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REVIEW ARTICLE

Inherited Focal, Episodic Neuropathies

Hereditary Neuropathy With Liability to Pressure Palsies and Hereditary Neuralgic Amyotrophy

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Abstract

Hereditary neuropathy with liability to pressure palsies (HNPP; also called tomaculous neuropathy) is an autosomal-dominant disorder that produces a painless episodic, recurrent, focal demyelinating neuropathy. HNPP generally develops during adolescence, and may cause attacks of numbness, muscular weakness, and atrophy. Peroneal palsies, carpal tunnel syndrome, and other entrapment neuropathies may be frequent manifestations of HNPP. Motor and sensory nerve conduction velocities may be reduced in clinically affected patients, as well as in asymptomatic gene carriers. The histopathological changes observed in peripheral nerves of HNPP patients include segmental demyelination and tomaculous or "sausage-like" formations. Mild overlap of clinical features with Charcot-Marie-Tooth (CMT) disease type 1 (CMT1) may lead patients with HNPP to be misdiagnosed as having CMT1. HNPP and CMT1 are both demyelinating neuropathies, however, their clinical, pathological, and electrophysiological features are quite distinct. HNPP is most frequently associated with a 1.4-Mb pair deletion on chromosome 17p12. A duplication of the identical region leads to CMT1A. Both HNPP and CMT1A result from a dosage effect of the *PMP22* gene, which is contained within the deleted/duplicated region. This is reflected in reduced mRNA and protein levels in sural nerve biopsy samples from HNPP patients. Treatment for HNPP consists of preventative and symptom-easing measures. Hereditary neuralgic amyotrophy (HNA; also called familial brachial plexus neuropathy) is an autosomal-dominant disorder causing episodes of paralysis and muscle weakness initiated by severe pain. Individuals with HNA may suffer repeated episodes of intense pain, paralysis, and sensory disturbances in an affected limb. The onset of HNA is at birth or later in childhood with prognosis for recovery usually favorable; however, persons with HNA may have permanent residual neurological dysfunction following attack(s). Episodes are often triggered by infections, immunizations, the puerperium, and stress. Electrophysiological studies

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show normal or mildly prolonged motor nerve conduction velocities distal to the affected brachial plexus. Pathological studies have found axonal degeneration in nerves examined distal to the plexus abnormality. In some HNA pedigrees there are characteristic facial features, including hypotelorism. The prognosis for recovery of normal function of affected limbs in HNA is good, although recurrent episodes may cause residual deficits. HNA is genetically linked to chromosome 17q25, where mutations in the *septin-9 (SEPT9)* gene have been found.

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Index Entries: Brachial neuritis; brachial plexus; episodic neuropathy; HNA; HNPP, tomaculous neuropathy.

Introduction

Inherited, focal peripheral neuropathies that are recurrent and from which affected individuals make full or partial degrees of recovery are unusual. This article discusses the two most prominent disorders that fall into this category, and they are hereditary neuropathy with liability to pressure palsies (HNPP) and hereditary neuralgic amyotrophy (HNA).

Hereditary Neuropathy With Liability to Pressure Palsies

Clinical Features in HNPP

HNPP (OMIM No. 162500; McKusick, 2000) is an autosomal-dominant disorder that typically leads to episodic, painless, recurrent, focal motor and sensory peripheral neuropathies (Lupski and Chance, 2004). First described by De Jong in 1947, HNPP is an entrapment or compressive neuropathy: many episodes are preceded by a minor compression or trauma of the affected peripheral nerve. The most vulnerable sites are the wrist, elbow, knee, and shoulder, affecting the median, ulnar, and peroneal nerve and brachial plexus, respectively (De Jong, 1947). A history of limb trauma or prolonged positioning of the limb may be obtained in some cases. The onset of HNPP is usually in adolescence, with a high degree of penetrance; however, clinically asymptomatic obligate gene carriers are sometimes noted. When palsies occur, they may be debilitating in that they may last for days to weeks and may require installation of a lower limb brace or ankle-foot orthosis in the cases of prolonged peroneal palsies. Hypoactive deep tendon reflexes and mild *pes cavus* may be observed in clinically asymptomatic patients. The spectrum of clinical presentation in HNPP is broad and may range from clinically asymptomatic or subclinical to, more typically, recurrent palsies and in some advanced cases progressive residual deficits mimicking indolent forms of Charcot-Marie-Tooth disease type 1 (CMT1) (Dyck et al., 1993; Windebank, 1993; Chance, 1996; Kumar et al., 1998). Although it is well established that symptoms of carpal tunnel syndrome (CTS) may be seen in patients having HNPP, or may even be the only symptom or the presenting symptom of HNPP (Potocki et al., 1999), it is clear that HNPP is only a rare cause of CTS and not causal for rare pedigrees having the so-called "familial CTS" (Gossett and Chance, 1998; Stockton et al., 2001). Guidelines for the diagnosis of HNPP have been reported previously (Dubourg et al., 2000).

