Neuralgic amyotrophy: an update on diagnosis, pathophysiology and treatment

Authors: Jeroen JJ van Eijk[1,3] MD, Jan T Groothuis[2] MD PhD, Nens van Alfen[3] MD PhD

1) Department of Neurology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

2) Department of Rehabilitation, Donders Centre for Neuroscience, Radboud university medical center, Nijmegen, the Netherlands

3) Department of Neurology and Clinical Neurophysiology, Donders Centre for Neuroscience, Radboud university medical center, Nijmegen, the Netherlands

Corresponding author

Nens van Alfen MD PhD

Neurologist / clinical neurophysiologist

Donders Center for Neuroscience, Radboud University Medical Center

PO Box 9101, 6500 HB Nijmegen, The Netherlands

Email: nens.vanalfen@radboudumc.nl

Phone: +31-24-3888746 / Fax: +31-24-3615097

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Abstract

This review provides a current overview of the clinical features, pathophysiology, epidemiology, and diagnostic and therapeutic strategies in neuralgic amyotrophy (NA). The disorder has several phenotypic variations, with a classic form in 70% of the patients. It is not rare, with an incidence ratio of 1 per 1000, but still often missed. Recurrences are common, but the proposed multifactorial etiology that includes genetic, biomechanical, and immunologic factors limits the possibility to predict or prevent them. NA is a clinical diagnosis, and ancillary studies serve to exclude infectious or malignant causes or to assess a differential diagnosis. If patients are seen early and are still in pain, a short trial of high-dose oral corticosteroids is advised, and adequate analgesia using opiods and NSAIDs is prescribed. Persistent complaints are common, and a multidisciplinary rehabilitation approach focusing on scapular coordination, energy distribution strategies and self-management is indicated.

Keywords: neuralgic amyotrophy, brachial plexus, clinical features, diagnosis, treatment

Introduction

Neuralgic amyotrophy, also known as idiopathic brachial plexus neuropathy, is a distinct clinical entity that has been known for some time. The first descriptions date from around 1880, and early images of the telltale winged scapula can be found online (http://www.artandmedicine.com, dr. Curschmanns' collection, plates 36 and 37).[1,2] Just after World War II, 2 English physicians published a large case series of 136 patients, and the disorder is also eponymously called Parsonage-Turner syndrome, although the authors themselves preferred to name it "neuralgic amyotrophy".[3] For this review we will use the term neuralgic amyotrophy, or NA, as it is the most common term in the literature and also neutral with respect to the extent and localization of nerve involvement.

The typical or "classic" NA phenotype is a patient who awakens with a new onset pain in the shoulder or upper arm that becomes unbearable (numerical rating scale score of ≥ 7/10) within a few hours. Several hours to days later paresis develops, typically involving the long thoracic, suprascapular, and anterior interosseus nerves, often with some tingling in the superficial radial or lateral antebrachial cutaneous nerve regions and a numb patch on the lateral upper arm in the axillary nerve distribution. The patient may not even notice or mention these symptoms because of the intense pain. The pain lasts 2-3 weeks and does not respond to usual analgesic treatment.[4]

Patients at this stage often seek help from a primary care practitioner or emergency physician. In practice, the disorder is quite often not recognized and is not in the differential diagnosis of these caregivers. In the Netherlands, the typical primary diagnosis from the general practitioner is glenohumeral bursitis, while the emergency physician often diagnoses a "muscle strain". This pattern can be recorded from the history of many patients and leads to a delay in the mean time to diagnosis of several months.[4] It also implies that many patients are not treated optimally in this acute phase, which is unfortunate for people who typically suffer excruciating pains for several weeks.

From a neurological point of view, the typical thing about NA is that the pain is usually not in the same nerve territory distribution as the paresis, and both are often not in the same territory as the

sensory symptoms (figure 1). This failure to fit symptoms in a classic neurologic localization paradigm is one of the typical features that can point to the diagnosis. However, the best clue to the diagnosis of classic NA is to evaluate the movement of the shoulder blades during a slow abduction-anteflexion movement, in which a unilateral disturbance of fluent scapulothoracic movement can be observed, resulting in winging. We have made it a practice to capture this manuever on smartphone video for later review.[5] A video example of the typical shoulder movement abnormalities in acute onset NA can be found here: https://www.youtube.com/watch?v=FRq5pcP6Sq0&feature=youtu.be.

While the classic phenotype is found in about two-thirds of patients, NA can also manifest with involvement of other peripheral nerves, solely or in varying combinations, such as the median nerve (resembling anterior interosseus nerve syndrome), radial nerve (resembling posterior interosseus nerve syndrome), lower brachial plexus with sympathetic nervous system involvement (resembling complex regional pain syndrome), lumbosacral involvement (resembling radiculopathy), and phrenic nerve involvement (often manifesting as "unexplained dyspnea"). This phenotypic variability has led to the concept of a neuralgic amyotrophy syndrome (figure 2) that encompasses all these acute onset, painful mono- or multifocal neuropathies with a monophasic course.[6,7,8] Interestingly there are also patients (about 4% in a large case series) with identical symptoms and disease course that do not have pain at onset.[4] Recognizing the diagnosis in these patients can be even more problematic, as they tend to present only with the more chronic complications seen in NA that have to be traced back carefully to a previous plexopathy or multifocal neuropathy.

The lumbosacral variant of neuralgic amyotrophy is also called lumbosacral radiculoplexus neuropathy (LSRPN)[9] It has been typically known to occur in patients with mild type 2 diabetes mellitus, but it can also occur in non-diabetics and fits within the phenotypical spectrum of NA. Recently, both forms where shown to be caused by ischemic injury due to a perivascular inflammatory process and microvasculitis.[10] Interestingly, some cases of postsurgical "idiopathic" peripheral neuropathy were also found to be caused by a microvasculitis.[11] Of note, there does not

seem to be a preponderance of diabetics or any other disorder in our cohort of 1200+ NA patients (about 10% of whom have lumbosacral involvement). This makes a definite association between NA and diabetes or other disorders uncertain, and it is possible that patients presenting with both might constitute a coincidence of 2 not uncommon disorders.

Epidemiology

Traditionally, NA was considered a rare disease, with an estimated incidence of 1-3 per 100,000 per year, although there were some indications in the literature that the actual incidence might be higher.[3,4,12,13,14,] A recent study prospectively determined the 1-year incidence in a primary care population, using a short training program for practitioners on how to recognize the classic phenotype, and found an incidence rate of 1 per 1000 per year.[5] A likely explanation for the discrepancy seems to be unfamiliarity with the phenotype. In addition, many neurologists rely on EMG findings to confirm the diagnosis, but the sensitivity of nerve conduction studies for this disorder is very low and needle EMG is fraught with sampling error.[15] In addition a type of self-fulfilling prophecy may also play a role, as in "because NA is so rare, this patient probably does not have it".

NA is more common in men than in women, occurring in a ratio of about 2:1, and it can affect people of all ages, with a median onset age of around 40 years for the idiopathic form and around 25 years for the hereditary form.[4] Several reports have described the disorder in children and newborns; the latter often seems to be associated with a concomitant osteomyelitis of the humerus.[16-20]

Recurrent episodes occur in a significant proportion of patients, with at least 25% of idiopathic cases and 75% of hereditary cases suffering a second episode during the first years after their initial attack.[4] In our clinical practice over the last 20 years we find recurrences occur even more often, and they seem to be a common feature of the disorder. Recurrences may involve the same extremity or manifest in a totally different pattern or limb. Currently, there is no way to predict or prevent them.

Pathophysiology

The exact pathophysiological mechanism in NA is not known, but it is thought to be complex and multifactorial. An interplay between environmental factors (i.e. infections or immune triggers), mechanical factors (repetitive or strenuous motor tasks), and individual (genetic) susceptibility are assumed to cause NA.

