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Hereditary Neuralgic Amyotrophy

[*Hereditary Brachial Plexus Neuropathy, Neuritis with Brachial Predilection*]

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Summary

Disease 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 and 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 (short stature, partial syndactyly of the fingers or toes, characteristic craniofacial features, and bifid uvula or cleft palate) are present.

Diagnosis/testing. The diagnosis of HNA is based on clinical findings. *SEPT9* is the only gene known to be associated with HNA. Molecular genetic testing is clinically available.

Management. *Treatment of manifestations:* Pain management is the primary goal of therapy and varies between acute and chronic stages. Consultation with a physiatrist is recommended for chronic pain and persisting paresis. 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* mutation is unknown. Each child of an individual with HNA has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation 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	Second or third decade of life (median: 28 years)	Earlier or later onset
Clinical Manifestations	Acute, uni- or bilateral brachial plexopathy Severe pain preceding the onset of weakness by days to a few weeks Predominantly motor deficits Number of episodes varies from one to 20 Precipitating factors are infections, immunizations, surgery, parturition, unusually strenuous exercise of the affected limb, or exposure to cold	Attack recurrence (75%) Sensory symptoms (70%) Lumbar plexus (33%) and/or phrenic nerve (14%) involved Cranial nerve involved [1] Dysmorphic features [2] Abortive attacks (pain is not followed by weakness) Weakness preceding the onset of pain by days to weeks Long intervals between attacks (up to many years) No pain during an attack (5%)
Family History	Autosomal dominant inheritance	Simplex case (i.e., single occurrence in a family)
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 with symptom-free intervals Recovery incomplete; persisting neurologic deficit especially after repeated attacks in the same limb	Complete recovery without residual deficit between attacks Chronic undulating course without completely symptom-free intervals
Electrophysiologic Findings [7]	Electromyogram (EMG) shows signs of denervation or reinnervation in clinically weak muscles.	Reduced amplitude of compound muscle action potential (CMAP) in muscles innervated by affected nerves Reduced amplitudes of sensory nerve action potentials in affected nerves
Molecular Genetics [8]	Identification of a presumed pathologic mutation in *SEPT9* Linkage to the *SEPT9* locus on chromosome 17q25	Absence of linkage to the *SEPT9* locus on chromosome 17q25

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: *PMP22* deletion or mutation (chromosome 17p11.2) that is diagnostic of hereditary neuropathy with liability to pressure palsies (HNPP)

Testing

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SEPT9* is the only gene known to be associated with HNA.

Other loci. In at least five reported families, markers flanking the *SEPT9* locus do not segregate with the HNA phenotype, suggesting the existence of another causal gene(s) [van Alfen, van Engelen 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).

Clinical testing

- **Sequence analysis** of the entire coding region, untranslated sequences, and intron-exon boundaries detects mutations in approximately 40% of families that appear to link to the *SEPT9* locus.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Hereditary Neuralgic Amyotrophy

Gene Symbol	Proportion of HNA Attributed to Mutations in This Gene	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
SEPT9	~85% [1]	Sequence analysis	*SEPT9* point mutations and intragenic insertions/ deletions	~40% [2]	Clinical Testing

1. Dependent on country or region of origin; may be much lower [M Hannibal, unpublished data]
2. M Hannibal, unpublished data

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirmation of the diagnosis in persons in whom a clinical diagnosis of HNA is suspected requires molecular genetic testing to identify *SEPT9* mutations.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with germline mutations in *SEPT9*.

The MLL oncogene may fuse with *SEPT9* in somatic cells to give rise to some forms of acute myeloid leukemia (AML).

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

Clinical Description

Natural History

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%.

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 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, van Engelen 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 diagnosis of their 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 ocular hypotelorism, shortened palpebral fissures, epicanthal folds, long nasal bridge, small mouth; facial asymmetry; and bifid uvula or cleft palate [Jeannet et al 2001]. The ocular hypotelorism in some families is striking, with interpupillary distance averaging about -1 standard deviation below the mean. As pointed out by several authors, the facial features of persons with HNA resemble portraits painted by the artist 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 *SEPT9* mutations, non-neurologic features may or may not be observed. Generally non-neurologic features are not observed in Dutch patients, which could indicate that typical dysmorphisms are associated with certain *SEPT9* mutations. Insufficient published data make correlation difficult at present.

