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Hereditary Neuralgic Amyotrophy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Hereditary Brachial Plexus Neuropathy, Neuritis with Brachial Predilection

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Summary

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Clinical characteristics

Hereditary neuralgic amyotrophy (HNA) is characterized by sudden onset of severe, non-abating pain in the shoulder girdle and/or the upper limb and amyotrophy (muscle wasting or atrophy) that typically develops within two weeks of the onset of severe pain. Other sites may also be involved in an attack; sensory symptoms, present in the majority of affected individuals, can include hypoesthesia (decreased sensation) and paresthesias. Onset is typically in the second or third decade (median age 28 years). Although attacks appear to become less frequent with age, residual deficits accumulate with subsequent attacks. In some families, non-neurologic findings (characteristic craniofacial features, bifid uvula or cleft palate, short stature, and/or partial syndactyly of the fingers or toes) are present.

Diagnosis/testing

The diagnosis of HNA is based on clinical findings. *SEPTIN9* (formerly *SEPT9*) is the only gene in which pathogenic variants are known to cause HNA; however, genetic heterogeneity exists.

Management

Treatment of manifestations: Pain management is the primary goal of therapy and varies between acute and chronic stages. Corticosteroids have been used in the acute phase to shorten the duration of pain and improve

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recovery. Consultation with a physiatrist is recommended for chronic pain and persisting paresis. Patients with phrenic nerve palsy need specialized respiratory consultation and can benefit from noninvasive nocturnal positive pressure ventilation. Cleft palate is managed by standard protocols.

Surveillance: Follow up every six to 12 months after the initial diagnosis to identify chronic pain resulting from altered biomechanics of the shoulder or arm.

Agents/circumstances to avoid: Overexertion of a limb with persistent weakness, especially if the scapula is unstable.

Genetic counseling

Hereditary neuralgic amyotrophy is inherited in an autosomal dominant manner. Most individuals diagnosed with HNA have an affected parent; the proportion of cases caused by a *de novo* pathogenic variant is unknown. Each child of an individual with HNA has a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in the family is known.

Diagnosis

Clinical Diagnosis

Hereditary neuralgic amyotrophy (HNA) is an episodic disorder diagnosed clinically using criteria developed by the European CMT Consortium; see modified criteria (Table 1) and Kuhlenbäumer et al [2000].

Sensory and motor nerves are typically affected; occasionally autonomic nerve injury also occurs.

HNA is characterized in 95% of cases by the following:

- **Sudden onset of severe, non-abating pain** in the shoulder girdle and/or the upper limb. The pain may be unusually debilitating and, in some cases, even refractory to narcotic medications. The intense pain typically lasts for up to several weeks and may give way to a chronic aching pain in the limb persisting for months [van Alfen & van Engelen 2006].
- **Amyotrophy (muscle wasting or atrophy)** that typically develops within two weeks of the onset of severe pain [van Alfen & van Engelen 2006]

Table 1. HNA Diagnostic Criteria

Feature	Inclusion Criteria	Compatible Criteria
Age of onset	• 2nd or 3rd decade of life (median: 28 yrs)	• Earlier or later onset
Clinical manifestations	• Acute, uni- or bilateral brachial plexopathy • Severe pain preceding onset of weakness by days to a few wks • Predominantly motor deficits • Number of episodes variable (1-20) • Precipitating factors: infections, immunizations, surgery, parturition, unusually strenuous exercise of affected limb, exposure to cold	• Attack recurrence (75%) • Sensory symptoms (70%) • Lumbar plexus (33%) &/or phrenic nerve (14%) involved • Cranial nerve involved [1] • Dysmorphic features [2] • Abortive attacks (pain is not followed by weakness) • Weakness preceding onset of pain by days to wks • Long intervals between attacks (up to many yrs) • No pain during an attack (5%)
Family history	• Autosomal dominant inheritance	• Simplex case (i.e., single occurrence in a family)

Table 1. continued from previous page.

