Title: Neuralgic Amyotrophy: Its Importance in Orthopedics Practice

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Abstract

The present academic work aims to contribute to an early diagnosis of neuralgic amyotrophy (NA) because of its high prevalence in the population. This disease is a neuromuscular syndrome with unclear etiology; it affects mostly the brachial plexus, causing acute pain in the affected shoulder, paralysis, and disabilities. Considering the importance of an early treatment that can modify the prognosis of the patient, knowing the last updates about the syndrome as its clinical presentation is important. Data analysis was conducted through an online non-systematic review that indicated the epidemiology, pathophysiology, and differential diagnosis and prognosis of NA. Knowledge of the clinical features of NA is not common; however, it is important in orthopedic practice because it requires differentiation from spine pathologies.

Keywords

“Neuralgic amyotrophy”; “orthopedics”; “Parsonage–Turner syndrome”

Introduction

Neuralgic amyotrophy (NA), also known as Parsonage–Turner syndrome (PTS), is a rare neuromuscular disease with unknown cause. It is a neuropathy that affects the brachial plexus, causing effects on the scapular girdle innervated by the plexus. Thus, depending on the affected innervation, different symptoms occur. The diagnosis of exclusion is influenced by the history of the patient, physical findings, and electromyographic (EMG) studies¹.

Epidemiology

NA has an incidence of 1 out of 1000 people. With this prevalence recently found, according to a prospective cohort study that covered more than 14,000 people, NA is 30–50 times more common than previously thought. This difference may be caused, according to the study, by the lack of knowledge of the
disorder and its clinical presentation\textsuperscript{2,3}. In a study evaluating the incidence of brachial plexus neuropathy in a military population, the incidence of NA found was 18 per 100,000 patients per year\textsuperscript{4}.

**Pathophysiology**

In NA pathophysiology, the precise etiology is unknown. It is believed to be related to a complex and multifactorial mechanism that involves mechanical factors, autoimmunity, and some genetic susceptibility\textsuperscript{1}. Genetically, two missense mutations in the \textit{SEPT9} gene (1 of 13 proteins that has the function to form higher molecular structures and are involved in biological processes such as cytoskeleton formation) was found in cases of hereditary NA from Europe and North America\textsuperscript{5,6}.

The autoimmunity hypothesis to NA is supported by some associations. For example, NA often occurs after manifestations that affect the immune system, including infections, such as cases with HEV infections and, more recently, SARS-CoV-2\textsuperscript{7}; surgeries; and pregnancy\textsuperscript{2}. Direct viral activity could also play a role in nerve damage\textsuperscript{8}. In observational studies, the tax of viral infections, vaccine, pre-op period, and post-strenuous exercises are responsible for 43.5\%, 4.3\%, 13.9\%, and 17.4\%, respectively, of prevalence in 115 cases, triggering NA in patients with those antecedent events. More risk factors, including the use of drugs; heroine; and some chronic diseases, such as diabetes and Guillain–Barré syndrome, are listed in some another studies\textsuperscript{2}.

An interesting evidence supporting the role of autoimmunity response from patients with NA is the association between complement factors, suggesting humoral autoimmunity mechanism, and the presence of antibodies in some groups of those patients with idiopathic form of NA. However, similar to other pathogenic mechanisms, the role of the association between antiganglioside and phenotype is unclear\textsuperscript{9}. Previous studies showed an 8\%–26\% increase of antiganglioside antibodies, and in the present study, 36\% of patients are positive for IgM antiganglioside antibodies\textsuperscript{10}.

**Hepatitis E**

Hepatitis E has been recently associated with some extrahepatic features\textsuperscript{11}. Among those complications, NA arises as a frequent one, appearing in 10\% of those infected with hepatitis E virus\textsuperscript{12}; this
can justify older studies in which a percentage of those with NA possessed elevated liver enzymes\(^2\). A recent systematic review found out that, among the neuromuscular manifestations in patients infected with HEV, NA was diagnosed in 56.98\% of cases (102/179 of patients), followed by Guillain–Barré syndrome, diagnosed in 20.11\% (36/179 of patients), becoming the two most common extrahepatic manifestations of HEV. Based on this study, it is possible that neurological symptoms are the most common extrahepatic complications among all others\(^11\). Another interesting feature in cases of HEV associated with NA is that patients most often present bilateral phenotype and the involvement of nerves outside the brachial plexus, especially the phrenic nerve\(^6,12,13\). Despite presenting more extensive nerve damage, the prognosis in these cases was not worse (however, half of the patients still needed some help after a year), but there remains an open debate as to whether this was due to the administered intravenous immunoglobulin therapy (IVIg) (HEV cases tend to receive more IVIg than non-HEV cases). An important aspect that stood out is that HEV infection due to the use of corticosteroids or IVIg did not worsen; nevertheless, future studies remain needed to determine a treatment\(^12\). Testing all patients with suspected NA is highly recommended to confirm a HEV infection.