In an analysis of 39 patients with HNPP from 16 unrelated pedigrees, two-thirds of patients had the typical presentation of acute mononeuropathy and the remaining subjects were thought to have features consistent with a more long-standing polyneuropathy. Furthermore, it was noted that more than 40% of affected persons were unaware of their illness and 25% of patients were essentially symptom-free at the time of observation (Pareyson et al., 1996). More recently, the spectrum of clinical and neurophysiological findings in 99 patients with HNPP was documented (Mouton et al., 1999). The majority of patients in this survey (70%) presented with a typical history of a single, focal episode of neuropathy, however, there were patients with short-term or chronic sensory syndromes, as well as asymptomatic gene carriers.

Recognizing HNPP in children may be challenging, especially in the absence of a family history. Presentation of HNPP in children under age 10 yr is unusual, and when it occurs, may not necessarily manifest itself as a simple, acute-onset case of limb palsy. There are reported cases of young children presenting with hypotonia and gross motor

delays, and yet others demonstrating toe-walking, pain, and stiffness.

Rarely, patients with HNPP may present with a more fulminant course in which palsies affecting more than one limb are seen (Crum et al., 2000). It is unknown whether HNPP could predispose a patient to developing an immune-mediated disorder such as acute inflammatory demyelinating polyneuropathy (AIDP; Guillain-Barré syndrome) or chronic inflammatory demyelinating polyneuropathy (CIDP). Interestingly, the HNPP deletion has been found in such patients who presented with either AIDP or CIDP, or at least had clinical syndromes initially suggesting those diagnoses. Other rare associations with HNPP include a report of central nervous system demyelination (Amato et al., 1996).

Very few studies have addressed the epidemiology of HNPP; one such study from western Finland reported a prevalence of 16 per 100,000 (Meretoja et al., 1997).

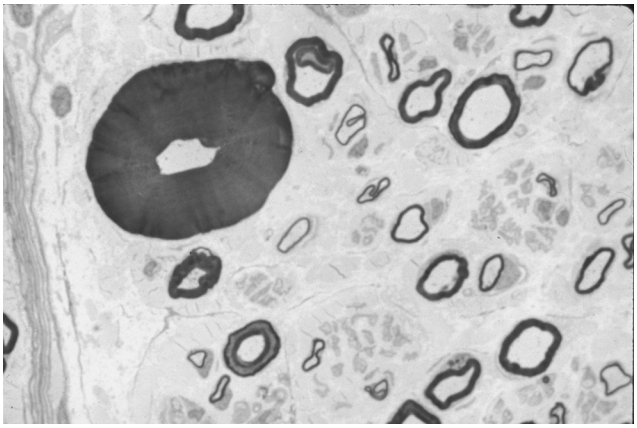

Fig. 1. Cross-section of a sural nerve biopsy from a patient with HNPP showing a tomaculum. Thinly myelinated axons are also seen. One-micron section prepared from plastic-embedded specimen, toluidine blue staining. Original magnification ×3400. (Courtesy of Dr. Zarife Sahenk, Department of Neurology, Ohio State University, Columbus, OH.)

Histopathological Features in HNPP

In 1972, Behse et al. documented the pathological features of HNPP (Behse et al., 1972). Histological assessment of sural nerve biopsies reveals segmental de- and remyelination. The presence of tomacula or "sausage"-shaped structures is the pathological signature of HNPP. They consist of massive redundancy or overfolding of variable thickness layers in the myelin sheath (Madrid et al., 1975). It should be noted that tomacula are not a pathognomonic feature of HNPP. They may also be seen in CMT 4B (with myelin outfolding), IgM paraproteinemic neuropathy, chronic inflammatory demyelinating polyneuropathy, and Dejerine–Sottas neuropathy (Sander et al., 2000). Tomacula have also been observed in cases of CMT1 and types associated with extrapyramidal syndrome, neurogenic scapuloperoneal syndrome, and multiple sclerosis (Alexianu et al., 1995; Drulovi, 1998). Although tomacula are generally considered an important diagnostic feature of HNPP (Fig. 1), rare patients showing axonal regeneration and lacking tomacula have been observed (Sessa et al., 1997).

Electrophysiological Features in HNPP

The abnormal neurophysiological features of HNPP were described by Earl et al. (1964) and are consistent with demyelination, showing mildly prolonged motor and sensory nerve conduction velocities (NCV) in a symmetrical, generalized pattern. Conduction blocks are characteristic of affected segments in symptomatic nerves, especially over entrapment sites. NCV abnormalities are not restricted to those nerves affected by a palsy, but are found in a generalized pattern, even in asymptomatic gene carriers. In HNPP, the parameters most commonly affected include (1) increased distal motor latencies in the median nerves, (2) slowed sensory NCV in median nerves at the wrists, and (3) increased distal motor latencies and mild slowing of NCV in the peroneal nerves (Mouton et al., 1999).