Individual (genetic) susceptibility

To date no genetic alterations have been found in a study of 56 idiopathic NA (INA) patients, but it is probable that at least the INA patients who suffer recurrent attacks have a (genetic) susceptibility.[6] This factor has not been identified yet, possibly because genetic research has mainly focused on alterations in the *SEPT9* gene that are associated with a predisposition to NA attacks in hereditary NA (HNA).[21] One in 10 NA patients have a positive family history for the disorder compatible with the hereditary variant of NA. The symptomatology of their attacks is similar to that in INA patients, but attacks tend to recur more often and more often involve nerves outside the brachial plexus.[4] Initially it was thought that HNA was identical to hereditary neuropathy with pressure palsies, but this was disproven in 1994.[22,23] It took a further 8 years after a susceptibility locus had been localized to chromosome 17q in 1996 and was mapped to 17q25.3 in 1997, to find 2 missense mutations in the *SEPT9* gene in several HNA families from Europe and North America (of European descent): c.278C>T (p.Ser93Phe) and c.262C>T (p.Arg88Trp), and a c.131G>C transversion in the 5'UTR of *SEPT9* in an additional Turkish HNA family.[24,25,26] The missense mutations were confirmed in 8 of 42 other HNA families.[27] Additionally, a founder haplotype (that had been reported previously) between markers 72GT1 and DS17S939 was confirmed in 12 North American families of European descent.[28,29,30] These 12 families harbored an identical intragenic duplication including the 645 bp exon in which previous mutations were found. In 2010, duplications containing the 645 bp exon were also discovered in kindreds without the founder haplotype.[31] These duplications varied in length and could even contain the whole *SEPT9* gene. In all, about 55% of the North American HNA families have a genetic

alteration in *SEPT 9* (either 1 of the 3 point mutations or a duplication) with an 80-90% penetrance. This leaves 45% of the families without an associated genetic alteration; HNA is thus genetically heterogeneous.

It remains speculative as to what way the *SEPT9* mutations and duplications cause HNA. *SEPT9* produces multiple mRNA transcripts through alternative 5' splicing. The 3 longest transcripts, *SEPT9*_v1, v2, and v3 produce proteins containing a proline-rich region and unique N-termini of 25, 18, and 7 amino acids, respectively. The majority of the proline-rich region is encoded by a 645 bp exon in which the 2 HNA-linked missense mutations are located. Also, the previously published intragenic microduplication results in an in-frame tandem duplication of this exon that is predicted to generate protein products with 2 proline-rich regions. This suggests that this region is important in the molecular pathology of HNA.[31]

Autoimmunity

No specific immunological vulnerability has been found in INA or HNA patients. There is no evidence of immunodeficiency or a generalized autoimmune status in a large cohort of NA patients.[4] NA can be categorized as an organ-specific immune-mediated disorder. The immune hypothesis is supported by the fact that half of affected patients report antecedent events that trigger the immune system, mostly infections but also surgery, childbirth, and physical or mental strain.[4] A recent report showed that about 10 percent of NA patients in the acute phase have a concomitant hepatitis E virus (HEV) infection, but many other types of infection preceding or accompanying the onset of NA have been reported.[32,33,34] Although the peripheral nerves of the brachial plexus, which are the supposed localization of the autoimmune target in NA, are not easily accessed for direct examination, a few peripheral nerve biopsies have been reported from patients in the (sub)acute stage of NA.[35,36] These biopsies of brachial plexus fascicles or the superficial radial nerve showed epineural perivascular mononuclear T-cell infiltrates, active multifocal axonal degeneration without vessel wall inflammation or necrosis, and perineural thickening, while sural nerve examination in the chronic phase and a single postmortem study of the brachial plexus only found evidence for axonal loss at a

single fascicle level and no signs of vasculitis.[37,38] In 1 case, a germinal center with CD20+ B-lymphocytes was seen in infiltrates surrounding epineurial and endoneurial vessels in brachial plexus biopsies[36] These lymphocytes have been associated with a number of autoimmune diseases.[39] More recently, Pan and co-workers reported marked to moderate inflammation found upon surgical exploration of brachial neuritis patients, with scattered CD8+ T-lymphocytes in nerve fibers and fascicles, abundant CD68+ macrophages and CD20+ B lymphocytes surrounding the endo- and perineurial vessels, and variable degrees of axonal loss and replacement by fibrous tissue.[40] Another study found increased levels of complement C5b-C9 and decreased levels of C3 without signs of immune complexes in brachial plexus tissue of acute phase NA patients.[41] Another study reported a decrease in peripheral blood CD8+ T-suppressor cytotoxic lymphocytes in the acute phase, which is also seen in Guillain-Barré syndrome and facial nerve palsy.[42] Taken together, these findings suggest an immune-mediated origin. The organ specificity of the immune response in NA is underscored by the experiments done by Sierra et al., which showed that lymphocytes from NA patients show mitogenic activity when brought into contact with brachial plexus tissue extracts from healthy subjects, but not in lumbosacral plexus extract.[42]

Biomechanical factors

Our NA cohort contains considerably more individuals who participate in sports or perform heavy labor compared to the general Dutch population. Ten percent of the NA attacks are reported to be preceded by unusual and/or strenuous upper extremity exercise.[4] Although still speculative, we hypothesize that the predilection of NA for the brachial plexus (especially the most mobile part, i.e. the upper trunk) is caused by mechanical stretching and compression of the nerves that follows from the large range of motion of our shoulder joints. This everyday wear-and-tear may induce focal loosening of the blood nerve barrier. A less tight blood nerve barrier on the one hand allows for development of autoantibodies, as the immune system is suddenly able to "see" peripheral nerve components, and on the other hand allows circulating autoantibodies or cells access to the brachial

plexus. As the perineurium forms the blood-nerve barrier, this would also explain why histological studies have found abnormalities at the level of single fascicles encircled by perineurium in NA.[38] Quite recently, data have been published that support another hypothesis about the interaction of biomechanical factors and inflammation. It has been postulated that rotational movements of the limbs can cause already inflamed nerves to become twisted, leading to neuralgic amyotrophy that shows typical ultrasound and intraoperative abnormalities appearing as hourglass constrictions and fascicular entwinement.[40,43] Thus, biomechanical factors may both contribute to nerve inflammation by causing wear and tear stress to the blood nerve barrier and by causing torsion of inflamed nerves that leads to additional damage.

Two examples of biomechanical-immune interplay in NA pathophysiology

The interaction of biomechanical factors in addition to an immune trigger, e.g. infection, added to an individual susceptibility to NA, is demonstrated by 2 examples. First, in 1949 an epidemic of NA occurred in Czechoslovakia, where inhabitants of a small village were infected by Coxsackie A2 virus through a contaminated water supply.[44] The common characteristic of the subgroup of people from that area who suffered NA was that most of them worked in a knitting factory nearby, where they had to bend and stretch their right arms for 8 hours daily. The epidemic ended in 1953 when the main water supply was replaced. More recently, 2 unrelated surfers developed HEV-associated bilateral NA.[33] There was an epidemiological link between the 2, as it turned out that they had surfed the same beach (which had a sewage system that drained from adjacent grazing land) during the same time period, which was about 4-8 weeks before their respective symptom onset. This suggested that both surfers had been infected with HEV at the same beach, while both performed strenuous exercise of the upper extremity (i.e. paddling the surfboard). In both examples, not all surfers exposed to HEV on the same beach and not all employees of the knitting factory who did the same work and drank the same water developed NA. This suggests an additional individual (genetic) susceptibility factor that is yet unknown. Individual susceptibility to NA is also underscored by the

fact that while the incidence ratio is 1: 1000, the chance of a recurrence once someone has had an attack is much higher (≥ 1: 4).[4,5]