Feature	Inclusion Criteria	Compatible Criteria
Clinical examination [3]	• Patchy or multifocal distribution of abnormalities	• More prominent motor loss than sensory loss • Sensory abnormalities (80%) • Autonomic symptoms (15%) [4] • Mononeuropathy [5] • Absent or diminished tendon reflexes in affected limbs • Muscle weakness and atrophy
Course and severity [6]	• Relapsing/remitting course w/symptom-free intervals • Recovery incomplete; persisting neurologic deficit especially after repeated attacks in the same limb	• Complete recovery w/out residual deficit between attacks • Chronic undulating course w/out completely symptom-free intervals
Electrophysiologic findings [7]	• Signs of denervation or reinnervation in clinically weak muscles seen on EMG	• Reduced amplitude of CMAP in muscles innervated by affected nerves • Reduced amplitudes of sensory nerve action potentials in affected nerves
Molecular genetics [8]	• Identification of a presumed pathogenic variant or duplication in *SEPTIN9* • Linkage to the SEPT9 locus on chromosome 17q25	• Absence of linkage to the SEPT9 locus on chromosome 17q25

CMAP = compound muscle action potential; EMG = electromyogram
Modified from Kuhlenbäumer et al [2000]
1. Most commonly recurrent laryngeal nerve (19%) or facial nerve
2. Most commonly ocular hypotelorism, epicanthal folds, cleft palate, bifid uvula, excessive neck or arm skin folds
3. Exclusion criterion: Signs of generalized neuropathy
4. Such as abnormal sweating in affected arm or, rarely, Horner syndrome
5. Most commonly long thoracic, anterior interosseus, or phrenic nerve
6. Exclusion criterion: Slow progression of motor impairment over >3 months
7. Exclusion criterion: Electrophysiologic signs of systemic generalized neuropathy
8. Exclusion criteria: a *PMP22* deletion or pathogenic variant (chromosome 17p11.2) that is diagnostic of hereditary neuropathy with liability to pressure palsies (HNPP)

Molecular Genetic Testing

Gene. *SEPTIN9* (formerly *SEPT9*) is the only gene in which pathogenic variants are known to cause HNA.

Evidence for locus heterogeneity. In at least five reported families, markers flanking the SEPT9 locus do not segregate with the HNA phenotype, suggesting the involvement of one or more as-yet unknown genes [van Alfen et al 2000, Kuhlenbäumer et al 2001, Watts et al 2001].

- The percentage of families in the US who appear not to be genetically linked to the SEPT9 locus is estimated at 15%.
- The percentage of families in other countries (e.g., the Netherlands) who appear not to be genetically linked to the SEPT9 locus may be much higher [unpublished/preliminary data].

Table 2. Molecular Genetic Testing Used in Hereditary Neuralgic Amyotrophy

Gene [1]	Proportion of HNA Attributed to Mutation of Gene	Method	Pathogenic Variants Detected [2]	Variant Detection Frequency by Method [3]
SEPTIN9	~55% [4]	Sequence analysis [5]	Sequence variants	See footnote 6.
		Deletion/duplication analysis [7]	(Multi)exon or whole-gene duplication [8]	See footnote 9.
Unknown	~45%			Unknown

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. The proportion may be higher or lower depending on country or region of origin [van Alfen 2011].
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. In families with HNA linked to *SEPTIN9*, sequence analysis identified a sequence variant in 8/42 families [Hannibal et al 2009], a roughly 20% pathogenic variant detection rate.
7. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
8. Both a founder duplication and nonrecurrent duplications (with unique breakpoints) have been reported [Landsverk et al 2009, Collie et al 2010]. See Molecular Genetics.
9. In families with HNA linked to *SEPTIN9,* CMA identified the founder haplotype duplication in 12/55 families [Landsverk et al 2009] and a tandem duplication in 6/55 families [Collie et al 2010], a roughly 33% variant detection rate.

Testing Strategy

To confirm/establish the diagnosis in a proband

- Confirmation of the diagnosis in persons in whom a clinical diagnosis of HNA is suspected requires molecular genetic testing to identify the pathogenic variant in *SEPTIN9*.
- If sequence analysis of *SEPTIN9* does not identify a pathogenic variant, deletion/duplication analysis should be considered.

Clinical Characteristics

Clinical Description

Neuralgic amyotrophy attacks. Typically, onset of painful attacks in hereditary neuralgic amyotrophy (HNA) occurs in the second or third decade of life (median age of onset 28 years), but children as young as age one year have had attacks. The male to female ratio is 2:1.

