Hereditary Motor and Sensory Neuropathy – Lom

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Abstract

Hereditary motor and sensory neuropathy Lom (HMSNL) is a severe form of demyelinating Charcot-Marie-Tooth (CMT) disease, associated with neural deafness in the majority of affected individuals. Diagnosis criteria include severe demyelinating neuropathy, severe reduction of nerve conduction velocities and of myelinated fibre density, and extensive endoneurial collagen deposition. The HMSNL phenotype is consistent and shows limited variation. The onset of the disease is at age 4-10 years. Gait disturbances, with easy fatigue, frequent stumbling and falling are the first symptoms. Difficulties in using the hands become apparent at 5-15 years of age. Distally accentuated muscle weakness and wasting develop rapidly and are particularly severe in the lower limbs. Sensory loss involving all modalities is also distally accentuated and most evident in the lower limbs. Neural deafness develops between 15 and 30 years of age. Apart from orthopedic surgery for the correction of deformities, no treatment is available. HMSNL is transmitted as an autosomal recessive trait and all known cases are of Romani (Gypsy) background. In Bulgaria, the average gene frequency for the entire Romani population has been estimated at about 1.5%. The disorder is caused by a single ancestral mutation (R148X) in the N-myc downstream-regulated gene 1 (NDRG1), mapped to chromosome 8q24 and with hypothetical functions in growth arrest and cell differentiation. All HMSNL individuals investigated to date are homozygous for the NDRG1 mutation, making molecular diagnosis straightforward and unambiguous.

Keywords

Hereditary motor and sensory neuropathy Lom, HMSNL, Charcot-Marie-Tooth disease type 4D, CMT4D, N-myc downstream-regulated gene 1, NDRG1.
Disease name and synonyms
Hereditary motor and sensory neuropathy Lom, HMSNL, Charcot-Marie-Tooth disease type 4D, CMT4D.

Excluded diseases
Other autosomal recessive demyelinating neuropathies.

Diagnostic criteria / Definition
HMSNL is a severe form of demyelinating CMT disease, associated with neural deafness in the majority of affected individuals. The diagnosis is based on:

Clinical signs: Severe neuropathy with onset in the first decade of life, distally accentuated muscle weakness and wasting more pronounced in the lower limbs, foot and hand deformities. Hearing loss develops almost invariably in the 2nd-3rd decade;

Electrophysiological signs: Nerve conduction velocities severely reduced in younger patients and usually unobtainable after age 15 years. Brainstem auditory evoked potentials (BAEPs) are markedly abnormal, with evidence of retrocochlear involvement of the central auditory pathways.

Neuropathological signs: Severe reduction in myelinated fibre density and extensive endoneurial collagen deposition, increasing in severity with age. Abnormalities in the myelin sheath include uncompacted lamellae, abnormally oblique Schmidt-Lanterman incisures, and variable myelin thickness in adjacent internodes and complete demyelination of scattered internodes. Small onion bulb formations in younger patients gradually disappear with age. Active myelinated fibre degeneration is occasionally present in young patients. There is no evidence of regeneration of myelinated fibres, but the density of unmyelinated fibres is increased. Occasional demyelinated axons are packed with curvilinear profiles, similar to experimental vitamin E deficiency and dystrophic axons.

Mode of inheritance and ethnic predilection: autosomal recessive; all known HMSNL cases are of Romani (Gypsy) background.

Differential diagnosis
HMSNL (and other neuropathies caused by mutations in the NDRG1 gene) should be considered in the differential diagnosis of any patient with early-onset autosomal recessive form of demyelinating CMT disease with severe axonal loss and neural deafness. It is the most likely diagnosis in Romani (Gypsy) patients presenting with the clinical phenotype described above. In Romani families, the differential diagnosis should include other peripheral neuropathies that occur in the same ethnic group, in the first place Hereditary Motor and Sensory Neuropathy Russe (HMSNR), characterized by later onset, milder clinical course, less severe reduction in nerve conduction velocity, and lack of deafness. Testing for the HMSNL mutation will resolve unambiguously the differential diagnosis.