Diagnostic studies

Neuralgic amyotrophy is a clinical diagnosis first and foremost; there is no ancillary "litmus" test that can confirm or refute the diagnosis with a sufficient degree of certainty. For most patients with the classical phenotype, the history is so typical that once it is heard, people will readily recognize the next person who tells it.[45] In our practice, we tend to use this fact to help patients self-diagnose or confirm the disorder, by providing them with an information booklet that recounts this story (https://www.radboudumc.nl/Informatiefolders/7130-Neuralgic_Amyotrophy__id-i.pdf). If patients read the booklet and do not recognize their symptoms, they usually do not have NA; but NA patients will usually read the text and state that they could have written it themselves. To establish the diagnosis in distal, painless, or other forms of neuralgic amyotrophy that do not involve the classic triad of abnormal shoulder blade movements, shoulder exorotation, and long thumb flexor weakness, one must carefully note the onset mode, specifically ask for difficulties patients experience when using the upper extremity that may point to patchy weakness, and ask for patchy sensory symptoms that might have been present during the first weeks only. As a rule, always check for shortness of breath on bending over or lying supine (orthopnea) and sleep disturbances, as phrenic nerve involvement is not uncommon (10% of patients) and has major implications for treatment and the overall prognosis.

Besides the typical history there are some other characteristic symptoms and signs that physicians and other caregivers can use to diagnose NA (summarized in the table). In addition to scapular movement abnormalities, one may observe other typical clinical signs, such as atrophy of the brachialis muscle underneath a more normal-appearing biceps brachii (figure 3), contraction pseudotremor (activation of enlarged motor units that can be seen through the skin, denoting collateral reinnervation) during slight antigravity contraction in periscapular muscles, and paradoxic

breathing/diaphragm movements especially when supine. In addition, as most patients with serratus anterior weakness will move the affected shoulder in a compensatory pattern that (over-)uses the levator scapulae, trapezius, pectorals, and to a lesser extent rhomboid muscles, hypertrophy and tenderness are very commonly found in these muscles and their attachment points (figure 4). Specific tender points to be palpated are the levator scapulae attachment to the superiomedial scapular spine and the coracoid process where the pectoralis minor attaches. On inspection, the affected shoulder is usually held in protraction, adduction, and elevation with tipping of the inferior medial scapular edge; after movement or strength testing relaxation may cause a slightly lower (i.e. more caudal) scapular position on the chest wall. During abduction and anteflexion, scapular winging may become obvious, especially during the eccentric (i.e. downward) phase of these movements, when scapular movement control is lost (see video at https://www.youtube.com/watch?v=c_zfVHVH17Y&feature=youtu.be). Many NA patients in the subacute or chronic phase will also show signs of glenohumeral rotator cuff impingements caused by the aberrant periscapular movement pattern.[5] A more extensive description of the physical examination used for NA patients can be found in reference 45.[45]

Differential diagnosis

In neuralgic amyotrophy cases with a typical history and typical findings on physical examination, there usually is no other diagnosis to consider for the combination of signs and symptoms. However, as the diagnosis and its findings are still unfamiliar to many physicians, it commonly takes several months for patients to receive the correct diagnosis, and most patients are either first diagnosed with glenohumeral bursitis by their primary care physician or a cervical radiculopathy by their neurologist.[4] A careful history and physical examination, however, would easily tell these entities apart. With glenohumeral bursitis or calcifying rotator cuff tendinitis (both of which can also be very painful) the pain will be localized in the deltoid area and lateral upper arm, and movement restrictions during abduction and anteflexion of the arm will be antalgic and present on both active

and passive motion because of the joint pathology. In acute NA, the pain is more often in the region of the trapezius muscle and acromion, movement restriction is usually just or mainly present during active attempts at motion (i.e. due to paresis), and scapular movement is often discoordinated. In case of acute cervical radiculopathy, all symptoms of pain, sensory disturbances, and paresis will be present in a single root distribution, while NA typically presents with patchy paresis with a localization that does not match the localization of the pain while both do not match the distribution of sensory symptoms. Typically, the symptoms in NA do not match a single root distribution, even though on superficial examination it might appear so; a thorough physical exam is therefore recommended. With respect to the differential diagnosis of NA versus other plexopathies or neuromuscular disorders that are commonly presented in textbooks and reviews, they are often only of theoretical interest, as most of these other disorders have either an obvious cause (for example traumatic plexopathy) or a different clinical onset and course (for example multifocal motor neuropathy).[46] However, the 2 categories the practitioner does need to keep in mind are patients with the typical NA phenotype that can be directly caused by an infectious peripheral neuropathy, such as a *Borrelia Burgdorferii* or HIV seroconversion, and patients who present with NA but have an insidiously progressive course over months caused by a progressive malignancy, such as a Pancoast tumor or neurolymphomatosis.[34,47,48]

If patients are first seen in the post-acute phase and the onset history was painless, unclear, or not explicitly explored, their symptoms will have changed and mainly show pain in the shoulder or arm area that increases during the day and with activities such as repetitive reaching, driving a car, keyboarding, or sitting with the arm insufficiently supported.[49] They often have to "pay back" their daily activities in terms of pain and fatigue. Painful, tender points are found along the cervical spine and around the scapula where strained, weak, and compensating muscles attach. In such cases, eliciting the onset history and looking for abnormal scapular movement patterns and specific weakness patterns such as anterior interosseus nerve paresis, is crucial to establishing or refuting the diagnosis and directing therapy (see below).

Laboratory testing

As a rule, no abnormalities are found during routine blood tests in NA patients. Inflammatory parameters such as ESR and CRP are normal, and testing for autoimmune antibodies such as rheumatoid factor is noninformative. Occasionally, abnormal liver function tests may be found in the acute phase, and they most likely point to an antecedent infection with Hepatitis E virus, an emerging infection in developed countries such as the Netherlands, as a precipitating factor for NA.[33] In patients with specific risk profiles, serology for *Borrelia Burgdorferii*, *Bartonella Henselae,* or HIV is indicated. Some studies report the presence of antiganglioside antibodies in NA, but the sensitivity of this finding is unknown and its specificity is limited.[4,50] When patients present with a relatively painless plexopathy and signs of multiple entrapment neuropathies, hereditary neuropathy with liability to pressure palsies may be ruled out by genetic testing for a deletion of the *PMP22* gene.[51] Cerebrospinal fluid abnormalities, consisting of increased protein content and sometimes an increased lymphocyte count, are occasionally reported in NA, but their diagnostic utility is questionable, except when used for establishing the presence of an underlying intrathecal infection or malignant cause.[4]

Electrodiagnostic studies

Many neurologists still rely on an EMG examination to confirm NA as a diagnosis, under the assumption that a plexopathy will lead to decreased sensory nerve action potential and compound motor action potential (CMAP) amplitudes, and needle EMG will show signs of denervation and/or reinnervation. But while EMG is a sensitive technique for detecting denervation and reinnervation when it can be performed properly, these assumptions are only partly correct for NA; in practice, there is a very real chance of performing a negative study due to sampling error. In our clinical experience this has led to diagnostic confusion on many occasions and had delayed the correct diagnosis and appropriate treatment.