**Clinical presentation**

The onset of NA is usually represented with sudden and severe pain in the affected shoulder. In the evolution of the condition, local paralysis and difficulty in controlling the muscles distal to the diseased shoulder occur days later. Very intense and continuous pain is usually the initial symptom, lasting approximately 4 weeks. In addition, as the syndrome progresses, a variable grade of atrophy and sensory deficits developed (Table 1)\(^2,3,14,15\). Most patients with NA have persistent fatigue and pain probably related to dysfunction in the affected shoulder; there is no evident relation with psychological suffering\(^16\).

A survey that analyzed the clinical spectrum of NA detected some characteristics common to this disease: in 90\% of patients, the first symptom that presented is pain, occurring in 60\% of the times during the middle of the night; the most common location was in one of the arms, with the right upper limb being the most affected; when the attack was on the right side, the dominance of the hand was, for the most part, also on the right side. These are some of the characteristics detected in patients with NA\(^2,3,14\).
The initial pain is generally severe, and this pain is described in two phases: initially continuous and then followed by strong neuropathic twists or caused by movement, lying down, or prolonged posture of the affected limb, which lasts from weeks to months and gradually dissipates. In 65% of patients, the pain was persistent musculoskeletal, and in 29%, chronic pain developed. Some factors were used to improve the pain condition, such as certain postures, avoidance of specific movements, use of analgesics, and application of local heat; however, the most effective pain relief found in the study was the combination of NSAID and opioid².

In another study conducted with more than 14,000 patients, in the primary setting, most patients with NA are men (75%), with an age of onset above 40 years. Pain, according to the provided data, occurred at the beginning of the condition, and the affected side does not vary significantly; bilateral involvement is also common. In most patients, the distribution of pain was greater in the lateral arm (43%) and trapezius (36%), with a small percentage of pain in the scapula, glenohumeral joint, and entire arm. The range of glenohumeral movement was limited in 43% of patients with NA. The most common types of events prior to disease onset were diseases and deformities; other events, such as childbirth and surgery, also occurred, although with smaller percentages¹⁷.

It is possible that the patient adducts the shoulder and flexes the elbow to have a comfortable position and consequently reduce the pain. Generally, the patient is not hypersensitive to touch on the dermatome; however, when performing the Spurling test, the patient has a lot of pain, showing that the nerve is affected. Valsalva maneuver will not increase the pain. There are also some factors that can exclude the diagnosis of NA, including the progression of pain or weakness for more than 3 months (except pain associated with abnormal compensatory movements of the shoulder); only passive restrictions of the range of motion in the glenohumeral joint; Horner syndrome; perfectly symmetrical weakness distribution; and diabetes mellitus¹⁷.

Normally, NA presents as previously described in this article: sudden attacks of neuropathic pain, in a unilateral upper extremity, and irregular paresis with atrophy in the glenohumeral muscles. However, atypical sites can be affected, such as isolated nerves (anterior or posterior interosseous nerve) or lumbosacral plexuses². An important fact is that unilateral or bilateral phrenic neuropathy occurs in 7.6% of patients with NA and causes respiratory symptoms like orthopnea¹⁸.
In a survey that included 246 patients, the clinic corresponded to that normally presented by the disease in 70.9% of the patients, but there was phenotypic variation in 29.3%, of which 3.7% had no pain, 3.3% had paresis prior to pain, and 22.4% exhibited involvement outside the brachial plexus.

**Differential diagnosis**

Since no diagnostic test can confirm the diagnosis of NA, some signs and symptoms that can lead to other diseases must be kept in mind when approaching a patient with suspected NA (Table 2). In addition, given the fact that NA remains far from knowledge of many physicians, it could affect the time for the correct approach and prognosis of the patient.