In one family that appears to have HNA but does not segregate with markers flanking *SEPT9*, 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, van Engelen et al 2000]. Whether other families with the chronic-undulating phenotype are also not genetically linked to *SEPT9* is unknown.

Penetrance

Studies based on clinical criteria suggest that the penetrance of HNA is between 80% and greater than 90% [Kuhlenbäumer et al 2000, van Alfen 2007].

Data regarding penetrance in relation to *SEPT9* 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 200 families are known worldwide.

The prevalence of HNA is estimated to be about an order of magnitude less than that of idiopathic neuralgic amyotrophy, 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, United Kingdom 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].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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 the *PMP22* gene. Usually there is a family history of nerve damage resulting from minor stretch or compressive trauma.

- Shoulder joint pathology, such as bursitis or 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 probably 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.

Excluding the holoprosencephaly syndromes, the one syndrome known to share some of the craniofacial features of HNA is autosomal dominant Schilbach-Rott syndrome [OMIM 164220]. Like HNA, Schilbach-Rott syndrome is characterized by short stature, cutaneous syndactyly, ocular hypotelorism, and cleft palate [Joss et al 2002]. The two families reported to have this disorder do not have neuralgic amyotrophy.

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

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

Treatment of Manifestations

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.

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.

Testing of Relatives at Risk

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

Therapies Under Investigation

Currently, a randomized placebo-controlled trial of oral prednisone is being conducted in the Netherlands.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

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

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]. 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]

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 new gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation 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* mutation include a clinical evaluation for findings of HNA. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or 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 mutation first occurred s/he may have somatic mosaicism for the mutation 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 disease-causing mutation 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 mutation.

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 found to be affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation in either *SEPT9* or another, as yet unknown gene. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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 of being affected.

Testing of at-risk asymptomatic adults. Although uncommonly requested, testing of at-risk asymptomatic adults for hereditary neuralgic amyotrophy is available using the same 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 disease-causing mutation 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 about 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.

Testing of at-risk individuals during childhood. 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 18 years of age who are symptomatic usually benefit from having a specific diagnosis established.

See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents (pdf; Genetic Testing).

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as hereditary neuralgic amyotrophy that do not affect intellect or life span are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hereditary Neuralgic Amyotrophy

Gene Symbol	Chromosomal Locus	Protein Name
SEPT9	17q25	Septin-9

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hereditary Neuralgic Amyotrophy

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

Table C. Genomic Databases for Hereditary Neuralgic Amyotrophy

Gene Symbol	Locus Specific	Entrez Gene
SEPT9	SEPT9	10801 (MIM No. 604061)

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *SEPT9* gene 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. 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 7 amino acids (septin-9 isoform c, NM_006640.4)

Pathologic allelic variants: Three mutations have been reported: a noncoding 5'-untranslated region mutation and two missense mutations. p.Arg88Trp is a recurrent missense mutation and is located at a presumably hypermutable CG dinucleotide. See Table 3.

Table 3. *SEPT9* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequence
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)	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

For more information, see Genomic Databases table.

Normal gene product: The *SEPT9* gene 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 shared only with the septin proteins encoded by the *SEPT4* and *SEPT8* genes. 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 *SEPT9*, *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 to the functional consequences of *SEPT9* mutations. One report suggests that the mutations alter 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 mutations 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].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Ardolino G, Barbieri S, Priori A. High dose intravenous immune globulin in the treatment of hereditary recurrent brachial plexus neuropathy. J Neurol Neurosurg Psychiatry. 2003;74:550;. [PubMed: 12640095]

Beghi E, Kurland LT, Mulder DW, Nicolosi A. Brachial plexus neuropathy in the population of Rochester, Minnesota, 1970-1981. Ann Neurol. 1985;18:320–3. [PubMed: 2996415]