Although their diagnostic value has not been formally assessed, sensory nerve conduction studies are usually informative in cases with structural PNS disease such as traumatic or malignant plexus neuropathy. However, in NA they fail to show abnormalities in 80% of patients, even when clinically affected nerves are studied.[15] A normal sensory NCS exam therefore does not exclude NA as a diagnosis. Motor nerve conduction studies are routinely performed in distal muscles of the upper extremity, with stimulation of the median and ulnar nerves, however recordings are made from hand muscles that are not often involved in NA. In addition, motor NCS are generally less sensitive to axonal loss in patients who have had time to reinnervate damaged nerves, such as in the subacute stage of NA, so that even when motor NCS of the more proximal radial, musculocutaneous, axillary, or suprascapular nerves are performed, the CMAP amplitudes may be within normal limits even when significant axonal loss has occurred. A normal motor NCS exam therefore does not exclude NA as a diagnosis. In contrast to NCS, needle EMG is sensitive for detecting signs of denervation or reinnervation, but only when clinically affected muscles are examined. As there are about 50 different muscles in the upper extremity, thus only a limited number can be examined during a needle study. Many of the muscles involved in NA do not belong to the routine set of muscles that practitioners most commonly explore during their EMG evaluation, thus sampling error is very common. In our tertiary center, patients will undergo repeat studies after referral from another practice with an electrodiagnostic report saying that "clinically this patient appears to have NA but the EMG was normal". Typically in those cases, the needle EMG exam will not have examined the high-yield muscles for NA, such as the serratus anterior (which is technically difficult to study), infraspinatus, pronator quadratus, and flexor pollicis longus. To complicate things further, needle EMG in NA can also show abnormalities in paraspinal muscles, which does not help to differentiate NA from cervical radiculopathy, especially as the sensory NCS are also usually normal in both disorders. This further underscores the importance of the clinical exam.

Of course the EMG can be very useful in cases where there is a genuine differential diagnosis to be explored, such as in painless cases with forearm involvement and suspected multifocal motor

neuropathy, in painful vasculitis mononeuritis multiplex with distal focal extremity involvement, or in patients with progression of weakness in whom regional motor neuron disease needs to be excluded. NA patients in the subacute phase often experience paresthesias in the forearm and hand territory that worsen with certain arm positions and at night and clinically resemble carpal tunnel syndrome or ulnar neuropathy. However, in our experience these symptoms are usually caused by what appears to be subpectoral lower brachial plexus entrapment caused by the altered, forwardly adducted and elevated position of the shoulder that leads to a decrease in the space between the first ribs and clavicle in the context of compensatory hypertrophy of the pectoralis minor muscle. This nerve entrapment does not lead to further nerve damage or EMG abnormalities; when uncertain it may be useful in these cases to use EMG to exclude CTS and UNE.

Imaging studies

Conventional X-ray studies of the shoulder or cervical spine are of little value in NA. Chest X-rays are sometimes used to exclude a superior sulcus tumor of the lung, but their sensitivity is too low to rely on for excluding this type of malignancy.[52] However, chest X-ray may show an (unexpected) elevation of one or both hemidiaphragms that points to concomitant phrenic nerve involvement.[53] Diaphragm ultrasound is a sensitive means of confirming phrenic nerve involvement (figure 5).[54] When the patient has a history of upper extremity trauma and the onset is unclear, X-ray studies may be used to rule out fractures or luxations as a cause of symptoms. If a Pancoast tumor is suspected, such as when a Horner syndrome is present or there is conspicuous involvement of the lower plexus with progression of pain and paresis, the imaging of choice would be an MRI and, if negative, a PET CT scan. When both techniques show no abnormalities the PET CT should be repeated after 1-2 months if the clinical suspicion remains.

A proportion of patients with NA show abnormalities on MR neurography of the brachial plexus and affected peripheral nerves, mostly showing as edema, focal thickening, T2 and short tau inversion recovery (STIR) hyperintensity, or gadolinium enhancement.[55-58] The same findings were also present

in 7% of the NA patients who underwent conventional MRI of the brachial plexus.[4] The MRI changes seem to resolve over time in line with the clinical symptoms.[59]

Cervical spine MRI will show abnormalities in over half of NA patients, ranging from mild degenerative pathology to spinal stenosis with subclinical myelopathy.[4] As cervical spine degeneration is very common in healthy adult subjects of any age, it is of paramount importance to assess whether the imaging findings can explain the (patchy) clinical picture before any intervention is considered.[60] A surprising finding in our practice has been that several patients have initially seemed to have developed a genuine cervical radiculopathy confirmed by imaging, but then after a few weeks suddenly developed additional pain and symptoms that fit into the clinical picture of NA. We suspect that the root compression may have been a factor in disturbing the blood-nerve barrier and development of auto-antibodies that subsequently lead to NA, but we currently have no way to prove this hypothesis.

Nerve ultrasound is an emerging technique to study PNS disorders.[61] So far there has not been a systematic study of ultrasound findings in NA, but anecdotal case reports and clinical experience have shown that NA patients can show focal nerve swellings that mostly seem to affect the perineurial compartment surrounding the fascicles (figure 6). These findings seem to be comparable to the abnormalities found in other inflammatory peripheral neuropathies such as multifocal motor neuropathy.[62] It is currently unknown if these findings reflect ongoing inflammation or are simply a signs of the pathology that has occurred. Severely affected nerve may show focal constrictions that probably reflect scarring due to Sunderland grade IV pathology caused by the inflammation, leading to a string of beads appearance in longitudinal scans (figure 7).[40]

Treatment in the acute phase

Analgesia

As 96% of NA patients at onset suffer severe, nerve trunk-type pain with a mean numerical rating scale score of 8/10 or more (i.e. "unbearable") for a mean of 3 weeks, adequate analgesic treatment is usually a priority. The pain typically does not respond to single first line analgesics such as acetaminophen or NSAIDs, and the various co-analgesics usually take too long to become effective to be of use in this acute phase. In a large cohort study, the best option was a combination of a long-acting opiod with an NSAID that was found to relieve pain in 60% of patients.[4]

Immunomodulation

Due to the possible autoimmune origin of NA, numerous attempts have been made to treat attacks with immunomodulants. A Cochrane review on the treatment of NA revealed no published randomized controlled trials.[63] One treatment trial was stopped after 3 years in 2007 because of logistic problems due to a too slow inclusion rate, with very few patients who were diagnosed and referred within the required first month. Preliminary data analysis showed no significant benefit of prednisone treatment, however, with only 38 of the calculated minimum of 80 patients included, this study was severely underpowered (unpublished observation). The Cochrane review identified 1 retrospective observational case series.[63,64] This study suggested that treatment with high dose prednisone within the first month from attack onset shortens the duration of pain and improves functional recovery in some patients. Insufficient data on other pharmacological treatments have been available; case reports or small series have reported on the use of intravenous immunoglobulin, but it is unclear if the clinical course described in these cases really differs from the natural history.[56, 65,66,67] It has recently been suggested that NA patients with surgical or postpartum attacks could benefit from prophylactic immunotherapy.[68] However, in our cohort we have observed that even in patients with earlier post-procedural attacks, recurrence cannot be predicted. In addition, multiple patients who were already on oral steroids (for another disorder such as rheumatoid arthritis or severe asthma) still suffered an NA attack. This suggests that one should very carefully weigh individual risks and benefits of such preventive strategies. In our opinion we would currently only

consider preventive immunotherapy for HNA patients with proven, predictable, recurrent post-procedural attacks.[69]

In addition to immunotherapy there have been several recent reports on surgical treatments of typical brachial neuritis patients in whom nerves that were affected by hourglass constriction (as shown by nerve ultrasound and intraoperatively) underwent successful neurolysis or resection with grafting.[40,42,70] In selected cases with severe axillary nerve damage with no signs of recovery after 6-9 months, a radial-to-axillary nerve transfer might be considered for reinnervating the deltoid muscle.[71] Future studies will have to show whether peripheral nerve surgery might become a routine treatment option for selected NA patients.