The attacks comprise severe aching, burning, or stabbing pains, most often in the shoulders, neck, and/or arm region, followed by multifocal atrophy and paresis. Usually the brachial plexus is involved. In one third of cases, the involvement is bilateral, although severity is usually asymmetric. Attacks appear to become less frequent with age.

The most comprehensive review of attack features in both HNA and sporadic idiopathic neuralgic amyotrophy (see Differential Diagnosis) was reported by van Alfen & van Engelen [2006]. The pain lasts an average of four weeks. Weakness most often begins in the periscapular or perihumeral muscles (see Figure 1) between one and two weeks after the onset of pain. In some instances the onset of weakness may follow within 24 hours of the onset of pain.

The long thoracic and suprascapular nerves are affected in about 70% of cases. Other frequently involved nerves are the axillary, musculocutanous, radial, and anterior interosseus. Lower plexus involvement (median motor and ulnar distribution) occurs in about 5% [van Alfen 2011].

In many cases the muscle weakness may go unnoticed, especially if it only affects the periscapular muscles such as the serratus anterior, rhomboids or subscapularis. Functionally, however, the resulting scapular instability often causes pain, limitation of movement, and exercise intolerance of the affected limb that can persist for months to years.

Sensory symptoms, present in the majority of affected individuals, are often overlooked. They can include the following:

- Hypoesthesia (decreased sensation) located anywhere from the shoulder to the fingertips; found in 85% of individuals
- Paresthesias; reported in more than 50% of attacks
- Vasomotor changes in the arm; reported in 15% of attacks. This autonomic dysfunction of the cervical sympathetic nerves can result in hand edema or vasomotor instability [van Alfen 2007].

While the shoulder and arm are primarily affected by attacks in HNA, other sites that may also be involved in an attack include the following:

- Lumbosacral plexus in ~33% of attacks
- Phrenic nerve palsy in 14% of attacks; may cause orthopnea, respiratory distress and sleep disturbance
- Recurrent laryngeal nerve in 3% of attacks; may cause vocal cord paresis resulting in hoarseness and hypophonia
- Facial nerve or other cranial nerves (rarely)

Two patterns of HNA attacks are described:

- **Common.** Classic remitting/relapsing type, characterized by rapid onset of attacks accompanied by complete or substantial slow recovery
- **Rare.** Chronic undulating type, characterized by slower onset of persistent pain with a protracted fluctuating but unremitting course of attacks resulting in severe residual neurologic deficits [van Alfen et al 2000]

The prognosis for eventual recovery of neurologic function in neuralgic amyotrophy is guarded, with residual deficits accumulating with additional attacks.

Characteristic physical features. In some families, HNA is associated with non-neurologic physical features that allow assessment of the risk for HNA before attacks appear. Typically, these non-neurologic findings include short stature; partial syndactyly of the fingers or toes; characteristic craniofacial features with relatively closely spaced eyes, short palpebral fissures, and epicanthus; and cleft (bifid) uvula or cleft palate [Jeannet et al 2001]. The ocular hypotelorism in some families is striking, with interpupillary distance typically between -1 and -2 standard deviations. As pointed out by several authors, the facial features of persons with HNA resemble portraits painted by the artist Amedeo Modigliani [Dunn et al 1978].

Excessive partial circumferential skin folds of the neck and arms are also characteristic features [Jeannet et al 2001].

Pathophysiology. Attacks may be triggered by periods of physical, immunologic, or emotional stress. Females appear to have a predilection for attacks after childbirth. This, and association of attacks following immunizations and recent viral or bacterial infections, raise a possible role of an immune system trigger. Prior strenuous usage of the upper limbs has also been reported to precipitate attacks suggesting that local trauma or

ischemia of the brachial plexus resulting from compression between muscle groups may underlay the plexopathy, making it more susceptible to (auto-) immune damage.

Biopsy of sural or superficial radial nerves is rarely performed in this disorder. The only finding described in the majority of biopsies is focal decreases in myelinated fibers within individual nerve fascicles [van Alfen et al 2005]. In one report, multiple epineural perivascular mononuclear infiltrates without necrosis were seen in three of four upper-extremity nerve biopsies, obtained three weeks, three months, and seven months after onset of an attack [Klein et al 2002]. These infiltrates were accompanied by active axonal degeneration.