Genetic Basis of HNPP

The genetic locus for HNPP maps to chromosome 17p12, where it is most commonly associated with a large, 1.4 Mb (megabase pair) DNA deletion (Chance et al., 1993). A duplication of exactly this 1.4 Mb region had previously been shown to be detrimental in CMT1A, the most common form of CMT1 (Lupski et al., 1991; Raeymaekers et al., 1991). In a study of 156 patients with HNPP, 84% were found to have the associated DNA deletion (Nelis et al., 1996). HNPP deletions and CMT1A duplications of different sizes have been observed, although they are very rare (Chapon et al., 1996). The 1.4 Mb

region, as well as the deletions and duplications of "aberrant" size, harbor the peripheral myelin protein (PMP)-22 gene. The *PMP22* gene encodes a 160-amino acid membrane-associated protein with a predicted molecular weight of 18 kDa that is increased to 22 kDa by glycosylation (Manfioletti et al., 1990). The PMP22 protein is localized to the compact portion of peripheral nerve myelin (Snipes et al., 1992), contains four putative transmembrane domains, and is highly conserved in evolution (Patel et al., 1992). Two different tissue-specific transcripts (neural and non-neural) of PMP22 arise through two alternatively used promoters (Suter et al., 1994).

Furthermore, other rare mutations have been reported in HNPP: two 2-basepair (bp) deletions, one single bp deletion, a single bp insertion, three point mutations, and two splice site mutations (Nicholson et al., 1994; Taroni et al., 1995; Pareyson and Taroni, 1996; Bort et al., 1997; Young et al., 1997; Haites et al., 1998; Lenssen et al., 1998; Sahenk et al., 1998; Bissar-Tadmouri et al., 2000; Meuleman et al., 2001).

Mechanism of the HNPP Deletion

The mechanism underlying the generation of the CMT1A DNA duplication and HNPP deletion has been the subject of numerous investigations. As the vast majority of the duplications and deletions in unrelated patients and in *de novo* duplication/deletion patients are the exact same size, it is hypothesized that a precise, recurring mechanism may account for the generation of the duplicated CMT1A chromosome and the deleted HNPP chromosome (Lupski et al., 1991; Raeymaekers, 1991; Raeymaekers et al., 1992; Chance et al., 1993; Wise et al., 1993; Reiter et al., 1998). As depicted in Fig. 2, it was proposed that the deleted chromosome in HNPP and the duplicated chromosome in CMT1A are the reciprocal products of unequal crossing-over, a likely mechanism for generating the DNA duplication and the deletion (Chance et al., 1993, 1994). A low-copy number repeat sequence (CMT1A-REP element) was identified flanking the 1.4 Mb segment on chromosome 17p12 (Pentao et al., 1992). The CMT1A-REP sequence, which is an intrinsic structural property of a normal chromosome 17, appears to mediate misalignment of homologous chromosomal segments during meiosis, with subsequent crossing-over to produce the CMT1A duplication or HNPP deletion.

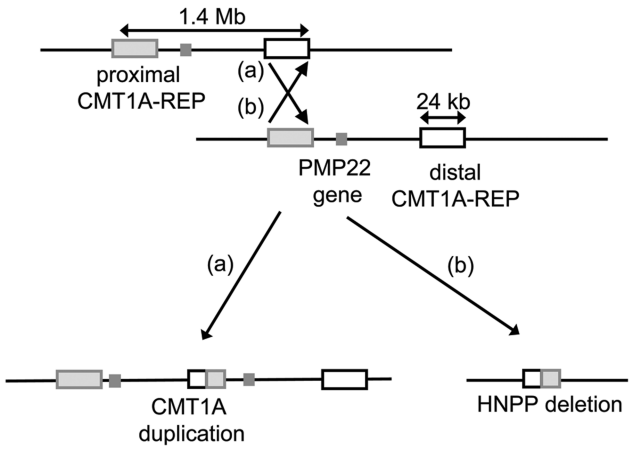

Fig. 2. Proposed mechanism of unequal crossing-over, leading to the CMT1A duplication and the HNPP deletion on chromosome 17p12. The proximal (shaded) and distal (unshaded) copies of the CMT1A-REP repeats have 99% sequence identity and may mediate misalignment of the chromosome 17 homologs during meiosis (top). One recombination pathway leads to the CMT1A tandem duplication (a) and the reciprocal recombination pathway leads to the HNPP deletion (b). Note that the CMT1A duplication chromosome has gained a 1.4-Mb segment and harbors two copies of the *PMP22* gene. Conversely, the HNPP-deleted chromosome has lost a 1.4-Mb segment from chromosome 17, including a copy of the *PMP22* gene.

Analysis of *de novo* rearrangements leading to either the CMT1A duplication or the HNPP deletion suggests that this process may be gender-dependent. Most *de novo* CMT1A duplications appear to be the result of unequal crossing-over between homologous chromosomes occurring during spermatogenesis. However, analysis of *de novo* HNPP deletions suggests that they are generated by unequal sister chromatid exchange during oogenesis (Lopes et al., 1997, 1998).

The origin of the CMT1A-REP repeat has been investigated through an analysis of homologous sequences in nonhuman primates. The CMT1A-REP repeat arose during primate evolution. Southern blot analysis indicated that the chimpanzee has two copies of a CMT1A-REP-like sequence, whereas the gorilla, orangutan, and gibbon have a single copy (Kiyosawa and Chance, 1996; Reiter et al., 1997). These observations suggest that the CMT1A-REP sequence appeared as a repeat before the diver-

gence of chimpanzee and human, but after gorilla and human around 6 to 7 million years ago (Kiyosawa and Chance, 1996; Keller et al., 1999).

