



# A rare cause of brachial plexopathy: hereditary neuralgic amyotrophy

Brakiyal pleksopatının nadir bir nedeni: herediter nevralkjik amiyotrofi

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## Abstract

Neuralgic amyotrophy is characterized by recurrent, painful, unilateral neuropathy involving mainly the upper brachial plexus followed by muscle weakness and muscle wasting. There are two forms: idiopathic and hereditary. Hereditary neuralgic amyotrophy is an autosomal dominant disease that is often linked to a mutation of SEPT9, a gene of the Septin family. The phenotypic spectrum of the disease may include hypotelorism, cleft palate, and other minor dysmorphisms. The age of onset is from infancy to adulthood. Hereditary neuralgic amyotrophy can be triggered by external stimuli such as infections, vaccinations, cold, stress, surgery, and strenuous exercise. Here, we report a six-year-old girl who was found to have mutation in the SEPT9 gene when she presented with recurrent attacks of painful brachial plexopathy following vaccinations, and was diagnosed as having hereditary neuralgic amyotrophy.

**Keywords:** Hereditary neuralgic amyotrophy, SEPT 9, vaccination

## Öz

Nevralkjik amiyotrofi, başlıca üst brakial pleksusu tutan ve sonrasında kas güçsüzlüğü gelişen, tekrarlayıcı, ağrılı, tek taraflı nöropatidir. İdiyopatik ve herediter olmak üzere iki formu vardır. Otozomal dominant formuna Herediter Nevraljik Amiyotrofi adı verilir ve septin ailesinin bir geni olan SEPT9 mutasyonu ile bağlantılıdır. Hastalığın fenotipik spektrumu hipotelorizm, yarı damak ve diğer minor dismorfizmleri içerebilir. Başlangıç yaşı bebeklikten yetişkinliğe kadar herhangi bir dönemde olabilir. Herediter nevralkjik amiyotrofi, enfeksiyonlar, aşular, soğuk, stres, ameliyat, şiddetli egzersiz gibi dış uyaranlarla tetiklenebilir. Burada, aşılamalardan sonra ağrılı brakiyal pleksopati ataklarının tekrarlama nedeniyle SEPT9 geninde mutasyon saptanan ve herediter nevralkjik amiyotrofi tanısı konulan altı yaşındaki bir kız olgu sunulmuştur.

**Anahtar sözcükler:** Aşılama, herediter nevralkjik amiyotrofi, SEPT9

## Introduction

Neuralgic amyotrophy (NA) is a recurrent, painful, unilateral neuropathy, which mainly involves the upper brachial plexus and leads to the development of muscle weakness subsequently. The more prevalent and sporadic type is called idiopathic neuralgic amyotrophy (INA), also known as “Parsonage Turner Syndrome.” The autosomal dominant form is named hereditary neuralgic amyotrophy (HNA) (1). Hereditary neuralgic amyotrophy is associated with a mutation in the SEPT9 gene, which is a member of

the Septin family (2). The onset may occur at any age from infancy to adulthood (3). Both INA and HNA may be triggered by external stimuli including infection, vaccination, cold, strenuous exercise, and stress (1, 4). In the differentiation of hereditary neuralgic amyotrophy from INA, onset in the first or second decade of life, positive familial history, accompanying dysmorphic characteristics, a course with recurrences and presence of pain lasting longer than two months are important (5). The dysmorphic characteristics found in some patients with hereditary neuralgic amyotrophy include hypotelorism, blepharophimosis, cleft

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uvula, cleft palate, epicanthal fold, mild ptosis, microstomy, dysmorphic ears, and partial syndactyly (1, 5).

### Case

A six-year-old female patient presented to our outpatient clinic with pain in the right shoulder and arm, numbness in the fingers of the right hand, and inability to move the right arm, which had lasted for two months. Measles-mumps-rubella (MMR) vaccine had been administered five days before the symptoms began. In her history, it was learned that she had a similar painful episode in the left arm three days after a diphtheria-pertussis-tetanus (DTaP) vaccination one year ago. This episode lasted for six months and recovered completely with physical therapy. A neurologic examination revealed pain induced by movement in the right arm, reduced biceps reflex on the right side, a muscle strength of 3/5 in the right upper extremity, and atrophy in the right forearm. Laboratory tests including complete blood count, erythrocyte sedimentation rate, creatinine kinase, liver enzymes, vitamin B12 levels and C3 and C4 levels were found to be within normal limits. Viral tests and antinuclear antibody (ANA) were found to be negative. Electromyography (EMG) revealed partial dysfunction in the lower truncus of the right brachial plexus and dysfunction in the middle and upper trunci. Brachial plexus magnetic resonance imaging (MRI) was found to be normal.

The diagnosis of reflex sympathetic dystrophy was excluded with electromyography findings and recurrent extremity pain. Gabapentin treatment was initiated for pain. HNA was considered because of recurrent brachial plexopathy episodes and accompanying hypotelorism. It was noted that the patient's mother also had hypotelorism. Therefore, the mother was interrogated in terms of similar episodes, but no history of plexopathy was defined. Gene analysis was performed for HNA because of a history of recurring plexopathy following vaccination and presence of dysmorphic characteristics.