Genotype-Phenotype Correlations

In families with pathogenic variants in *SEPTIN9*, non-neurologic features may or may not be observed. In many cases these dysmorphisms are related to the *SEPTIN9* pathogenic variant p.Arg88Trp [van Alfen 2011]. Generally, non-neurologic features are rarely observed in Dutch individuals, which could indicate that the p.Arg88Trp pathogenic variant is rare in this population.

In one family that appears to have HNA but does not segregate with markers flanking *SEPTIN9*, affected individuals show the chronic undulating phenotype: slowly increasing pain before the onset of the first severe attack followed by an undulating course without complete recovery or cessation of symptoms [van Alfen et al 2000]. Whether other families with the chronic undulating phenotype are also not genetically linked to *SEPTIN9* is unknown.

Penetrance

Studies based on clinical criteria suggest that the penetrance is between 80% and greater than 90% for all individuals with HNA, not taking into account the underlying cause of the disorder [Kuhlenbäumer et al 2000, van Alfen 2007].

Data regarding penetrance in relation to *SEPTIN9* mutation status have not yet been published.

Nomenclature

Out-of-date terms previously used for hereditary neuralgic amyotrophy include the following:

- Familial brachial plexus neuritis
- Heredofamilial neuritis with brachial plexus predilection

Prevalence

The prevalence of HNA is unknown. About 300 families are known worldwide.

The prevalence of HNA is estimated to be about an order of magnitude less than that of idiopathic neuralgic amyotrophy (Parsonage-Turner syndrome), which has an estimated incidence of 1.64:100,000/year to 3:100,000/year [Beghi et al 1985, MacDonald et al 2000].

Prevalence of any brachial neuritis was estimated to be 3:10,000 in the London (UK) area [MacDonald et al 2000].

The actual prevalence of these disorders is likely to be higher because of underdiagnosis. Sixty percent of individuals with neuralgic amyotrophy seen at the Nijmegen clinical center were first diagnosed with a different disorder [van Alfen & van Engelen 2006].