Prognosis

Although NA is reported to show good recovery after 2-3 years in 80-90% of patients, several more recent studies describe a far less optimistic prognosis for most patients.[4,49,72-78] A large cohort study found that the majority had a mean Rankin scale score of 2 after several years of follow up, and only 10% of patients reported that they had made a full recovery after 3 years or more.[4] Additionally, over 25% of patients were still unable to work because of NA. A more detailed follow up study of another large cohort showed that 60% of NA patients still suffered pain on follow up after 6 to over 24 months. It was continuous in 56% and restricted daily activities in 54%.[49] A similar proportion still had impaired shoulder movements, over 80% reported difficulties with performing overhead tasks, and two-thirds reported decreased hand strength in the affected extremity. On a validated questionnaire for experienced fatigue, 50% of patients also had a score indicating severe fatigue.[49]

No relationship could be established between the neurological parameters on follow up (such as MRC paresis grade) and the functional outcome, but a clear correlation was found between persistent pain and fatigue and the presence of scapular instability.[49,73] In practice, it appears that the "hardware" recovery of peripheral nerve function in NA follows the standard rules we commonly explain to patients, of several months needed for collateral sprouting in not too-damaged nerves and

proximal reinnervation progressing at 1 mm/day for nerves with severe axonal loss (i.e. MRC grade <3). Also, most patients clearly have substantial recovery of strength in their paretic muscles over the course of 6-18 months, with the notable exception of distal upper limb involvement and phrenic nerve recovery that can take up to 3-4 years. But the data above show that all this "hardware" improvement does not automatically lead to restoration of activities of daily living function, sports and work abilities, nor to resolution of pain and disappearance of fatigue. The answer to this apparent discrepancy seems to lie in the changed, adaptive, movement patterns that occur after peripheral nerve lesions around the shoulder and in an imbalance between physical possibilities and requirements of daily life, discussed below.

Long-term consequences

Persistent pain, both neuropathic and musculoskeletal, severe fatigue, and impairments of daily life activities and participation are present in a large proportion of NA patients. Many NA patients in the subacute and chronic phase still used analgesic agents to manage their pain and can make only limited use of the arms during walking, keyboard use, or overhead tasks without an increase in pain.[49,73] No indications were found for either underlying psychopathology, a chronic pain or chronic fatigue syndrome, but residual symptoms are strongly correlated with altered biomechanics of the shoulder girdle, and the altered movement pattern can lead to strain of the paretic and compensating muscles even when no (more) paresis is present.[73] As this causes persistent myalgia and fatigue, any rehabilitation program for NA should address these issues specifically.

Central motor representation changes in NA

The long thoracic nerve (LTN), which innervates the serratus anterior muscle, is affected in about 70% of NA patients, and a winged scapula caused by LTN dysfunction is a clinical hallmark of the disorder. However, over time, patients seem to develop dysfunction of central motor representations, with specific deficits in the execution of functionally relevant trained movements that seem to affect shoulder coordination. Clinical experience shows that many patients demonstrate

scapular dyskinesia during abduction and anteflexion, as shown in a YouTube video: [https://www.youtube.com/watch?v=c_zfVHVH17Y&feature=youtu.be]. Movements are impaired in reaching with the affected hand, but there is much less difficulty reaching or pushing forward with the elbow of the affected limb, a functionally non-relevant and untrained movement. Crucially, both movements involve the same stabilization of the scapula that is mainly performed by the serratus anterior muscle. These clinical findings suggest that central neural adaptations contribute to altered motor control in NA, most likely as the underlying mechanism for compensatory movement strategies. It is a finding that is easily translated back to the patient who will often notice that his or her shoulder "does not seem to know how to move anymore". With rehabilitation focused on normalizing scapular coordination and stability, scapular dyskinesia and its complications (i.e. strain and fatigue of the muscles involved) can be reversed, indicating that the altered motor control can be restored in NA patients via a motor retraining strategy.[79,80]

Exercise intolerance or decreased endurance of affected muscles

Almost all NA patients exhibit increased fatigability of the affected arm and shoulder muscles during repeated movements or postures.[49] Even in patients with 'full' recovery of strength, fatigability of the affected muscles does not return to normal (i.e. as it was before the attack). This is an important factor limiting occupational performance and employment that is often not recognized. Decreased endurance is inherent to muscles recovering from denervation by means of collateral reinnervation. As fewer axons and hence motor units are available, they cannot alternate their activation pattern between fatigued and rested motor units during sustained contractions as fully as before. In addition to peripheral fatigue, central activation failure may also play a role, as it does in Guillain-Barré syndrome.[81] For the patient, these mechanisms translate into a movement or posture that can be done once or sustained for a few minutes, after which the limb will feel increasingly "heavy" and the movement or posture progressively more difficult to sustain. If circumstances require that patients then continue their task (e.g. during work), they will need to deploy increasingly more compensatory

strategies to accomplish it. Such strategies always use larger body parts (e.g. bending the trunk when shoulder movement cannot be sustained) and require more energy, which contributes to overall fatigue and strain.

Rehabilitation strategies

Almost all NA patients have received some kind of therapy, usually physical therapy, but also occupational therapy, manual therapy, acupuncture, osteopathic therapy, and other more alternative treatments. Often the duration of therapy sessions is prolonged, sometimes indefinitely. However, many fewer patients get referred to a physiatrist for multidisciplinary rehabilitation treatment.[49,73]

Regular physical therapy, mostly consisting of strength training and/or massage, is ineffective or worsens symptoms in half of NA patients.[49] This is most likely due to an inappropriate focus on regaining strength and endurance in a stage where muscles are still too weakly innervated to be trainable at all (i.e. when not being able to reach 70% or more of a maximal voluntary contraction needed for a training effect), suffer from decreased endurance (i.e. are easily fatigable), and coordination of movement is poor (i.e. scapular dyskinesia). It is also our clinical experience that focusing on only the physical aspect of rehabilitation is often insufficient for treatment success, and therefore it is important to use a multidisciplinary treatment approach for post acute NA. Previous symptom analysis confirmed the relationship between pain, scapular instability, and increased muscle fatigability that leads to strain.[49] This suggests that an intervention to improve scapular stability, periscapular muscle endurance, and an evenly distributed periscapular load during daily life is most likely to reduce persisting pain and residual complaints in NA. In a recent pilot study, such a specific outpatient multidisciplinary rehabilitation program for NA patients was proven to be effective in improving daily life activities, performance, and participation.[79] The aim of this program is to improve scapular coordination, overall fitness, and patient knowledge about how to regain control

over their own complaints and again manage their lives with the existing residual symptoms. The specific components addressed in the program are depicted in figure 8.

Within the multidisciplinary rehabilitation program, the emphasis is on the interaction between the different therapists and the physiatrist that form a team to coach the patient. Physical therapy focuses on training of scapular coordination, careful endurance training of shoulder muscles, and patient education about the disorder and its physical consequences. It may include progressive resistance training of rotator cuff muscles, but only after scapular muscular balance and movement control has been regained. All exercises are performed without or with only minimal pain during and directly after. The intensity of the exercises is adjusted when pain is experienced. Scapular proprioceptive taping is used as a feedback mechanism to increase awareness of scapular position when retaining scapular control during daily activities is difficult for the patient. For patients with paresthesias in the forearm and hand caused by subpectoral nerve entrapment due to a protracted, elevated, and adducted shoulder, extra attention is paid to attaining and maintaining a correct glenohumeral position in combination with gentle neural mobilization techniques.[79]