A heterozygous mutation was found in NM\_006640.4p.R88W (c.262C>T) in the SEPT9 gene. Gene analyses were performed in the patient's mother and brother because their facial appearances were similar to the patient's facial appearance, and the same mutation was detected (SEPT9 gene NM\_006640.4p.R88W (c.262C>T)). Two months after our patient's diagnosis, a brachial plexopathy episode occurred for the first time in the mother following an upper respiratory tract infection. Recovery was observed in the mother following steroid treatment and physical therapy. Continuance of the vaccination schedule was recommended for the younger sibling. Written consent was obtained from the patient's mother for case presentation.

### Discussion

Hereditary neuralgic amyotrophy is an autosomal dominant disorder characterized by recurrent neuropathy episodes that primarily affect the brachial plexus and thus results in muscle weakness (1, 6). Some patients may have dysmorphic characteristics including hypotelorism, blepharophimosis, mild ptosis, epicanthal fold, microstomy, dysmorphic ears, cleft uvula, cleft palate, long nasal bridge, partial syndactyly in the fingers or toes, circular skin creases and short stature (1, 5). Laccone et al. (1) described the phenotypical characteristics of HNA in a family who were diagnosed as having HNA in three generations. In the differential diagnosis of the presented patient, hypotelorism found in the patient's mother and brother played an important role.

The SEPT9 gene is a member of the Septin family, which is associated with the regulation of cytotogenesis and cellular turnover. Hereditary neuralgic amyotrophy is associated with a mutation in the Septin-9 protein (SEPT9) in the 17q25 chromosome and with some recurring patterns that change linkage and enfold microtubules (6). The mechanism of how these mutations cause brachial neuritis and dysmorphic characteristics is not known (1). In the genetic analyses of our patients, a heterozygous mutation was found in the SEPT9 gene.

Large series and case reports have reported that trauma, simple or strenuous exercise, pregnancy, surgery, exposure to cold, numerous bacterial and viral infections and vaccines facilitate episodes (4, 5). Many vaccines, especially the flu vaccine, have been reported to be associated with brachial plexopathy (7). Both episodes in our patient developed secondary to vaccination (the first episode following DaPT vaccine and the second episode following MMM vaccine). However, this should never be considered a drawback for vaccination. Therefore, it was recommended that the vaccination schedule should be continued for the patient and her sibling.

Van Alfen et al. (3) reported a total of 246 cases of neuralgic amyotrophy and a diagnosis of HNA was made in 47 of these cases. In that study, the mean age of onset of HNA was reported as 28.4 (range, 3-56.3) years. The first episode occurred in childhood in 22.7% of patients. Electromyography findings supported the diagnosis in all patients. Brachial plexus magnetic resonance imaging (MRI) could be performed in 50 patients; T2 hyperintense lesions were found in two of these patients and focal thickening was observed in the brachial plexus in one patient. Similar to the literature, brachial plexus MRI was found to be normal in our patient and EMG findings supported the diagnosis of brachial plexopathy. The rate of recurrence was re-

ported to be 74% in hereditary neuralgic amyotrophy (3). Although van Alfen et al. (3) reported that the mean time between plexopathy episodes was six years (300 weeks), our patient had two episodes in a short period (one year).

Treatment of neuralgic amyotrophy depends on the phase of the disease. When treatment is initiated immediately after the onset of the episode, corticosteroid treatment is considerably useful. Corticosteroids shorten the painful phase and provide recovery. However, it is difficult to make a diagnosis of NA in clinical practice and it takes time for patients to reach physicians who are familiar with NA. Actually, only patients with recurrence can find the opportunity to benefit from corticosteroid treatment (5). We did not administer corticosteroid treatment because our patient presented two months after the onset of the episode. Gabapentin treatment was initiated for controlling pain and was effective. Early initiation of corticosteroid treatment was possible during the episode of the mother because of the known diagnosis of HNA.

In cases of NA with typical history and typical findings on physical examination, there is no other diagnosis to be considered in the presence of the association of symptoms and signs. Neurologic or non-neurologic disorders should be considered in the differential diagnosis in patients presenting with acute pain in the shoulder and upper arm region. In the differential diagnosis, cervical radiculopathy, complex regional pain syndrome involving the shoulder or arm and mononeuritis complex (peripheral nervous system vasculitis) should be considered. Electromyography and nerve conduction studies are helpful in differentiating radiculopathies (3, 5, 8). The main differential diagnosis is hereditary or idiopathic neuralgic amyotrophy in patients presenting with painful brachial plexopathy with multiple foci and acute onset. Hereditary neuralgic amyotrophy is differentiated from INA with familial recurrence, earlier age of onset, more severe pain in the acute stage, more frequent involvement of the nerves other than the brachial plexus, a higher rate of recurrence, and higher rate of disability (3, 5). In our patient, HNA was considered because of the age of onset, presence of severe pain in the acute stage, and recurrence with an interval of one year.

Hereditary neuralgic amyotrophy is a rare disease with an unknown prevalence. Therefore, it should be included in the differential diagnosis in pediatric patients who develop recurrent brachial plexopathy following vaccination.

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