

# Neuralgic amyotrophy: an underrecognized entity

Journal of International Medical Research

49(4) 1–7

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DOI: 10.1177/03000605211006542

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## Abstract

Neuralgic amyotrophy (NA) is markedly underdiagnosed in clinical practice, and its actual incidence rate is about 1 per 1000 per year. In the current article, we provide an overview of essential information about NA, including the etiology, clinical manifestations, diagnostic investigations, differential diagnosis, treatment, and prognosis. The causes of NA are multifactorial and include immunological, mechanical, or genetic factors. Typical clinical findings are a sudden onset of pain in the shoulder region, followed by patchy flaccid paralysis of muscles in the shoulder and/or arm. A diagnosis of NA is based on a patient's clinical history and physical examination. Gadolinium-enhanced magnetic resonance imaging and high-resolution magnetic resonance neurography are useful for confirming the diagnosis and choosing the appropriate treatment. However, before a diagnosis of NA is confirmed, other disorders with similar symptoms, such as cervical radiculopathy or rotator cuff tear, need to be ruled out. The prognosis of NA depends on the degree of axonal damage. In conclusion, many patients with motor weakness and pain are encountered in clinical practice, and some of these patients will exhibit NA. It is important that clinicians understand the key features of this disorder to avoid misdiagnosis.

## Keywords

Neuralgic amyotrophy, motor weakness, pain, diagnosis, treatment, narrative review

Date received: 2 March 2021; accepted: 8 March 2021

## Introduction

Neuralgic amyotrophy (NA) was first described by Feinberg in 1897.<sup>1</sup> Patients present with sudden-onset pain in the shoulder region, followed by patchy flaccid paralysis of muscles in the shoulder and/or arm.<sup>2</sup> NA is also known as “Parsonage–Turner syndrome” after the names of the

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researchers who first reported this disorder.<sup>2</sup> Many cases of NA involve the brachial plexus, and NA is thought to develop because of sudden inflammation; hence, this disorder is also known as “brachial plexitis.” After the report by Parsonage et al., several other reports of NA have been published.<sup>2–5</sup> Although NA affects the brachial plexus, this disorder also affects various other peripheral nerves, such as the suprascapular, long thoracic, phrenic, anterior interosseous, and radial nerves.<sup>6–10</sup>

In many studies, NA has been described as a rare disorder. However, recent reports suggest that NA is significantly underdiagnosed in clinical practice and has an actual incidence rate of about 1 in 1000 per year.<sup>11</sup> Although individuals of any age can be affected, NA onset usually occurs between 20 and 60 years.<sup>12</sup> The pediatric incidence of NA varies according to age (from 3 days to 15 years of age) and has a biphasic peak of onset; the first is in the neonatal period, and the second peak is in adolescence (7 to 15 years).<sup>12</sup> Patients in the acute stage of NA usually visit primary local clinics or emergency rooms, and NA is often misdiagnosed as rotator cuff tendinopathy, cervical radiculopathy, glenohumeral bursitis, or muscle strain.

In the current article, we review essential information about NA and discuss its accurate diagnosis and appropriate treatment.

## **Etiology**

Although the exact pathophysiological mechanisms of NA have not yet been established, multiple factors are involved. Immunological, mechanical (e.g., repetitive strain or strenuous exercise), and genetic factors are all known to be associated with the development of NA.<sup>13</sup>

## **Immunological factors**

Over 50% of patients with NA have a history of an event that triggered the immune system, such as infection, vaccination, surgery, pregnancy, or physical or mental stress.<sup>14</sup> It has been reported that about 10% of patients with NA have a concomitant hepatitis E virus infection.<sup>15,16</sup> In previous studies, peripheral nerve biopsies in patients with acute or subacute NA revealed epineural perivascular T-cell infiltrates.<sup>17</sup> In addition, CD8+ T-lymphocytes, CD68+ macrophages, and CD20+ B-lymphocytes have been reported to infiltrate the surrounding epithelial and endothelial vessels in the involved peripheral nerves.<sup>18</sup> Moreover, hyperintensity of the involved peripheral nerves on T2-weighted magnetic resonance imaging (MRI) in the acute phase of NA also supports the hypothesis that immunological factors are involved in the occurrence of NA.<sup>19</sup>

## **Mechanical factors**

In one study, significantly more patients with NA reported antecedent events that can cause mechanical stress on the peripheral nerves, such as participation in sports or heavy labor, compared with the general population.<sup>14</sup> In this study, approximately 10% of the patients with NA had a history of strenuous upper extremity exercise.<sup>14</sup> In NA, the most commonly involved peripheral nerve is the brachial plexus (especially the upper trunk), which supports the hypothesis that mechanical factors can contribute to the occurrence of NA.<sup>20</sup> The shoulder joint is one of the most mobile joints in the human body, and allows a wide range of movements.<sup>21</sup> This leads to the wear and tear of blood–nerve barriers around the brachial plexus, and a weakened blood–nerve barrier allows immune factors or cells to come into contact with the brachial plexus.<sup>13</sup> In addition, studies have reported

cases of hourglass-like constriction neuropathy caused by the twisting of a peripheral nerve.<sup>8,22</sup> This disorder can be diagnosed using high-resolution magnetic resonance neurography. Although it remains debatable, in our opinion, hourglass-like constriction neuropathy seems to be a subtype of NA.