Frequency
HMSNL is the most common peripheral neuropathy among the Roma, with cases reported from all parts of Europe. Reliable data are available only for Bulgaria, where the average gene frequency for the entire Romani population has been estimated at about 1.5%. The distribution among different endogamous Romani groups is very uneven, with carrier rates ranging from 0% to as high as 15% (for the highest risk groups).

Clinical description
The HMSNL phenotype is consistent and shows limited variation. The onset of the disease is at age 4-10 years. Gait disturbances, with easy fatique and frequent stumbling and falling are the first symptoms. Difficulties in using the hands become apparent at 5-15 years of age. Distally accentuated muscle weakness and wasting develop rapidly and are particularly severe in the lower limbs. Tendon reflexes are absent in the lower limbs and, depending on the age of the patient, depressed or absent in the upper limbs. Sensory loss involving all modalities is also distally accentuated and most evident in the lower limbs. Skeletal deformities, particularly clawing of the fingers and toes, are common. Neural deafness is a nearly invariable feature of HMSNL and usually develops between 15 and 30 years of age.

Motor nerve conduction velocity (MNCV) is measurable in the upper limbs in young patients, and subsequently unobtainable. Reported values for the ulnar nerve range from 8 to 16 m/s, and a single measurement achieved for the lower limbs in a 9 year-old patient has shown MNCVs of 20.4 m/s for the peroneal and 18.0 m/s for the tibial nerve (3-8). The BAEP recordings are crudely abnormal in all patients years before the appearance of subjective hearing loss.

Management
Apart from orthopedic surgery for the correction of deformities and supportive measures with regard to increasing disabilities due to progressive weakness, no treatment is available.
Etiology
HMSNL is caused by a single ancestral mutation in the N-myc downstream-regulated gene 1 (NDRG1), which has been mapped to chromosome 8q24. NDRG1 mutation consists in a C to T transition in exon 7 at nucleotide position 564 (following the numbering of sequence accession number #D87953). This substitution results in the replacement of arginine by a premature termination signal at codon position 148. All HMSNL individuals investigated to date are homozygous for the R148X mutation, making molecular diagnosis straightforward and unambiguous.

Diagnostic methods
The diagnosis is based on:

Family history and ethnicity. HMSNL does not interfere with normal reproduction, and a pseudo-dominant pattern of inheritance may be observed in some Romani families with multiple affected individuals. Electrophysiological examination of the parents of the proband will help to establish the autosomal recessive nature of the disorder.

Clinical history, indicating early onset, severe neurological deficit progressing to serious disability as a result of the severe axonal loss and, in adult patients, progressive hearing loss.

Electrophysiological studies, revealing severely reduced or unobtainable nerve conduction velocities and profoundly abnormal BAEPs.

Nerve biopsy for neuropathology.
Molecular genetic analysis. The demonstration of the R148X mutation in NDRG1 is based on a simple PCR-restriction analysis assay, which relies on a TaqI site abolished by the mutation.

Genetic counseling
Since HMSNL is an autosomal recessive trait, the recurrence risk for each pregnancy of a carrier couple is 25%. The risk is higher (50%) for couples where one parent is an affected homozygote. Since carrier rates may be very high in some Romani groups, carrier testing should be offered for unaffected siblings of reproductive age. In the case of extended kindreds with multiple affected individuals, the possibility of an independent segregation of two or even more genetically distinct neuropathies needs to be taken in consideration. Genetic counseling in such families should be based on the molecular analysis of all members requesting counseling.

Prenatal diagnosis
HMSNL is a severe disabling condition and prenatal diagnosis with selective abortion of affected fetuses is considered an important option by families planning further pregnancies. The diagnosis is based on the detection of the mutation as indicated above.

Unresolved questions
The hypothetical functions of the NDRG1 gene, derived from studies of non-neural tissues, include cell signaling, growth arrest, terminal cell differentiation, and the maintenance of the differentiated state. Its role in the peripheral nervous system (PNS) is unclear, and the question why the phenotype, resulting from a truncating mutation in the gene, is confined to the PNS is also unresolved. The relative contribution of other mutations in the NDRG1 gene to the etiology of peripheral neuropathies seems limited, but the investigations conducted are far from extensive.

References