Occupational therapy focuses on enabling daily activities including work, by training problem solving and role management skills, planning and pacing, practical solutions for practical situations (e.g. better arm support or the use of speech recognition during keyboard work), and improving self management. It addresses both necessary adaptation of activities and the context of these activities (environment), with the purpose of preventing or reducing overuse of the affected and compensating muscles and teaching patients how to control their pain and other complaints. This is done in order to attain a situation where patients can (again) manage their lives in terms of activities and participation. They gain insight into activities that provoked pain and learn strategies focused on preventing and reducing pain caused by overuse that is either due to decreased endurance or increased energy expenditure arising from compensation strategies. Energy conservation strategies are used, including taking mini-breaks, practicing optimal body ergonomics, and adapting activities or

the environment with or without use of aids. Patients learn strategies to reduce stress and physical strain. For optimal therapy adherence, motivational interviewing techniques are used to achieve readiness and willingness to change strategies and implement them in daily life.[82] It is important that the program is tailored individually to each patient's possibilities, needs, and style. The program that has been successfully implemented in our outpatient plexus clinic consists of 8 sessions of 1 hour of physical and 1 hour of occupational therapy over a period of 16 weeks.[79]

This core rehabilitation program can be supported by additional medical interventions if needed. They may include NSAIDs in case of musculoskeletal pains that impede therapy progress, or corticosteroid infiltration for shoulder capsulitis or tendinitis. As persistent pain in NA is almost always related to musculoskeletal strain, we rarely need to make use of co-analgesics for persisting neuropathic pain components. Dry needling or other means of muscle triggerpoint release can be tried in case of increased muscle tone and tender muscle attachment sites. If physical therapy alone is unable to decrease tone in strained, compensatory muscles such as the levator scapulae, trapezius, and pectoralis minor, we consider using botulinum toxin infiltration to lower muscle tone and make the shoulder accessible to rehabilitation treatment. Patients with symptomatic concomitant phrenic neuropathy that interferes with lying supine, disturbs sleep, or causes daytime dyspnea are referred to a specialized center for home-ventilation for night-time positive pressure ventilation treatment.

Table. Points that help making the correct diagnosis of neuralgic amyotrophy [adapted from PLoS One 2015 May 27;10(5):e0128361].

Consider:

• Any patient with acute onset of very severe (NRS pain scale score ≥ 7/10), analgesic resistant unilateral or bilateral shoulder and/or upper arm pain

• Pain often worse at night and also severe when arm is at rest

• Multifocal peripheral nervous system symptoms and signs that can be bilateral but asymmetric

• Abnormal shoulder movement (glenohumeral and/or scapulothoracic) during maximum abduction/ anteflexion movement

• When first seen 3 weeks after onset: paresis of long thoracic nerve, suprascapular nerve, anterior interosseus nerve

Optional signs and symptoms:

• Less severe initial pain with otherwise typical clinical multifocal distribution of weakness and monophasic course

• More extensive multifocal paresis of upper extremity (-ies)

• Asymmetric involvement of other upper extremity

• Areas of hypesthesia and/or paresthesia in the upper extremity

• Involvement of other peripheral nerves: lumbosacral plexus, phrenic, recurrent laryngeal nerve

Table - continued. Points that help making the correct diagnosis of neuralgic amyotrophy (table adapted from PLoS One 2015 May 27;10(5):e0128361).

Test:

• Inspect and palpate shoulder with upper body and arms bared for scapular asymmetry and muscle atrophy

• Look for scapular dyskinesia from dorsal viewpoint with one slow shoulder abduction—anteflexion and *vice versa* movement (Some video examples of this type of movement can be seen following the links on this Radboudumc website page: https://www.radboudumc.nl/Zorg/Ziektebeelden/Pages/neuralgischeamyotrofie.aspx)

• Test and compare bilateral strength of serratus anterior, shoulder exorotation, long thumb and index finger flexors, and forearm pronation. Any weakness found in a combination of these is suspect for NA and rare in other disorders with similar presentations

Exclude neuralgic amyotrophy as a diagnosis when patients have:

• Only passive range of motion constraints in the glenohumeral joint

• Progression of pain and/or weakness > 3 months (except for pain associated with abnormal compensatory shoulder movements)

• Perfectly symmetric weakness distribution

• Horner syndrome (use MRI and PET-CT scan to look for superior sulcus lung tumor and repeat scans when initially negative).

List of abbreviations

CMAP = compound muscle action potential

CRP = C-reactive protein

CTS = carpal tunnel syndrome

EMG = electromyography

ESR = erythrocyte sedimentation rate

HEV = hepatitis E virus

HIV = human immunodeficiency virus

HNA = hereditary neuralgic amyotrophy

INA = idiopathic neuralgic amyotrophy

LSRPN = lumbosacral radiculoplexus neuropathy

LTN = long thoracic nerve

MRC = Medical Research Council

MRI = magnetic resonance imaging

NA = neuralgic amyotrophy

NCS = nerve conduction studies

NRS = numerical rating scale

NSAID = non-steroidal anti-inflammatory drug

PET CT = positron emission tomography computed tomography

PNS = peripheral nervous system

STIR = short tau inversion recovery

UNE = ulnar neuropathy at the elbow

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Figure legends

Figure 1: Schematic representation of classic (A) versus distal neuralgic amyotrophy (B) distrubution in the brachial plexus.

Figure 2: Illustration of the phenotypic variability of the neuralgic amyotrophy syndrome, showing several subforms that can occur. However, other nerves or combinations can be affected as well. Reproduced with permission from *Nat Rev Neurol* 2011 May 10;7:315-322.

Figure 3: Brachialis muscle atrophy on the right versus normal appearance of left upper arm.

Figure 4: Compensatory muscles that are often the cause of persistent pain in subacute NA cases who have serratus anterior muscle weakness.

Figure 5: Diaphragm ultrasound scan showing decreased thickening during maximum inspiration on the patient's right (A) versus normal thickening on the patient's left (B). Diaphragm thickness is measured between the"+" calipers and was 33 mm on the right versus 96 mm on the left. Sc fat = subcutaneous fat layer, * = intercostal muscles, D = diaphragm.

Figure 6: Transverse nerve ultrasound scan showing focal abnormality of the radial nerve as it pierces the intermuscular septum in neuralgic amyotrophy. Cross-sectional area of the nerve was 29 mm^2 (normal <11mm^2). SC = subcutaneous fat layer, T = triceps muscle, H = humerus; arrow indicates enlarged nerve.

Figure 7: Longitudinal nerve ultrasound scan showing string of beads appearance in an affected nerve element of the right brachial plexus in NA. SC = subcutaneous fat layer, M = muscle, N = nerve; arrows indicate affected nerve segments.

Figure 8: Schematic overview of the components of our NA specific rehabilitation program. Reproduced with permission from *NeuroRehabilitation* 2013;33:657-665.

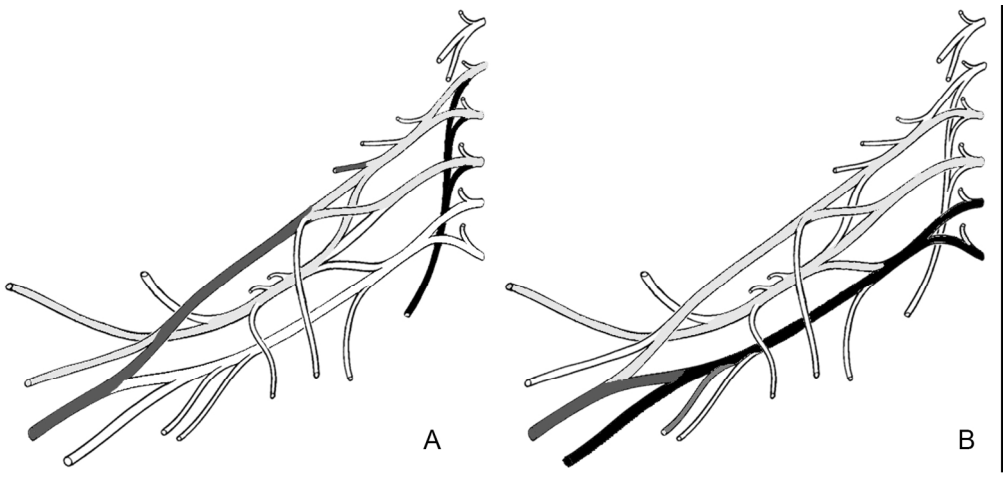

Figure 1. Schematic representation of classic (1a) versus distal neuralgic amyotrophy (1b) distrubution in the brachial plexus.
159x74mm (300 x 300 DPI)