### Genetic factors

In most patients with NA, no genetic alterations have been identified. However, some patients experience recurrent attacks of NA; these cases can be linked to genetic susceptibility, and are referred to as hereditary NA.<sup>14,23</sup> Hereditary NA is a rare autosomal dominant disorder that is about 10 times less common than idiopathic NA.<sup>24</sup> Approximately 50% of patients with hereditary NA have an associated point mutation or duplication of the susceptibility gene *SEPT9* on chromosome 17q25.3.<sup>25–27</sup> In addition, 10% of patients with NA have a positive family history of NA,<sup>11</sup> which indicates that genetic factors are associated with the development of NA.

### Clinical presentation

NA often involves only one limb; however, in 10% to 30% of patients, NA is bilateral (typically in an asymmetric fashion).<sup>14</sup> The initial symptom of NA in 96% of patients is an acute onset of pain (within a few hours) in the shoulder girdle.<sup>13</sup> This pain usually radiates to the neck, arm, and forearm. A small proportion (1%–2%) of patients with NA have pain in a restricted area, such as the neck, scapula, or upper arm only.<sup>14</sup> In about 60% of cases, the episodes initiate at night.<sup>13,14</sup> Many patients therefore wake up early in the morning with severe pain, which then gains maximal intensity over the next few hours. The pain is usually of a “sharp”, “stabbing”, “throbbing”, or “aching” nature, and its intensity is typically

relentless, with a numerical rating scale score  $\geq 7$  (0: no pain, 10: worst pain that a human can imagine).<sup>13,14</sup> The pain is commonly aggravated by movement of the shoulder or limbs.<sup>13,14</sup> The duration of pain caused by NA usually varies from several hours to several weeks before it subsides, and the average duration of pain is 4 weeks. In approximately 5% of patients, the pain resolves within 24 hours, while in 10% of patients, the pain persists for more than 2 months.<sup>13,14</sup>

Muscle weakness is a conspicuous finding in NA, and occurs days to weeks after the onset of symptoms.<sup>13,14</sup> It characteristically worsens when the pain becomes less severe. After the onset of pain, weakness appears within 24 hours in about 30% of patients, and it occurs within 2 weeks of the pain initiation in approximately 70% of patients. In approximately 30% of patients, weakness is manifested  $>2$  weeks after the initiation of pain. In about 70% of patients, weakness occurs in the muscles innervated by the upper trunk of the brachial plexus, either with (50%) or without (20%) involvement of the muscles innervated by the long thoracic nerve.<sup>13</sup> The next most common location in NA is the middle and lower trunk of the brachial plexus. In addition, the lumbosacral plexus and the anterior and posterior interosseous, cranial, and phrenic nerves are peripheral nerves that are frequently involved.<sup>6–10</sup>

Approximately 70% to 80% of patients manifest sensory deficits during episodes of NA; however, these deficits are usually mild compared with the degree of weakness.<sup>14</sup> Hyperesthesia and/or paresthesia are the most common sensory symptoms of NA, and hypoesthesia can also occur.<sup>14</sup> The deltoid and lateral upper arm regions are the most common sites of sensory deficits, accounting for about 50% of all such deficits. Pure sensory NA without motor impairment occasionally occurs (e.g., sural and superficial radial sensory nerves).<sup>13,28,29</sup>

## Diagnostic investigations

A diagnosis of NA is based on a patient's clinical history and physical examination.<sup>30</sup> However, other possible disorders must be excluded. To confirm a diagnosis of NA and exclude other disorders, electrophysiological and radiographic studies are conducted. Using electrophysiological studies, the site of the lesion in the peripheral nerves can be localized, and the degree of involvement can be evaluated.<sup>31</sup> However, during the acute stage, abnormal findings are not observed in electrophysiological studies: abnormal findings are only manifested after 1 and 3 weeks of onset of NA in nerve conduction studies and electromyography, respectively. In nerve conduction studies, there are reduced amplitudes of compound muscle action potentials in the involved nerves. Abnormal sensory nerve conduction study findings are observed in 30% to 45% of all patients with NA.<sup>32</sup> On electromyography, there is reduced recruitment (which can be seen in acute and subacute cases), positive sharp waves, and fibrillation potential in the muscles innervated by the affected peripheral nerves.