Genetic Defects and Their Results/Effects in HNPP

In order to elucidate the exact cause of the HNPP phenotype, several facts have to be taken into account, the first of which is the 1.4 Mb deletion on chromosome 17p12. Because the majority of patients with HNPP carry this deletion, they are haplo-insufficient at this locus. They are, therefore, predicted to have only 50% of the normal expression of the *PMP22* gene in peripheral nerves, whereas CMT1A patients, carrying the 1.4-Mb duplication, would have a 50% increase in PMP22 expression. Indeed, various sural nerve biopsy studies showed that *PMP22* mRNA levels are increased/decreased in CMT1A/HNPP patients respectively, in comparison to unaffected persons (Yoshikawa et al., 1994; Schenone et al., 1997). An interesting question is whether *PMP22* is the only gene within this 1.4 Mb segment of which the dosage effect is contributing to the HNPP/CMT1A phenotype. A first hint was provided by the deletions and duplications of aberrant size, which did still include *PMP22* (Chapon et al., 1996). However, the different *PMP22* mutations in patients without the HNPP deletion (mentioned earlier) are the best proof of the critical, detrimental character of *PMP22* in the HNPP phenotype. A 1-bp insertion, as well as a 1-bp and two different 2-bp deletions in *PMP22* cause a frameshift, leading to an altered, nonfunctional protein (Nicholson et al., 1994; Taroni et al., 1995; Young et al., 1997; Lenssen et al., 1998; Bissar-Tadmouri et al., 2000). Two point mutations create an early stop codon, leading to a truncated protein (Pareyson and Taroni, 1996; Haites et al., 1998). Two splice mutations are predicted to cause exon skipping, also resulting in an altered, nonfunctional protein (Bort et al., 1997; Meuleman et al., 2001). The pathogenic mechanism of these *PMP22* mutations is hypothesized to be that they either mimic the dosage effect of the HNPP deletion by creation of a null allele, or dominant negatively interfere with the function of the remaining normal PMP22 protein. So far, only one point mutation has been reported to cause an amino acid substitution. This Val30Met is predicted to occur at the border of the first transmembrane domain and the extracellular loop. Patient nerve xenografts onto mice sciatic nerve showed a marked delay in the onset of myelination with an impairment of regenerative capacity and an increased neurofilament density, in comparison with nerve xenografts from unaffected individuals. These observations demonstrated the effect of the HNPP point mutation on the ability of Schwann cells to myelinate axons and pointed to perturbations in the axonal cytoskeleton resulting from a hypothesized interaction between the mutant Schwann cells and their axons. The function of *PMP22* will need to be clarified in order to reconcile the various mutational mechanisms involving this myelin component in HNPP and other associated peripheral neuropathies.

Genesis of the HNPP Phenotype

Several attractive hypotheses for the function of PMP22 have evolved from observations on the structure and expression of this critical myelin component. The *PMP22* gene is specifically expressed in Schwann cells and is identical to a growth arrest-specific gene, gas3 (Manfioletti et al., 1990; Suter et al., 1992; Spreyer et al., 1991; Welcher et al., 1991). A direct role in mitosis is suggested by the observation of impaired differentiation of Schwann cells in transgenic mice carrying increased copies of PMP22 as well as the observation that in NIH-3T3 cells an apoptotic phenotype may be induced through increased expression of PMP22 (Magyar et al., 1996; Fabbretti et al., 1995). Furthermore, a role in cell adhesion may be suggested because the PMP22 protein is known to carry an L2/HNK-1 carbohydrate adhesion epitome (Snipes et al., 1994). Unfolded separation of the inner myelin lamellae in HNPP may also suggest decreased cell adhesion when PMP22 is partially deficient (Yoshikawa and Dyck, 1991).

Animal Models for HNPP

A powerful tool to obtain more information on the pathomechanism of a disease is the study of animal models. Several animal models are available involving PMP22. According to the hypothesis that the pathomechanism of HNPP is a dosage effect, one might predict that the total absence of the *PMP22* gene would also cause demyelinating neuropathy, likely more severe than HNPP. Such patients have

not yet been described, but a murine model with this genotype has been described (Adlkofer et al., 1995). Homozygous deletion *(pmp22–/–* "knockout" mice develop a severe demyelinating neuropathy with very slow conduction velocities (7 m/s) and striking demyelination on pathological examination, including the evolution of demyelinated axons in *pmp22–/–* mice, as tomaculous myelin sheaths are replaced by thin to absent ones. Heterozygous deletion *($pmp22^{+/-}$)* mice are less affected, with minimal slowing of conduction velocities and little evidence of demyelination in biopsies, although numerous tomaculi eventually develop in affected nerve. These data confirm that the loss of the *pmp22* gene, and not another gene in the 1.5-Mb deletion, is detrimental for HNPP. The precise mechanism of demyelination in *pmp22+/–* mice is unknown. It can be speculated that these mice synthesize only half as much PMP22 protein as their wild-type counterparts, thereby altering the stoichiometry of the proteins in compact myelin, which in turn leads to demyelination. A naturally occurring bovine illness appears to resemble HNPP. This bovine neuropathy shows tomaculous neuropathy with the clinical features of weak shuffling gait, dysphagia, and chronic rumenal bloat (Hill et al., 1996).