Because of its symptoms, NA is commonly misdiagnosed with shoulder and elbow joint pathology (in primary care or orthopedic setting), cervical spondylosis with referred brachialgia, and complex regional pain syndrome, and mononeuropathy forms can be misdiagnosed as an entrapment neuropathy or could be related to synovial cyst. Other diseases, such as acute bursitis, cervical radiculopathy or nonsystemic vasculitis, and peripheral neuropathy, could reassemble NA diagnoses.

One important red flag for NA diagnosis is the spontaneous relief from the acute pain and the progression of muscular weakness. Although cervical spondylotic amyotrophy (CSA) can appear with pain at onset, this is much more common in patients with NA. Other important differentiation is that the median age of patients with CSA is higher, but the major differentiation is sensory symptoms that are present in 78.4% of patients with NA.

For acute bursitis, the pain is best noticed during end-arc flexion due to increased peribursal pressure. In those cases, movement limitation is the main symptom that could show some potential diagnosis.

Cervical radiculopathy has also some similarities and is included in the differential diagnosis list. However, pain could not be present in patients with cervical radiculopathy. Moreover, the abduction of the shoulder should relieve the symptoms. Those cases of cervical radiculopathy could be for degenerative or disk rupture causes. Vasculitic neuropathy is another disease that could potentially be thought of in NA scenario; its single extremity course can have similarities with plexopathy or poly radiculopathy. The etiology
tends to be lower extremity-predominant, causing some distal symptoms and signs; however, there are cases of upper progression causing nerve deficits. Other important causes, including trauma, postradiation, post-op complications, neurogenic thoracic outlet syndrome, or even insidious causes, such as tumors, more specific peripheral nerve malignancies, and Pancoast, could be confused with NA. The differences can be noticed in the force direction that predicts damage localization, slower progression 2–10 years after radiotherapy, relation with most recent surgeries (although NA can appear in the postoperative setting), progressive pain, and the presence of Horner’s syndrome, for example, respectively.

In rarer cases, the similar symptoms seen in NA can be proportioned for some infection that directly acts on the peripheral nervous system, such as neuroborreliosis or HIV. Another important and under-recognized differential diagnosis of NA is leprosy neuropathy, which usually manifests as a mononeuritis and mononeuritis multiplex, the two most frequent patterns with preference to the upper body. In addition, although distal neuropathy is the most common presentation, plexopathy cases has been described as well.

**Diagnosis**

The diagnosis is imminently clinical, but there are some tests that can help confirm the suspicion of NA. The investigation and examination can begin with EMG, but when conducted earlier, it may not be so useful since it can take up to 4 weeks to cause denervation in the roots and peripheral nerves and be fully apparent in EMG, as the disease affect more the upper trunk the median and ulnar nerves studies are abnormal in only 15% of the patients. If it can be done, the EMG will show whether the distribution is irregular, according to a branch of the plexus or nerve, allowing to know the severity of the problem. Needle examination provides additional and more characteristic features, such as numerous denervation signs, with neurogenic pattern. Velocity conduction studies remain normal, excluding demyelination disorders. Multifocal characteristics, such as the difficulty in localizing a specific trunk or branch, with a brachial plexus pattern, are hallmarks of NA.

Imaging studies, such as magnetic resonance imaging (MRI) of the brachial plexus, do not provide much help in the diagnosis of NA as only 6.3% of the patients have and altered study. Although imaging
studies are important in the differential diagnosis for spine pathologies\textsuperscript{23}, half of the patients with NA were found to have degenerative changes on the MRI that did not justify the clinical features; this shows the importance of a careful clinical evaluation in these patients\textsuperscript{2}. Another important differential diagnosis that image studies can help clarify with is hourglass-like constriction neuropathy, which can present in a similar clinical matter as NA but can be surgically explored\textsuperscript{27,29}.