On conventional MRI, no abnormal findings are usually apparent. However, gadolinium-enhanced MRI can be helpful for the diagnosis of NA because inflammatory sites in the involved nerves show high signal intensity.<sup>7,33</sup> Before confirming a diagnosis of NA, MRI of the spine and ultrasound or MRI of the shoulder should be performed to rule out radiculopathy caused by a herniated disc or spinal stenosis and rotator cuff tear, respectively.<sup>13</sup> In addition, high-resolution magnetic resonance neurography is helpful for the diagnosis of hourglass-like constriction neuropathy (a subtype of NA).<sup>8,22</sup>

Among routine laboratory investigations, the erythrocyte sedimentation rate and complete blood count are usually normal, unless the disorder is associated

with a systemic infection or connective tissue disease.<sup>34</sup> Cerebrospinal fluid analysis may reveal a mild elevation of proteins without pleocytosis.<sup>34</sup>

## Differential diagnosis

NA is frequently misdiagnosed because other disorders have similar symptoms. In addition, for the confirmation of NA, other disorders, such as cervical radiculopathy and rotator cuff tear, should be excluded.<sup>13</sup> We have summarized the disorders that need to be ruled out before confirming a diagnosis of NA and listed their distinguishing clinical features in Table 1.

## Treatment

Because patients with NA experience severe pain, the active management of pain using various analgesic drugs is necessary; however, the options for complete recovery are very limited. The treatment for NA varies according to the phase in which the patient is seen. Two weeks of corticosteroid therapy is the best treatment during the painful stage—it hastens pain relief and increases the chances of recovery after 1 year.<sup>35</sup> NA treatment usually includes a combination of corticosteroids, analgesics, immobilization, and physical therapy. Standard regimens for NA are supportive, and include a combination of analgesics (non-steroidal anti-inflammatory drugs, opioids, or neuroleptics) and immobilization to minimize pain during activities in the initial phase.<sup>36</sup> In cases with extensive NA, intravenous corticosteroids and immunoglobulins have been used to improve functional outcomes.<sup>37</sup> Intravenous immunoglobulin therapy with methylprednisolone pulse therapy may help to decrease symptom duration.<sup>37</sup> If NA is diagnosed more than 1 or 2 months after onset, the pain has usually lessened, and symptomatic pharmacological treatments are usually sufficient. However, in

**Table 1.** Disorders that should be ruled out before diagnosing neuralgic amyotrophy, and their distinguishing clinical features.

Disorder	Distinguishing features
Cervical radiculopathy caused by disc rupture	Acute onset, Spurling sign (+), sensory and motor deficits in the same dermatome
Cervical radiculopathy caused by spinal stenosis	Insidious onset, slow progression, Spurling sign (+), sensory and motor deficits in the same dermatome
Rotator cuff tear	Pain during shoulder movement, easily differentiated by ultrasound
Mononeuritis multiplex (or vasculitic neuropathy)	Sudden onset, severe pain, distal parts of the limbs usually involved, elevated C-reactive protein, skin lesions (e.g., purpura, petechiae, and ulcer)
Multifocal motor neuropathy	Slow progression, no sensory symptoms, no pain, distal parts of the limbs usually involved
Hereditary neuropathy with pressure palsies	Recurrent episodes of palsy, family history, focal neuropathy at susceptible pressure points
Complex regional pain syndrome	Diffuse pain; predominant vasomotor features; history of stroke, trauma, or peripheral nerve injury
Nerve injury caused by trauma	Trauma history to an injured site
Infectious neuritis	Fever (+), resting pain, elevated C-reactive protein
Peripheral nerve neoplasm	Severe resting pain
Entrapment neuropathy	Localized or referred pain, local tenderness (+)

severe cases, opioids, corticosteroids, and intravenous immunoglobulins may still be considered.<sup>38</sup> Most cases do not require analgesics during the palsy phase; however, in cases with neuropathic pain, specific neuropathic pain relief medications may be required. In other cases, residual pain is related to muscular compensation caused by weakness within the palsied muscles, and rehabilitation is necessary. In addition, compensatory orthotic or surgical procedures may be considered in cases of persistent weakness.

Surgical options include intrafascicular neurolysis and neurorrhaphy/grafting; however, many authors recommend waiting for at least 3 months for spontaneous recovery because many patients show spontaneous recovery during this period. If no clinical signs of recovery are noted in 3 months, magnetic resonance neurography is recommended.<sup>35,39</sup> If nerve constriction is revealed, surgery can be considered. If the

percentage of nerve thinning caused by nerve constriction is less than 75%, intrafascicular neurolysis is recommended. When nerve constriction is  $\geq 75\%$ , neurorrhaphy/grafting should be considered.<sup>40</sup>

## Prognosis

The prognosis of NA depends on the degree of collateral reinnervation. Overall, patients with NA recover to 80% to 90% of their previous state in 2 to 3 years; however, >70% of patients with NA have residual motor weakness.<sup>13,41</sup> Electrodiagnostic studies and evaluations of motor strength can be helpful for predicting the prognosis of patients with NA. If the amplitude of compound motor action potentials is reduced by more than 70% or there is an initial paresis of grade  $\leq 3$  on the Medical Research Council scale for muscle strength, collateral reinnervation will be incomplete and the prognosis is likely to be poor.<sup>13</sup>

## Conclusions

In clinical practice, many patients are encountered who have motor weakness along with pain. Many of these patients are likely to have NA. However, because there is a lack of awareness about this disorder, NA is often misdiagnosed.


## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

## Funding

The present study was supported by a National Research Foundation of Korea grant, funded by the Korean government (grant no. NRF-2019M3E5D1A02069399).

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