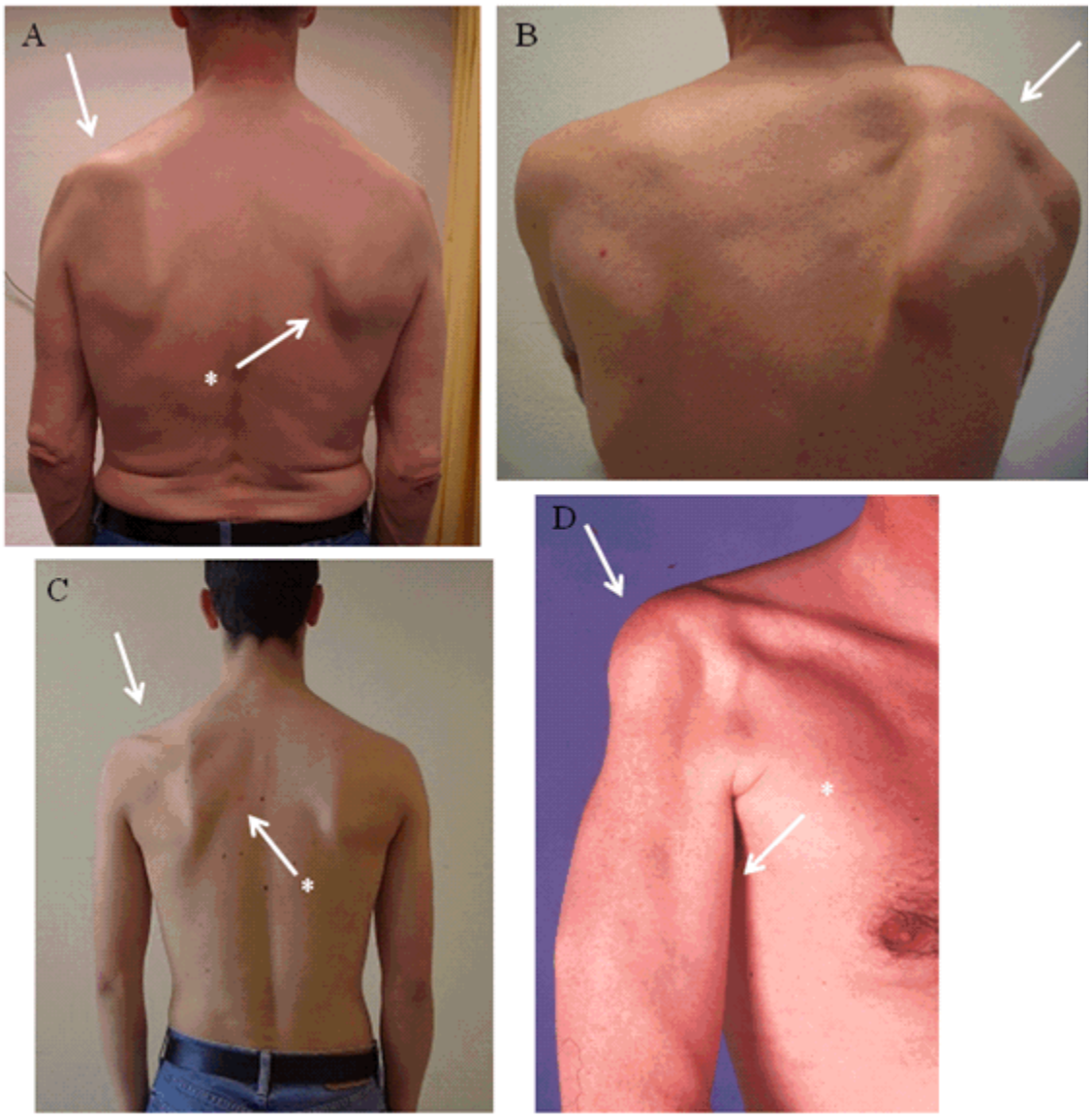

Figure 1. Different presentations of upper-extremity atrophy and paresis

A. On the left: atrophy of supraspinatus and infraspinatus muscles and rhomboid muscles (white arrow); on the right: scapular tilting and rotation caused by serratus anterior muscle weakness (white arrow with *)

B. On the right: severe scapular winging caused by serratus anterior paralysis (white arrow)

C. On the left: atrophy of supraspinatus and infraspinatus muscles (white arrow), and trapezius muscle (white arrow with *) showing underlying rhomboid muscles

D. Severe atrophy of the deltoid muscle (white arrow) and moderate atrophy of the biceps brachii muscle (white arrow with *)

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with germline pathogenic variants in *SEPTIN9*.

The *MLL* oncogene may fuse with *SEPTIN9* in somatic cells to give rise to some forms of myelodysplasia and acute myeloid leukemia (AML).

Note: There is no known relationship between HNA and AML.

Differential Diagnosis

Acute pain in the shoulder and upper arm region may be caused by neurologic or non-neurologic disorders.

- If all the pain, paresis, and sensory symptoms are in the same cervical root distribution, a degenerative or acute disk rupture cervical radiculopathy must be considered.
- Cervical spondylosis may have referred arm pain that is position- or activity-dependent, with no focal deficits and a fluctuating course. Imaging studies such as MRI or CT scan may exclude vertebral or space-occupying causes. The focus, however, should be on the clinical picture, as approximately 50% of affected adults usually show degenerative changes on cervical spine MRI.
- Complex regional pain syndrome involving the shoulder or arm has predominantly vasomotor symptoms, with subacute onset of diffuse pain and weakness with progression.
- Other rare neurologic disorders could include mononeuritis multiplex (peripheral nervous system vasculitis), multifocal motor neuropathy, or brachial amyotrophic diplegia, but these tend to have subacute onset and the latter two disorders are usually painless. Electromyography (EMG) and nerve conduction studies help to distinguish radiculopathies; examination of unaffected limbs excludes generalized peripheral neuropathies.
- In extremely rare cases, an acute painful brachial plexopathy is found as the only sign of an underlying hereditary neuropathy with liability to pressure palsies (HNPP). HNPP is an autosomal dominant disorder caused by the deletion or mutation of *PMP22*. Usually there is a family history of nerve damage resulting from minor stretch or compressive trauma.
- Shoulder joint pathology (e.g., bursitis, calcifying tendonitis) or rotator cuff injury may cause pain that is exacerbated by joint movement and relieved by rest or passive immobilization.

Brachial plexopathy may also be caused by trauma, surgery, or prior irradiation:

- Lower plexus lesions may be seen in the case of a Pancoast tumor or true neurogenic thoracic outlet syndrome.
- A peripheral nerve or nerve sheath tumor may involve the plexus, as could direct peripheral nervous system infections such as neuroborreliosis or HIV.

