutations, 8993T>C [Santorelli et al., 1994] and 9176T>G [Santorelli et al. 1995] may also occur less commonly.

Furthermore, NARP patient are frequently observed among maternal relatives of infants suffering from MILS in association with mtDNA mutations in the MTATP6 gene. MILS can be associated with other MTATP6 mutations, including the 8993T>C and the 9176T>G transversions [Carrozzo et al., 2001].

**Clinical description**
NARP usually presents in young adults. Clinical presentation includes a combination of the following symptoms: early salt and pepper retinopathy; retinitis pigmentosa; sluggish pupils; nystagmus; blindness; proximal muscle weakness; developmental delay; corticospinal tract atrophy; dementia; hearing loss; seizures; ataxia; sensory neuropathy; proximal neurogenic muscle weakness. Lactic acidosis is rare in NARP patients. There is no histochemical evidence of mitochondrial myopathy. The activities of the respiratory chain complexes in muscle are usually normal.

The index case in the family, which was first described [Holt et al., 1980], was a 47-year-old female who developed night blindness at the age of 12 years and was diagnosed as having retinitis pigmentosa. She was blind by age 30. At the age of 24 years, she had a generalized seizure. In her early 30's, she suddenly noticed unsteadiness on walking which subsequently progressed; there had been no evidence of anticonvulsant toxicity. Sensory action potentials were reduced in amplitude, indicating an axonal sensory neuropathy. Quadriceps-muscle biopsy showed mild chronic partial denervation with collateral reinnervation.

Kerrison et al. (2000) described the progression of retinopathy in NARP syndrome due to the T-to-G point mutation at the mtDNA nucleotide position 8993 in the MTATP6 gene. Prior to the onset of visual field constriction, ophthalmoscopy revealed salt-and-pepper retinopathy. After the visual fields had become constricted, fundus examination showed diffuse peripheral bone spicule formation, optic nerve pallor, and arteriolar attenuation consistent with retinitis pigmentosa. Porto et al. (2001) reported an otherwise healthy 42-year-old woman with isolated late-onset cone-rod dystrophy characterized by difficulty driving at night beginning at age 40 years with deterioration of central and color vision due to the 8993T>G mitochondrial mutation. Two of her sons had NARP syndrome. A third son was clinically diagnosed with Leigh syndrome and died at age 4 years, prior to the recognition of the mutation in this family. The mother's mutation load was 50% mutant mtDNA, while her sons with NARP had 75% mutant mtDNA. The authors stated that Leigh disease is related to 90% of heteroplasmia (varying mixture of mutant and normal mitochondrial DNA). This family illustrated the remarkably variable expression of retinal and systemic manifestations related to the 8993T>G
mutation, ranging from an isolated late-onset cone-rod dystrophy to a severe neurodegenerative process with a dramatic outcome.

The clinical phenotype of NARP may worsen in subsequent generations and usually presents as MILS, the onset of which is in the first few months of life. MILS patients have a rapidly progressive neurodegenerative disorder pathologically characterized by bilateral lesions in the brainstem, basal ganglia, thalamus and spinal cord, and clinically by psychomotor delay, respiratory distress, and basal ganglia dysfunction.

Diagnostic methods
Electromyography and nerve conduction velocities show findings compatible with a sensory-motor peripheral neuropathy. Neuroimaging is usually silent in early stages but it may reveal signs of brainstem degeneration in the course of the disease. Ophthalmological examination is strongly recommended since it may reveal a salt-and-pepper retinopathy even prior to the onset of visual field constriction, and night blindness. Fundus examination usually shows diffuse peripheral bone spicule formation, optic nerve pallor, and arteriolar attenuation consistent with retinitis pigmentosa. Electroretinogram (ERG) is also suggested. It usually evidence markedly decreased amplitudes and prolonged implicit time of the photopic b wave and the flicker response, with a significant, but relatively smaller, decrease in amplitude and prolonged implicit time of the scotopic b wave [Chowers et al., 1999].

Muscle biopsy is usually unremarkable, though neurogenic changes can be observed. Respiratory chain enzyme studies in a biopsy of skeletal muscle specimen might be unnecessary because results usually fall within normal values. Screening for alterations in the MTATP6 gene from peripheral blood is practical in NARP patients since identification of a point mutation reinforces the clinical diagnosis. Mutant load usually remains constant in different tissues at different ages [White et al., 1999a].

Genetic counseling
NARP is maternally transmitted. Affected women can transmit their mutation to all of their offspring.

Prenatal diagnosis
Prenatal diagnosis for mtDNA mutations in chorion villi or amniocytes has been hindered by an inability to predict accurately the clinical severity expected from a mutant load measured in fetal tissue. After reviewing 44 published and 12 unpublished pedigrees, White et al. (1999b) considered the possibility of prenatal diagnosis for the common mtDNA mutations at nucleotide 8993 associated with NARP. They correlated the severity of symptoms to the mutant load and predicted the clinical outcome of a given mutant load. They also used the available data to generate empirical recurrence risks for genetic counseling, which may be used in conjunction with prenatal diagnosis.

Management
The therapeutic tools currently available for the treatment of NARP, as for many mitochondrial diseases due to mtDNA mutations, are limited and their efficacy is not yet well established. Coenzyme Q10 has been proposed at high dose.

Unresolved questions
Our lack of knowledge on the pathological mechanisms underlying NARP syndrome reflects the present lack of efficient therapies. Geromel et al. (2001) investigated the oxidative stress resulting from the mutation in MTATP6 using cultured skin fibroblasts from two NARP patients presenting with an isolated complex V deficiency. A massive induction of the superoxide dismutase (SOD1) activity was observed in these fibroblasts harboring more than 90% of mutant mitochondrial DNA. The oxidative stress denoted by the high SOD1 activity was associated with increased cell death. Complex V-deficient fibroblasts were successfully rescued by perfluoro-tris-phenyl nitrone, an antioxidant spin-trap molecule. The authors hypothesized that the superoxide production associated with the ATPase deficiency triggered by the NARP mutation could be sufficient to override cell antioxidant defenses and to result in cell commitment to die. More recently the effectiveness of antioxidant agents (namely, N-acetylcysteine, coenzyme Q10 and dihydrolipoic) in cultured NARP cells suggests that they might have a potential beneficial role in the treatment of patients with NARP [Mattiazzi et al., 2004]. Allotopic expression of the wild-type MTATP6 gene and subsequent transfer to the mitochondria may be a future application of gene therapy [Manfredi et al., 2002].

References


http://www.orpha.net/data/patho/GB/uk-NARP.pdf