Therapy in Patients With HNPP

There is no specific treatment for HNPP. The current therapy consists of conservative management and symptom-easing measures. The first, and perhaps most important element of the treatment is early detection and diagnosis of the disease. The knowledge that HNPP is often triggered by compression or trauma of the peripheral nerves gives the patient the possibility to avoid those movements or joint positions that most often evoke an HNPP episode. As mentioned earlier, diagnostic guidelines have been reported previously (Dubourg et al., 2000). Furthermore, several genetic tools have been designed for a reliable diagnosis (Raeymaekers, 1992; LeGuern et al., 1996; Shaffer et al., 1997). These techniques have even been used for the prenatal diagnosis of CMT1A (Navon et al., 1995; Kashork et al., 1999) and could therefore eventually also be used in genetically diagnosed HNPP patients.

The second element of the treatment is conservative management to avoid evoking HNPP episodes (Liebelt and Parry, 2000). Overall, two basic rules apply: (1) excessive force or repetitive movements should be reduced to a minimum; (2) extreme, awkward, or static joint positions should be avoided. Because the wrist, elbow, knee, and shoulder are the most vulnerable sites, special management rules can be considered. At the wrist (carpal tunnel), episodes are mostly caused by forceful gripping, repetitive movements, or extreme wrist bending. Tools and gloves can be used to improve grip, and wrist splints can prevent extreme wrist bend during the night. At the elbow, episodes are mostly triggered by repetitive or sustained bending and by habitual leaning on the elbows. Management consists of elbow pads to reduce pressure, a headset for use during long telephone conversations, and eventually an elbow splint during the night. The most frequent trigger at the knee is habitual crossing of the legs. A lower leg brace can stabilize ankles in case this causes recurrent stretch injury at the knee. The complexity of the brachial plexus means that many factors can evoke an HNPP episode at the shoulder. Avoiding overhead work or sleeping with the arms overhead, and maintaining a good posture can reduce the risk.

A single case report mentions surgery to reduce pressure on the ulnar nerve, however, a follow-up study is not yet available (Taggart and Allen, 2001). Although various surgical treatments of CTS exist (Gerritsen et al., 2001), no reports have been published on such surgery in patients with HNPP. Given the vulnerability of the peripheral nerves in patients with HNPP, surgery is generally considered unfavorable.

As HNPP is mainly caused by the dosage effect of *PMP22* owing to the 1.5-Mb deletion on chromosome 17p12, one could reason that increasing the gene dosage might rescue the defect. The reverse would be true for the CMT1A patients carrying a duplication increasing the PMP22 expression. However, several hurdles have to be overcome. First of all, increasing *PMP22* expression requires either the stimulation of the endogenous *PMP22* or a gene transfer introducing another copy of the *PMP22* gene. Further study of the *PMP22* promoters and the recent discovery of a positive regulatory element of *PMP22* (Hai et al., 2001) could provide a future avenue for therapeutic research. A gene transfer to correct the shortage of PMP22 has the difficulty of the limited accessibility of the peripheral nerves. Furthermore, this strategy would need to

correct the *PMP22* expression without increasing the dosage too much, which would lead to the CMT1A phenotype. Although several animal models are available to study the possibilities of gene therapy, it might take years before a safe and efficient therapy became available.

Chemotherapeutic agents known to affect peripheral nerves should be used with great caution in patients with inherited neuropathies, and in the case of vincristine, total avoidance is strongly advised. A number of reports have documented the serious consequences of vincristine treatment administered in standard oncological dosages in patients with CMT, including well-documented CMT1A and CMT2. The complications ranged from the precipitation of severe neuropathies in clinically asymptomatic at-risk individuals, through degrees of marked clinical worsening, and even death as a result of respiratory collapse. Acute deterioration leading to severe weakness, inability to ambulate, and sensory disturbances has also been observed in a patient with occult HNPP, suggesting that patients with this diagnosis should not be given vincristine therapy (Kalfakis et al., 2002).

Hereditary Neuralgic Amyotrophy

The Brachial Plexus and Neuralgic Amyotrophy

The brachial plexus is one of the largest structural components of the peripheral nervous system, providing innervation to the upper limbs and a major portion of the pectoral girdle (Harris, 1939). The brachial plexus is a complex neural network consisting of more than 100,000 axons receiving contributions from spinal roots C5, C6, C7, C8, and T1 (Bonnel, 1977). This network gives rise to the principal nerves of the upper limb including the ulnar, median, and radial nerves. Impairment of the brachial plexus leads to various combinations of pain, paralysis, amyotrophy (muscle atrophy), and sensory disturbances. Because of its structural complexity and location amidst a number of other movable anatomical structures in the thorax, the brachial plexus is especially vulnerable to physical insult. Most frequently, brachial plexus dysfunction results from traumatic injuries, such as traction injuries (e.g., Erb or Klumpke palsies) or gunshot wounds, malignant invasion or radiation-induced sequelae (Wilbourn, 1993).