The main differential diagnosis in an individual presenting with an acute-onset, painful, multifocal, brachial plexopathy is neuralgic amyotrophy in either its hereditary or idiopathic form. HNA is clinically similar to its sporadic counterpart, idiopathic neuralgic amyotrophy (INA). The disorders share the same precipitating factors, signs, and symptoms. INA, also called brachial neuritis or Parsonage-Turner syndrome, is estimated to be about ten times more common than HNA. HNA is distinguished from INA by its familial recurrence, earlier average age of onset, more severe pain in the acute stage, more frequent involvement of nerves outside of the brachial plexus, higher rate of recurrence, and greater eventual disability. However, no single feature in a given individual can distinguish hereditary from sporadic neuralgic amyotrophy; this distinction is based on a positive family history and/or the presence of the typical dysmorphic features.

Excluding the holoprosencephaly syndromes, a couple of syndromes known to share some of the craniofacial features of HNA are autosomal dominant Schilbach-Rott syndrome (OMIM 164220) and Michelin tire baby syndrome (OMIM 156610).

- Like HNA, Schilbach-Rott syndrome is characterized by short stature, cutaneous syndactyly, ocular hypotelorism, and cleft palate [Joss et al 2002]. The families reported do not have neuralgic amyotrophy.
- A subset of individuals with Michelin tire baby syndrome (with what now may be known as "circumferential skin creases, Kunze type") also may share the following with HNA: craniofacial features (including relatively closely spaced eyes and short palpebral fissures), cleft palate, and circumferential skin folds [Wouters et al 2011].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hereditary neuralgic amyotrophy, the following evaluations are recommended:

- Comprehensive neuromuscular evaluation
- Needle EMG to identify the severity and extent of denervation and reinnervation
- Evaluation of phrenic nerve involvement by chest x-ray, ultrasound/fluoroscopic evaluation of diaphragm movement, and pulmonary function tests in seated and supine positions
- Clinical genetics consultation

For a practical overview of the physical examination and the value of additional investigations in neuralgic amyotrophy see pn.bmj.com.

Treatment of Manifestations

Currently, no effective therapy is proven to abort or shorten an HNA attack.

Treatment of acute episodes of pain and weakness with corticosteroids has been proposed based on retrospective analysis of cases [van Alfen et al 2009, van Eijk et al 2009]. These reports summarize retrospective, anecdotal evidence that corticosteroids can have a favorable effect on pain and recovery. Additional immunomodulatory treatments with such agents as corticosteroids and immune globulin may be considered, but no prospective trials have been performed [van Alfen et al 2009, Johnson et al 2011].

Pain management is the primary goal of therapy:

- **In the acute stage,** a combination of a long-acting nonsteroidal anti-inflammatory drug (NSAID) such as ketorolac and a narcotic such as controlled-release morphine are used.
- **In the second phase** of chronic pain resulting from damaged, hypersensitive nerves, co-analgesics such as gabapentin, carbamazepine, and amitryptiline may be used.
- **In the third chronic phase,** persistent pain in the neck and shoulder region usually points to strain of the paretic or compensating muscles or to a complication in the glenohumeral joint, such as rotator cuff pathology. As the weakness has to recover by itself, therapy focuses on arm support in a sling, rest, physical therapy, range of motion stretching, and modification of activities. This rehabilitation and prevention of further injury is best managed by a physiatrist.

For persistent paresis, physical therapy is recommended to maintain exercise tolerance and prevent joint or ligament contractures. Care must be taken to avoid post-exercise pain in the affected area, as this is often a sign of strain. In this case, exercise should be temporarily deferred, or at least be without extra added weights and with fewer repetitions per set. The patient must find his or her personal level of exercise tolerance; in practice, this is often much lower than estimated (or desired) by the patient or therapist.

For severe paresis of the serratus anterior muscle persisting more than one year, corrective surgery can be considered to increase scapular stability, for example by a split pectoralis major muscle transfer.

Patients with phrenic nerve palsy need consultation with a respiratory specialist and can benefit from noninvasive nocturnal positive pressure ventilation.

For a clinical overview of neurologic and rehabilitative management, see van Alfen [2007].

Cleft palate is best managed by a local craniofacial team.