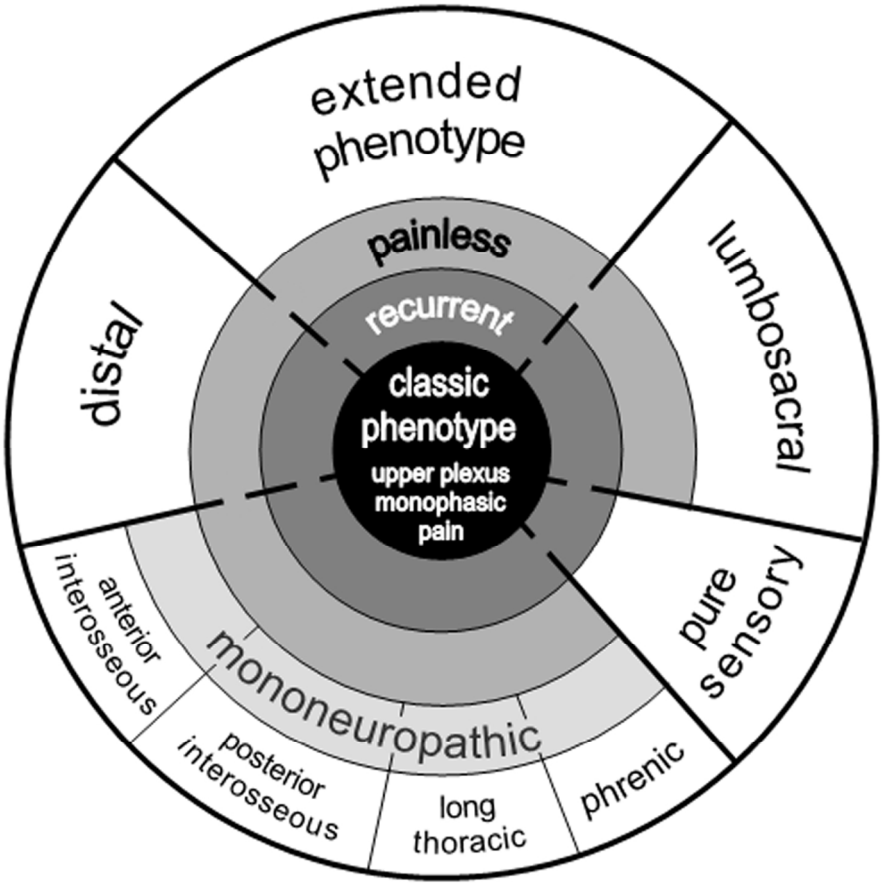

Figure 2. Illustration of the phenotypic variability of the neuralgic amyotrophy syndrome, showing several subforms that can occur. However, other nerves or combinations can be affected as well. Reproduced from Nat Rev Neurol 2011 May 10;7:315-322.
138x134mm (300 x 300 DPI)

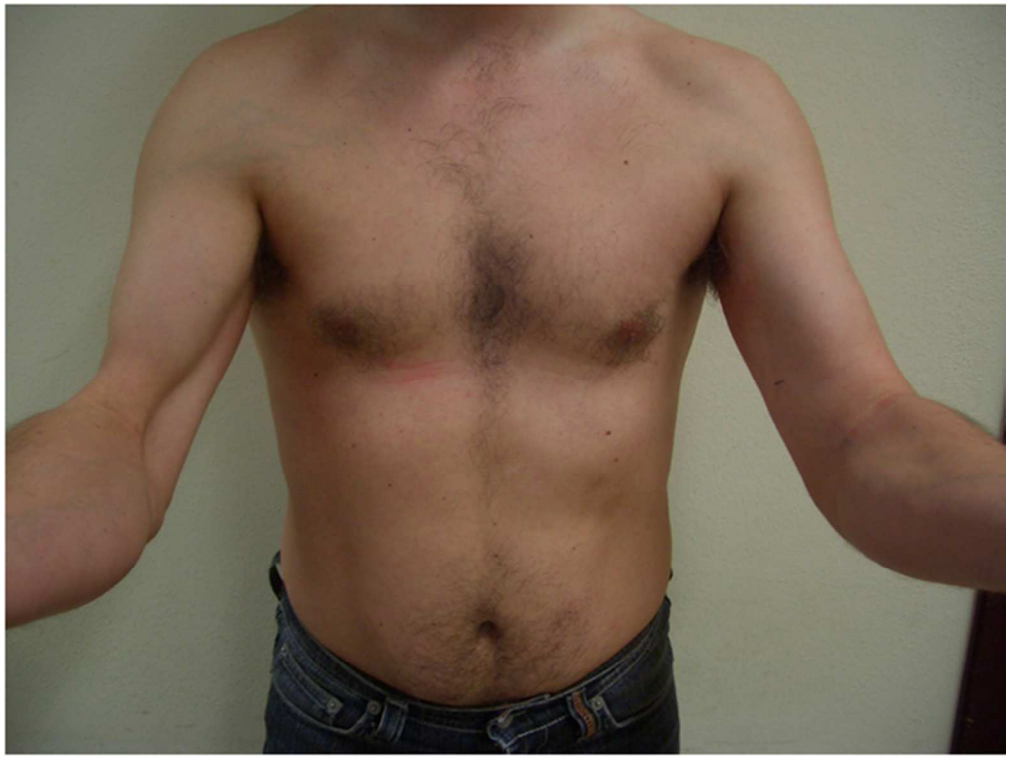

Figure 3. Brachialis muscle atrophy on the right versus normal aspect of left upper arm.
82x62mm (300 x 300 DPI)

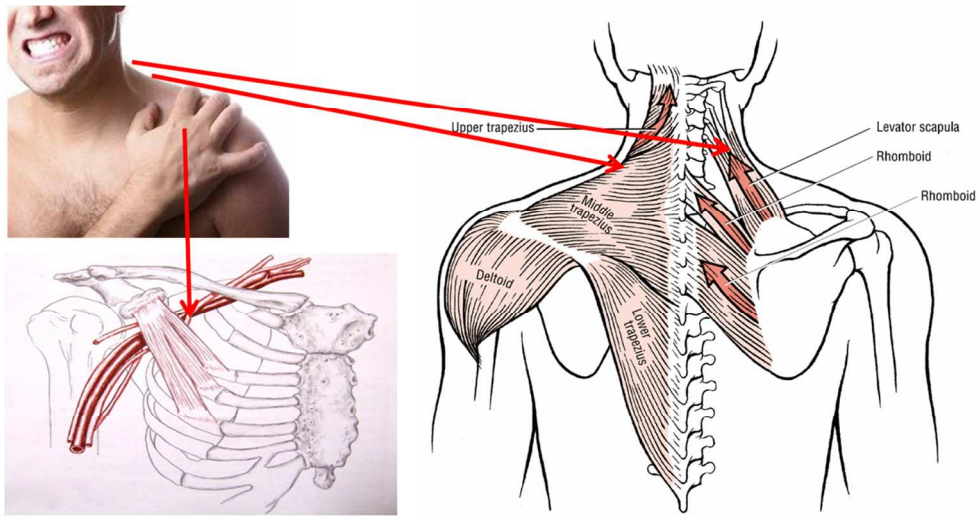

Figure 4. Compensatory muscles that are often the cause of persistent pain in sub acute NA cases who had serratus anterior muscle weakness.
129x66mm (300 x 300 DPI)