For cases in which a specific, nontraumatic etiology for brachial plexus neuropathy cannot be identified, the term "neuralgic amyotrophy" is applied. Although there are numerous synonymous terms for this likely heterogeneous condition including, "acute brachial plexitis," "idiopathic brachial neuritis," "Parsonage-Turner syndrome," and many others, neuralgic amyotrophy avoids assumptions with respect to etiology and specific site perturbed within the plexus (Wilbourn, 1993). Such cases of idiopathic neuralgic amyotrophy (INA) occur as sporadic instances and are usually thought to be noninherited. INA occurs at any age and has an estimated population incidence of 1.64/100,000–3/100,000 (Beghi et al., 1985; MacDonald et al., 2000), possibly an underestimation, as cases of neuralgic amyotrophy may be under diagnosed or misdiagnosed as other illnesses including bursitis and cervical spondylosis.

INA is clinically characterized by the sudden onset (in most cases) of severe pain in the shoulder girdle, followed paralysis or weakness and sensory disturbances in the upper limbs. Autonomic dysfunction may also occur. The intense painful symptoms typically last for up to 2 wk and may give way to a chronic aching pain in the limb persisting for months. Amyotrophy typically develops within 2 wk of the onset of severe pain (Parsonage and Turner, 1948). It should be emphasized that the pain associated with INA may be unusually debilitating and in some cases even refractory to narcotic medications (Wilbourn, 1993). Generally the prognosis for recovery of neurological function in INA is favorable. One long-term follow-up analysis of 99 cases found that 80% of patients had recovered functional use of the affected limb by 2 yr and more than 90% had recovered by 4 yr (Tsairis et al., 1972).

Clinical Features of Hereditary Neuralgic Amyotrophy

An uncommon, inherited form of neuralgic amyotrophy exists. Hereditary neuralgic amyotrophy (HNA) with predilection for the brachial plexus (HNA, OMIM No. 162100; Mckusick, 2000) is an autosomal-dominant disorder that causes recurrent attacks of pain, weakness, and sensory disturbances in a brachial distribution frequently beginning in childhood (Windebank, 1993; Klein and Windebank,

2005). HNA is a member of the hereditary recurrent, focal neuropathies, that are a subgroup of the hereditary peripheral neuropathies. The episodes associated with HNA may develop in infancy, childhood, or adulthood, but are most common in the second or third decade of life. Similar to sporadic INA, HNA episodes may be triggered by periods of physical, immunological, or emotional stress. Females appear to have a predilection for postpartum attacks, suggestive of a specific immune dysregulation during this period. The underlying pathogenesis remains unknown for HNA and INA, but antecedent events suggest a possible autoimmune etiology. Prior strenuous usage of the upper limbs has been reported to precipitate attacks for both forms, suggesting that local trauma or ischemia of the brachial plexus resulting from compression between muscle groups might also underlay the plexopathy (Taylor, 1960). Associations with immunizations, recent viral or bacterial illnesses, and parturition are seen and raise a possible role of the immune system (Ungley, 1933; Tsairis, et al., 1972; Geiger et al., 1974). Emotional stresses have been observed and may be important factors precipitating a plexopathy in genetically predisposed individuals (Bardos and Samodska, 1961).

As mentioned earlier, neuralgic amyotrophy occurs more commonly as an idiopathic, sporadic form of brachial neuritis, INA (Parsonage and Turner, 1948; Wilbourn, 1993). Given the overlap in clinical presentation between HNA and INA, there are relatively few clinical features that might distinguish patients, other than an obvious presence of multiple affected family members in HNA. HNA is typically a recurrent syndrome, whereas recurrences are rare in INA. Additionally, patients with HNA may experience an episode of plexopathy at an earlier age, or even present at birth with features indistinguishable from an Erb or Klumpke paralysis (Dunn et al., 1978). For INA, the presentation is usually later and episodes during the first decade of life are rare. It is possible that some cases of brachial neuritis diagnosed as INA on the basis of their lacking a family history may represent HNA, in particular those having an early onset and experiencing multiple episodes.

Interestingly, besides brachial neuritis there are a few physical features associated with some families that may distinguish HNA from INA. Reported features have included short stature, hypotelorism, long nasal bridge, small oral openings, cleft palate, epicanthal folds, facial asymmetry, and partial syndactyly (Jacob et al., 1961; Gardner and Maloney, 1968; Airaksinen et al., 1985), raising the question of a role for the HNA gene in morphogenesis. As pointed out by several authors, the facial features of patients with HNA bear a striking resemblance to portraits painted by Modigliani (*see* Fig. 3; Dunn et al., 1978). These features may help distinguish isolated patients with HNA from those with noninherited forms and indicate that the pathological actions of the HNA gene are not limited to the brachial plexus.

As discussed earlier, the long-term prognosis for eventual recovery of limb function in INA is favorable, however, there is evidence suggesting that the prognosis of individuals in HNA families may not be as favorable. This difference may reflect the consequence of repeated episodes of brachial neuritis in HNA. An analysis from the Netherlands studied 17 patients with HNA who were followed for an average period of 26 yr (van Engelen et al., 1997, van Alfen et al., 2000). The mean number of attacks of brachial neuropathy per patient was five episodes. On follow-up examinations, all 17 patients still suffered loss of strength in a brachial plexus distribution and 4 additionally had weakness in a lumbosacral plexus distribution. Interestingly, ongoing studies by this same group describe two clinical patterns (van Alfen et al., 2000). The first consisted of a more classical relapsing-remitting pattern of HNA attacks; the other included patients with a more chronic, undulating form of HNA.