Surveillance

As chronic pain resulting from altered biomechanics of the shoulder or upper extremity tends to develop during the first one to two years, follow up every six to 12 months after the initial diagnosis is recommended.

Agents/Circumstances to Avoid

Although immunizations have been known to precede and possibly trigger attacks, it is still recommended that they be given on the usual recommended schedule because the risk of immunization precipitating an attack is probably low [based on expert opinion].

Patients with persistent weakness and especially scapular instability should be cautioned to avoid overexerting the affected limb.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Women with HNA should be monitored in the post-partum interval for the development of symptoms. Prompt treatment with corticosteroids or similar agents may ameliorate an HNA attack.

Therapies Under Investigation

In an open-label study of oral prednisone in adults with INA or HNA (60 mg/day for one week, followed by a one week taper by 10 mg/day with a last dose of 5 mg) the only statistically significant finding was a reduction in the time for paresis recovery [van Alfen & van Engelen 2006]. Other variables showed no statistical difference from an untreated group of persons with neuralgic amyotrophy; variables included the duration of the initial pain, maximum present Numerical Rating Scale score and use of analgesics, the occurrence of a chronic pain syndrome, maximum Medical Research Council level of strength recovery, complications such as frozen shoulder or shoulder dislocation, and Rankin score.

An additional review of the Dutch experience revealed the following:

- Relative to the untreated patients, a significantly higher proportion of the patients receiving oral prednisolone recovered early from their pareses.
- Taken in the first month, prednisolone tended to decrease the average duration of the initial pain, although this finding was not statistically significant.
- Functional recovery set in earlier, with significantly more treated patients achieving full recovery within a year or reporting a "good" outcome within six months.
- Side effects occurred in 20% of patients, but did not result in discontinuation of treatment [van Eijk et al 2009].

A randomized placebo-controlled trial of oral prednisone conducted in the Netherlands was terminated after three years because of insufficient recruitment within the specified time frame. No treatment effect could be demonstrated in the 13 persons in the primary treatment and placebo arm; however, the small number of participants precluded any definite conclusions.

Experimental immunosuppressive therapies that have been used in other inflammatory polyneuropathies, but for which there are limited data available for treatment of attacks in HNA, include the following:

- Methylprednisolone, intravenous 30 mg/kg (or 1.0 g in adults) every 24 hours for three days [Klein et al 2002, Nakajima et al 2006]. Cessation or tapering of corticosteroid therapy has resulted in relapse.

- Intravenous immune globulin, 0.4 g/kg/day for five days [Ardolino et al 2003, Moriguchi et al 2011]

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary neuralgic amyotrophy is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with hereditary neuralgic amyotrophy have an affected parent.
- A proband with hereditary neuralgic amyotrophy may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for parents of a proband with an apparent *de novo* pathogenic variant include a clinical evaluation for findings of HNA. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: (1) Although most individuals diagnosed with hereditary neuralgic amyotrophy have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. (2) If the parent is the individual in whom the pathogenic variant first occurred s/he may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the pathogenic variant found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with hereditary neuralgic amyotrophy has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has the disorder as a result of a *de novo* pathogenic variant in either *SEPTIN9* or another as-yet unknown gene. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Testing of at-risk asymptomatic adults. Although uncommonly requested, testing of at-risk asymptomatic adults for hereditary neuralgic amyotrophy is possible using the techniques described in Molecular Genetic Testing. Such testing is not useful in predicting whether symptoms will occur, or if they do, what the age of onset, severity and type of symptoms, or rate of disease progression in asymptomatic individuals will be. When testing at-risk individuals for hereditary neuralgic amyotrophy, an affected family member must be tested first to confirm the molecular diagnosis in the family.

Testing for the pathogenic variant in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of hereditary neuralgic amyotrophy, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled regarding possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow up and evaluations.

Molecular genetic testing of asymptomatic individuals younger than age 18 years. Because no proven preventive or ameliorating treatment is available, individuals younger than age 18 years who are at risk of having inherited and developing HNA are typically not offered testing during childhood. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications.

Individuals younger than age 18 years who are symptomatic usually benefit from having a specific diagnosis established.