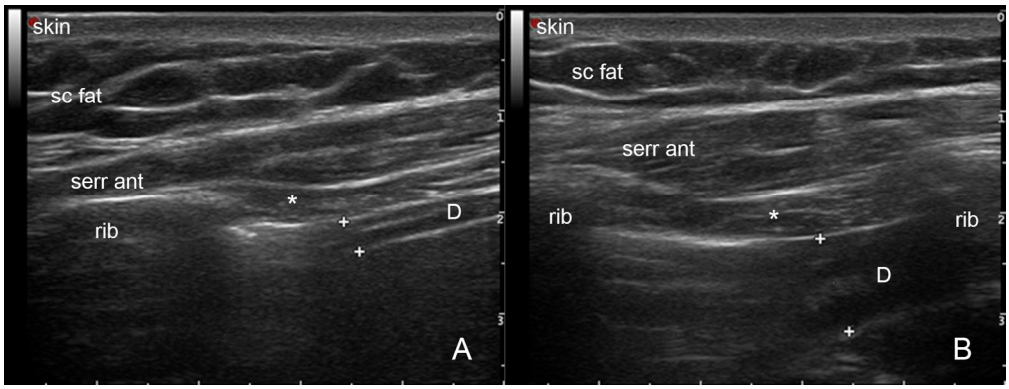

Figure 5. Diaphragm ultrasound scan showing decreased thickening during maximum inspiration on the right (5a) versus normal thickening on the left (5b). Diaphragm thickness is measured between the"+" calipers and was 33 mm on the right versus 96 mm on the left. Sc fat = subcutaneous fat layer, * = intercostal muscles, D = diaphragm.
165x62mm (300 x 300 DPI)

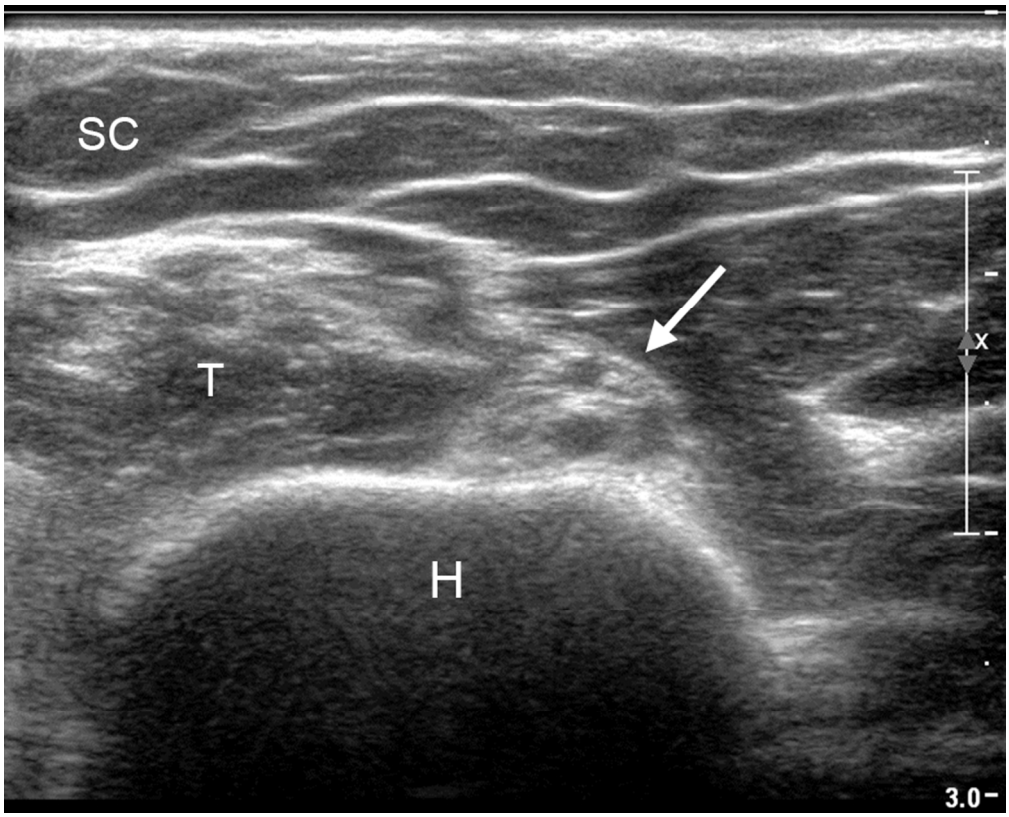

Figure 6. Transversal nerve ultrasound scan showing focal abnormality of the radial nerve as it pierces the intermuscular septum in neuralgic amyotrophy. Cross-sectional area of the nerve was 29 mm2 (normal < 11mm2). SC = subcutaneous fat layer, T = triceps muscle, H = humerus; arrow denotes enlarged nerve.
77x62mm (300 x 300 DPI)

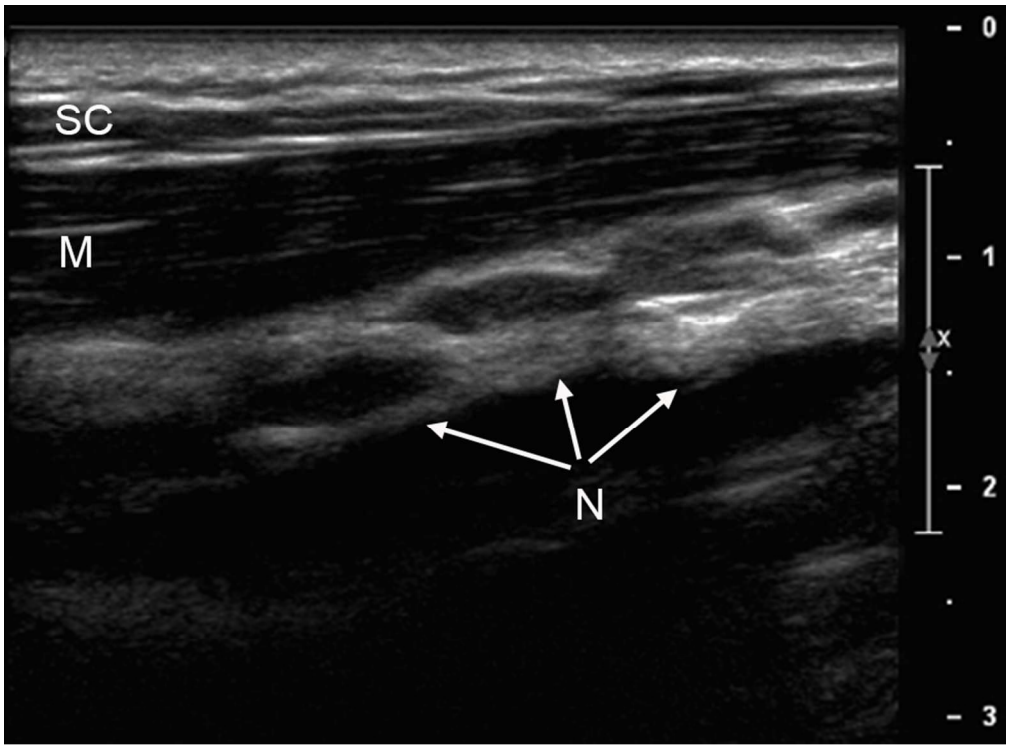

Figure 7. Longitudinal nerve ultrasound scan showing string of beads appearance in affected nerve element of the right brachial plexus in NA. SC = subcutaneous fat layer, M = muscle, N = nerve; arrows denote affected nerve segments.
82x60mm (300 x 300 DPI)

Figure 8. Schematic overview of the components of our NA specific rehabilitation program. Reproduced from NeuroRehabilitation 2013;33:657-665.
82x82mm (300 x 300 DPI)