Dunn HG, Daube JR, Gomez MR. Heredofamilial branchial plexus neuropathy (hereditary neuralgic amyotrophy with branchial predilection) in childhood. Dev Med Child Neurol. 1978;20:28–46. [PubMed: 205473]

Jeannet PY, Watts GD, Bird TD, Chance PF. Craniofacial and cutaneous findings expand the phenotype of hereditary neuralgic amyotrophy. Neurology. 2001;57:1963–8. [PubMed: 11739810]

Joss SK, Paterson W, Donaldson MD, Tolmie JL. Cleft palate, hypotelorism, and hypospadias: Schilbach-Rott syndrome. Am J Med Genet. 2002;113:105–7. [PubMed: 12400075]

Klein CJ, Dyck PJ, Friedenberg SM, Burns TM, Windebank AJ, Dyck PJ. Inflammation and neuropathic attacks in hereditary brachial plexus neuropathy. J Neurol Neurosurg Psychiatry. 2002;73:45–50. [PubMed: 12082044]

Kuhlenbaumer G, Meuleman J, De Jonghe P, Falck B, Young P, Hunermund G, Van Broeckhoven C, Timmerman V, Stogbauer F. Hereditary Neuralgic Amyotrophy (HNA) is genetically heterogeneous. J Neurol. 2001;248:861–5. [PubMed: 11697522]

Kuhlenbaumer G, Stogbauer F, Timmerman V, De Jonghe P. Diagnostic guidelines for hereditary neuralgic amyotrophy or heredofamilial neuritis with brachial plexus predilection. On behalf of the European CMT Consortium. Neuromuscul Disord. 2000;10:515–7. [PubMed: 10996784]

MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain 123 (Pt. 2000;4): 665–76. [PubMed: 10733998]

McDade SS, Hall PA, Russell SE. Translational control of SEPT9 isoforms is perturbed in disease. Hum Mol Genet. 2007;16:742–52. [PubMed: 17468182]

Sudo K, Ito H, Iwamoto I, Morishita R, Asano T, Nagata K. SEPT9 sequence alternations causing hereditary neuralgic amyotrophy are associated with altered interactions with SEPT4/SEPT11 and resistance to Rho/Rhotekin-signaling. Hum Mutat. 2007;28:1005–13. [PubMed: 17546647]

van Alfen N. The neuralgic amyotrophy consultation. J Neurol. 2007;254:695–704. [PubMed: 17446996]

van Alfen N, Gabreels-Festen AA, Ter Laak HJ, Arts WF, Gabreels FJ, van Engelen BG. Histology of hereditary neuralgic amyotrophy. J Neurol Neurosurg Psychiatry. 2005;76:445–7. [PubMed: 15716548]

van Alfen N, van Engelen BG. The clinical spectrum of neuralgic amyotrophy in 246 cases. Brain. 2006;129:438–50. [PubMed: 16371410]

van Alfen N, van Engelen BG, Reinders JW, Kremer H, Gabreels FJ. The natural history of hereditary neuralgic amyotrophy in the Dutch population: two distinct types? Brain 123 (Pt. 2000;4):718–23. [PubMed: 10734003]

Watts GD, O'Briant KC, Borreson TE, Windebank AJ, Chance PF. Evidence for genetic heterogeneity in hereditary neuralgic amyotrophy. Neurology. 2001;56:675–8. [PubMed: 11245726]

Suggested Readings

van Alfen N, Schuuring J, van Engelen BG, Rotteveel JJ, Gabreels FJ. Idiopathic neuralgic amyotrophy in children. A distinct phenotype compared to the adult form. Neuropediatrics. 2000;31:328–32. [PubMed: 11508556]

Chapter Notes

Revision History

- 27 February 2008 (me) Review posted to live Web site
- 11 June 2007 (mch) Original submission