Electrophysiological and Pathological Features in HNA

Electrophysiological studies found evidence for axonal interruption at the level of the brachial plexus in the affected limb (Tsairis et al., 1972). Distal to the plexus, motor, and sensory NCVs are either normal or mildly prolonged. Pathological studies demonstrated axonal degeneration in nerves distal to the plexus abnormality but, importantly, tomaculous changes are not present in HNA (Tsairis et al., 1972).

Although both HNA and INA have long been presumed to be inflammatory disorders, very little primary evidence for such a basis exists and no specific role for the immune system in the pathogenesis of either has been explored. In both HNA and INA, accumulating evidence for an inflammatory response may be found on nerve biopsies. Epineural perivascular mononuclear cell infiltrates were found

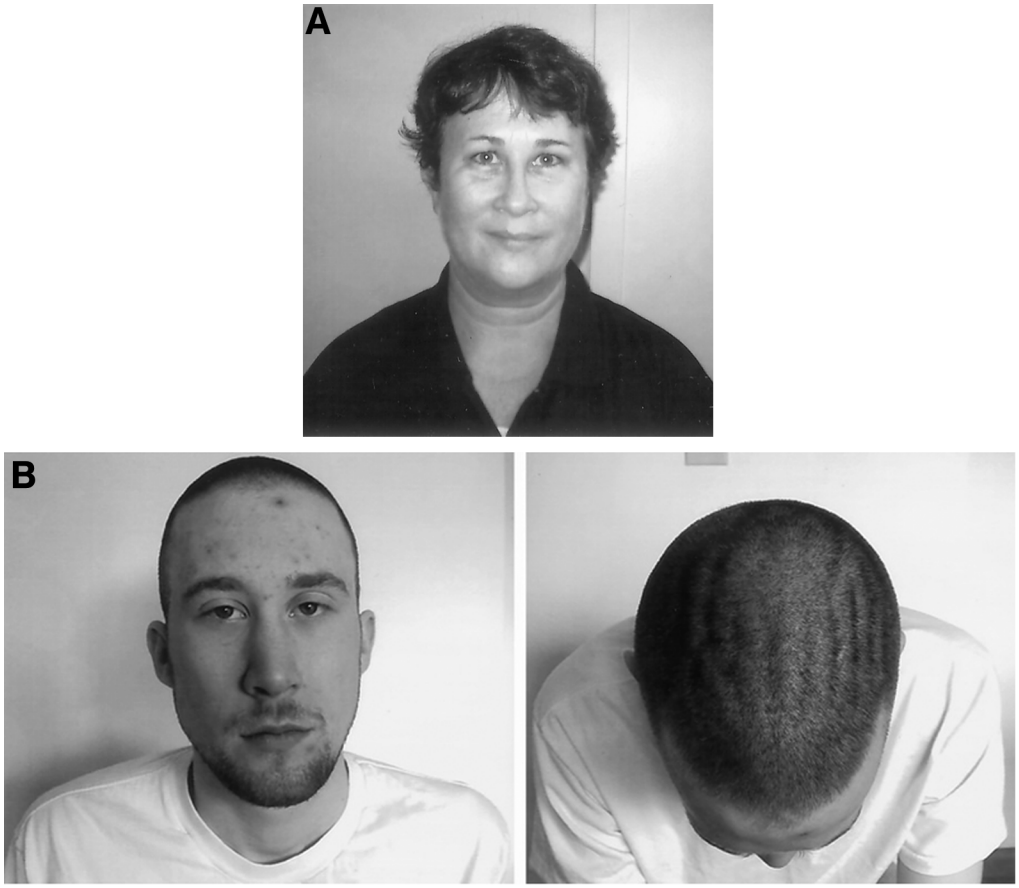

Fig. 3. Portraits of two individuals with HNA. **(A)** Female, 47 yr, with narrow interpupillary distance and pronounced neck folds. **(B)** Male, 19 yr, with narrow interpupillary distance and cutis verticis gyrata of the scalp.

in superficial radial nerve biopsies taken from three of four patients with recent attacks of brachial neuritis associated with HNA (Klein et al., 2002). Other reports have documented inflammatory infiltrates in peripheral nerve biopsies, including biopsies of the brachial plexus in INA, some suggesting microvasculitis (Cusimano et al., 1988; Suarez et al., 1996; Dyck et al., 2001). Specific brachial plexus uptake of Gallium-67 citrate has been reported by scintigraphy, suggesting that the majority of acute inflammation is located proximally (Hsieh and Chang, 2003). Clearly, a role for the immune system in the pathogenesis of INA and HNA needs further investigation.

Although the serious consequences of the mutant HNA gene affect peripheral nervous system function, it cannot be assumed that the primary or exclusive site of HNA gene expression resides within the nervous system. It is possible that the critical tissues involved in HNA pathogenesis are actually non-neural, and HNA may be crucial to establish normal structural relationships during development. For example, vascular endothelium, connective tissues, or other supportive structures encasing the brachial plexus and its nutrient vessels might be critical sites of HNA gene expression. Support for this more generalized developmental hypothesis includes the presence of mildly dysmorphic facial features of hypotelorism, short palpebral fissures, and palatal clefts mentioned earlier (Jacob et al., 1961; Gardner and Maloney, 1968; Windebank, 1993).