Until a while ago, there was no evidence that immunological tests (looking for anti-myelin, anti-axon, or antiganglioside antibodies) could prove the diagnosis of NA \textsuperscript{2}. However, new studies suggest that antiganglioside antibodies, which are commonly seen in other autoimmune diseases, such as Guillain–Barré and Miller–Fisher syndromes, were found in 36% of patients with NA (11/31 of them), predominantly of the IgM type\textsuperscript{10}. In addition, a remarkable number of patients with NA of this same research demonstrated a prevalence of $\geq2$ antiganglioside antibodies, but a specific pattern (single or combination of ganglioside antibodies) for this disease has not been found yet. Cerebrospinal fluid (CSF) is not helpful; it was found as abnormal only in 29\% of cases, which is less than a third of the cases, in a NA cohort study (9/31 of the patients), demonstrating elevated white blood cells count or oligoclonal bands. However, CSF is important in excluding differential diagnoses\textsuperscript{10}. Future research in new biomarkers can help identify and classify subtypes of patients and thus lead to a more guided therapy with the pathogenesis on sight.

**Treatment and prognosis**

The treatment of NA is limited because of the unclear etiology and the amount of studies that could not prove the efficiency of treatments. Some old articles, as the one led by Tsairis et al. in 1972, show that early administration of steroid drugs did not change the course of the disease, with a few reports of pain\textsuperscript{30}. Despite this, more recent studies, guided to the possible autoimmune mechanism, engage in immunomodulation therapy. In that case, those studies that failed to prove the effect of this approach suggest that the use of prednisone or a high-dose of attack of this drug could have some painkiller effects and improve the functional recovery in some patients\textsuperscript{3}. In that scenario, the immobilization of the affected extremity could be indicated to control the pain during the acute phase. Those approaches lead to a sequence of treatment to
follow that should provide a better prognosis for the patient (Figure 1). Physical therapy, such as strengthening and stretching exercises, when the pain is relieved, can also be recommended\textsuperscript{31}. The autoimmune hypothesis led some authors to try IVIg, as in four cases in 2011 led by Moriguchi et al., in which positive antiganglioside antibody were exposed and good response from IVIG was achieved\textsuperscript{9}. Another case report shows a positive response of immunotherapy in a patient that initially had chronic brachial plexus neuritis that evolved to typical NA manifestation. The patient laboratory analysis also detected antiganglioside antibodies\textsuperscript{32}. The presence of anti-GD1a-IgG suggested some autoimmune mechanism, and based on the clinical findings, they started methylprednisolone pulse therapy and IVIg. The result was promissory, and in two years, the patient started to have some good mobility and stable movements. Moreover, there are some anecdotal reports that plasma exchange had successful results in treatment. Those studies show an example of a possible good approach with immunoglobulin therapy and even a possible approach with plasmapheresis in patients with those laboratorial similarities that should be more analyzed in the future, because of the fact that humoral immunity association is possible and that there are no high-quality trials for NA yet.

Although NA is a self-limited condition, the prognosis ended up tending to a less optimistic evolution that once was thought to have. A study proposed by Cup et al. in 2013 concluded that persisting pain and disabilities are important outcomes suffered by patients with NA, with signs of scapular instability and fatigue of the affected muscles in terms of residual symptoms; there are some reports of sleeping problems in the consequence of pain that could contribute to the fatigue\textsuperscript{33}. The pain could be persistent because of some peripheral nerve damage, developing a type of chronic pain syndrome. In that case, the persistent pain could not be correlated with any other physical disturbance. According to van Alfen et al. in 2009, the study that was leaded by them with 53 patients that did the McGill Pain Questionnaire showed that 10% of patients did not have any type of persisting pain; 55% complained about right periscapular pain; and 13.2% had a score of severe pain, 20.8% had a score of moderate pain, and 66% had slight to no pain, using a visual analog scale\textsuperscript{16}.

In terms of how the recovery affected the life routine of patients with NA, van Alfen and colleagues exposed that, in 200 cases of hereditary NA and idiopathic NA (separated into follow-up time without
treatment) in the first 6 months (59 patients) of follow-up, there was no report of full recovery, and 56.2% was unable to work. In 3 years (49 patients) of follow-up, only 7.7% achieve full recovery, according to the patients, and 26.7% was unable to work; in the idiopathic NA group of those 49 patients, 22.3% were unable to work and 36.8% had to find different job because of NA.

Conclusion

In conclusion, because of its anatomical characteristic, clinical presentation, and age of onset, patients with NA are prone to knock in the orthopedic clinic door as it is the first doctor’s consultation. Knowing these prevalent diseases is of crucial importance in orthopedic practice, especially because of the possibility that earlier immunotherapy can alter the prognosis of the patient. NA is also a rich field of future research, and a multidisciplinary approach is needed; therefore, the involvement of different fields on the research front can bring a brighter future to patients suffering from these disabled conditions.