See also the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SEPTIN9* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for hereditary neuralgic amyotrophy are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Muscular Dystrophy UK**
  61A Great Suffolk Street
  London SE1 0BU
  United Kingdom
  Phone: 0800 652 6352 (toll-free); 020 7803 4800
  Email: info@musculardystrophyuk.org
  www.musculardystrophyuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Neuralgic Amyotrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SEPTIN9	17q25.3	Septin-9	IPN Mutations, SEPT9 SEPT9 homepage - Leiden Muscular Dystrophy pages	SEPTIN9	SEPTIN9

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Neuralgic Amyotrophy (View All in OMIM)

162100	AMYOTROPHY, HEREDITARY NEURALGIC; HNA
604061	SEPTIN 9; SEPT9

Gene structure. *SEPTIN9* and septin-9 protein have numerous published aliases, including MSF, SepD1, Ov/Br septin, and PNUTL4. At least 17 exons spanning 213 kilobases are used to generate alternatively spliced transcripts (see Table A, **Gene**). In the seven most abundant transcripts, variation in splicing occurs in the alternate use of 5' exons to include 10-12 exons that generate polypeptides ranging from 586 to 335 amino acids. The three transcripts that encode the longest proteins encode short, distinct N-terminal polypeptides of 25 amino acids (septin-9 isoform a, NM_001113491.1), 18 amino acids (septin-9 isoform b, NM_001113493.1), and seven amino acids (septin-9 isoform c, NM_006640.4).

Pathogenic variants. Three small intragenic pathogenic variants have been reported: a non-coding 5'-untranslated region variant and two missense variants, p.Arg88Trp and p.Ser93Phe [Kuhlenbäumer et al 2005, Hannibal et al 2009]. Both missense variants occur within a 645-bp exon of *SEPTIN9* (hg18 chr17:72,909,736-72,910,380; p.Arg88Trp is a recurrent missense variant located at a presumably hypermutable CG dinucleotide [Kuhlenbäumer et al 2005, Hannibal et al 2009, Klein et al 2009, Ueda et al 2010]. See Table 3.

Six intragenic duplications and one whole-gene duplication have been identified in families with HNA [Landsverk et al 2009, Collie et al 2010]. Each of these minimally duplicates a 7,592-bp genomic region containing a 645-bp exon within *SEPTIN9* (hg18 coordinates chr17:72,904,532-72,912,123). A larger septin-9 protein is produced from some of the intragenic duplication alleles.

Note: Human Mar. 2006 (NCBI36/hg18) Browser Sequences are available at genome.ucsc.edu.

Table 3. Selected *SEPTIN9* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.-134G>C (SEPT9_v3 5'-UTR-131G>C)	--	NM_006640.4 NP_006631.2
c.262C>T	p.Arg88Trp (SEPT9_v3 R88W)	
c.278C>T	p.Ser93Phe (SEPT9_v3 S93F)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

For more information, see Table A.

Normal gene product. *SEPTIN9* appears to be ubiquitously expressed, but studies of the distribution of septin-9 protein isoforms in normal tissues are limited. Septin-9 is thought to play a role in cytokinesis and tumorigenesis. The long isoforms of septin-9 have unique N-terminal polypeptides with a proline-rich domain. Only the septin proteins encoded by *SEPT4* also have a nonhomologous proline-rich domain. Septin-9 shares a polybasic and GTP-binding domain with all septins, but lacks a C-terminal coiled-coil domain found in all septins, except those encoded by *SEPTIN9*, *SEPT3*, and *SEPT12*. Septin-9 has been shown to be localized with other septins to intermediate filaments that associate with actin microfilaments and microtubules.

Abnormal gene product. Several hypotheses have arisen regarding the functional consequences of a *SEPTIN9* pathogenic variant. One report suggests that mutation of *SEPTIN9* results in alteration of a putative internal ribosome entry site in the mRNA transcript that controls the choice of the initiating ATG codon for protein translation [McDade et al 2007]. Another paper proposes that the *SEPTIN9* pathogenic variants alter the interaction of septin-9 with septin-4 and perturb the regulation of septin-9-containing filaments by Rho/

Rhotekin signaling [Sudo et al 2007]. The limited range of pathogenic variants seen to date (i.e., 2 pathogenic missense variants with the 645-bp exon and *SEPTIN9* duplications that produce a larger protein product containing 2 tandem copies of the peptide encoded by the 645-bp exon) suggest that a novel gain-of-function mechanism may account for pathogenesis.

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Chapter Notes

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