Mapping a Gene for HNA

Early attempts to map a gene for HNA by linkage studies with serum and red blood cell polymorphic

Table 1
Differential Criteria for HNPP and HNA

	HNPP	HNA
Neuropathy	Generalized with focal episodes	Focal episodes, not generalized
Localization	Mainly entrapment sites	Brachial plexus, rarely lumbosacral
Phenotype	Painless in most cases	Painful
Preceding events	Compression/trauma	Infections, immunizations, puerperium, stress, exercise
Electrophysiology	Reduced NCV, conduction block over entrapment sites	Normal to slightly reduced NCV in affected nerves, normal elsewhere also measurable in unaffected nerves
Histopathology	Tomacula	Minor, focal axonal degeneration distal to affected brachial plexus, normal elsewhere
	De- and re-myelination	
Genetics	1.4Mb deletion at 17p12 or rare point mutations in PMP22	Linked to 17q25, mutations in *SEPT9*
		Genetic heterogeneity

NCV, nerve conduction velocity.

genetic markers found no linkage associations (Arts et al., 1983). After excluding about 30% of the genome in two HNA families, linkage to four short tandem repeat (STR) markers on chromosome 17q24-q25 was found (Pellegrino et al., 1996). This observation was confirmed in a German family, using the same STR markers (Wehnert et al., 1997). The analysis of six STR markers in an extended pedigree of Turkish origin delineated the HNA locus to a 16-cM region between the STR markers *D17S1301* and *D17S784* (Stögbauer et al., 1997). The analysis of six HNA families refined this region to 4 cM between *D17S1603* and *D17S802* and suggested that HNA could be genetically homogeneous. Large chromosomal rearrangements were ruled out by G-banding and the HNA locus was assigned to the chromosomal band 17q25 by polymerase chain reaction analysis of STR markers on a human/mouse somatic cell hybrids (Pellegrino et al., 1997). The analysis of additional STR markers and additional HNA families further refined the locus to 3.5 cM between *D17S785* and *D17S802*. An informative recombination in an unaffected individual reduced this region with a likelihood of 95% to a 2.2 cM region between *D17S785* and *D17S939* (Meuleman et al., 1999). A common disease- linked haplotype constructed with markers from a 3.5 cM interval was observed in six of seven American pedigrees (Watts et al., 2002).

One study from the Netherlands suggested that there may be two different clinical phenotypes within HNA regarding painful episodes associated with brachial neuritis, one presenting with "classic" relapsing-remitting symptoms, and the other showing a chronic undulating pattern (van Alfen et al., 2000). The "classic" HNA phenotype demonstrated linkage to the HNA locus on chromosome 17q25, whereas the chronic undulating phenotype was not linked to this region. However, four other HNA families that have been shown to be unlinked to chromosome 17q25, showed the classical, remitting-relapsing pattern suggesting that locus heterogeneity cannot account for this phenomenon (Kuhlenbäumer et al., 2001; Watts et al., 2001).

Mutation of the SEPT9 *Gene in HNA*

Recently, mutations in the septin 9 gene (*SEPT9*) were identified in six chromosome 17q25-linked pedigrees establishing mutations in this gene as the molecular basis of HNA (Kuhlenbaumer et al., 2005). HNA is the first monogenetically inherited disease caused by mutations in a gene of the septin family. Septins are implicated in the formation of the cytoskeleton and cell division and have been associated with tumorigenesis. The SEPT9 protein forms filaments and colocalizes with cytoskeletal elements such as actin and tubulin, suggesting a structural

function in the cell (Surka et al., 2002; Nagata et al., 2003). Finally, generalized overexpression of *Sept9* was described in mouse models of human breast cancer and in human breast cancer cell lines (Montagna et al., 2003). Mutations in *SEPT9* appear to be the primary cause of HNA. Further studies will be needed to provide critical insights into the molecular pathogenesis of the unique combination of a recurrent hereditary neuropathy triggered by environmental factors.

Conclusion: Differential Diagnosis of HNPP vs HNA

HNPP may be clinically confused with HNA. As mentioned earlier, a brachial plexus neuropathy is sometimes the only clinical sign of HNPP (ørstavik et al., 2001). Approximately 10% of HNPP patients have had involvement of the brachial plexus, and in some patients a brachial plexopathy is the initial or only expression of HNPP. Furthermore, both diseases were earlier speculated to represent the same condition, or allelic variants of the same locus (Bradley et al., 1975; Madrid and Bradley, 1975; Martinelli et al., 1989), justifying the need for differential diagnostic tools to distinguish between HNPP and HNA. Almost three studies have shown that HNPP and HNA are distinct clinical, electrophysiological, and genetic diseases (Chance et al., 1994; Gouider et al., 1994; Windebank et al., 1995). Diagnostic guidelines for both HNPP and HNA have been published (Dubourg et al., 2000; Kuhlenbaumer et al., 2000). The main differential criteria are summarized in Table 1.

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