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None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**Figure Legends**

Figure 1. Treatment algorithm for patients with NA.
Patient with clinical symptoms, or even previous diagnosis of NA

Confirmation of NA (EMG or clinical confirmation)

Affected member mobilization + corticotherapy to control the pain and functional recover

Figure 1. Treatment Algorithm for patients with NA.
| Clinical presentation of neuralgic amyotrophy | Characteristics |
|---------------------------------------------|-----------------|
| **Common syndrome presentation**            | Sudden attacks of neuropathic pain in a unilateral upper extremity and irregular paresis with atrophy in the glenohumeral muscles |
| **Atypical presentation of the syndrome**   | Isolated nerves (anterior or posterior interosseous nerve) or lumbosacral plexuses; unilateral or bilateral phrenic neuropathy occurs (7.6%) |
| **Onset of pain**                           | Sudden and severe pain in the affected shoulder |
| **Disease progression** (days later)        | Local paralysis and difficulty in controlling the muscles distal to the diseased shoulder; atrophy and sensory deficits |
| **Symptoms of most patients**               |                          |
| **First symptom of most (90%) patients**    | Pain occurring in 60% of the times during in the middle of the night |
| **Most affected location**                  | Right upper limb |
| **Most affected sex and age**               | Male, 75% |
|                                            | Above 40 years |
| Distribution of pain in the most patients | In the lateral arm (43%) and trapezius (36%), with a small percentage of pain in the scapula, glenohumeral joint, and entire arm |
|------------------------------------------|---------------------------------------------------------------------------------------------------|
| The most common types of events prior to the disease | Diseases and deformities
Childbirth and surgery (smaller percentages) |
| Attitudes made to reduce pain | Shoulder adduction and elbow flexion |
| Exclude the diagnosis AN | Progression of pain or weakness for more than 3 months; only passive restrictions of range of motion in the glenohumeral joint; Horner syndrome; perfectly symmetrical weakness distribution; diabetes mellitus |

Table 1. Summary of the clinical features of patients with NA.
| Differential diagnosis                | Main differences between differential diagnosis and NA                                      |
|--------------------------------------|---------------------------------------------------------------------------------------------|
| **Shoulder and elbow joint pathology** | Pain resulting from joint movement and specific posture and could be relieved with passive restriction of movement. |
| **Cervical spondylosis**              | When pain is present, its course usually has some activity or posture dependence, with no focal deficits. |
| **Acute bursitis**                   | Pain occurs during the end-arc flexion and peribursal pressure.                             |
| **Cervical radiculopathy**           | Symptoms and signs of cervical radiculopathy are attached to a single nervous root level.  |
| **Vasculitic neuropathies**          | Most frequently affects the lower body, causing distal symptoms and signs. It could have an acute progression involving multiple nerves, leading to a generalized sensorimotor neuropathy. |
| **Trauma**                           | Direct relation with trauma history in symptomatic area and proportional to the impact occurred. |
| **Postradiation**                    | 2–10 years after radiotherapy and with slower progression.                                  |
| **Post-op**                          | Direct relation with surgery history with faster resolution.                                |
| **Neurogenic thoracic outlet syndrome** | Slower progression, medial forearm hypesthesia, and more wasting of thenar than hypothenar area. |
| Tumors                | Description                                                                 |
|----------------------|-----------------------------------------------------------------------------|
| Pancoast tumor       | Clinically has progressive pain, insidious progression, symptoms rise from   |
|                      | the lower to upper parts of the plexus and may course with Horner’s         |
|                      | syndrome\(^{14}\)                                                           |
| Peripheral nerve tumor | Initially has a gradual evolution and a slower progression, fluctuating with |
|                      | the location of affection\(^{14}\)                                         |
| Leprosy              | Cutaneous manifestations, mononeuritis, and mononeuritis multiplex           |
|                      | patterns, usually with a distal neuropathy characteristic and more insidious |
|                      | development\(^{24}\)                                                       |

**Table 2.** The main differential diagnosis of NA and the clinical characteristics that help distinguish them from NA.