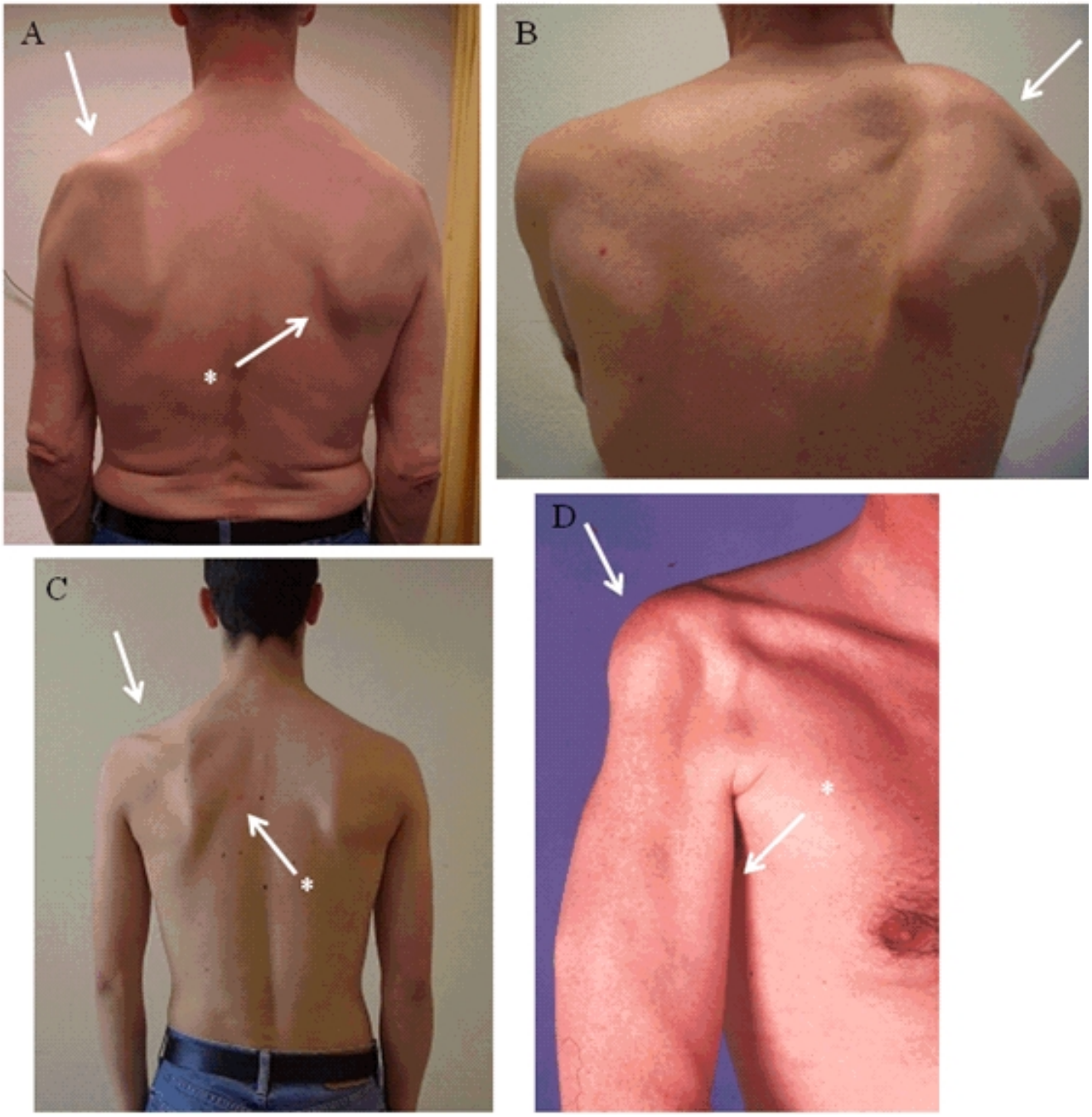

Figure 1. Different presentations of upper-extremity atrophy and paresis
A. On the left: atrophy of supraspinatus and infraspinatus muscles and rhomboid muscles (white arrow); on the right: scapular tilting and rotation caused by serratus anterior muscle weakness (white arrow with *)
B. On the right: 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 *)