REVIEW

Neuralgic amyotrophy: a paradigm shift in diagnosis and treatment

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ABSTRACT

Neuralgic amyotrophy (NA), also known as Parsonage-Turner syndrome, is characterised by sudden pain attacks, followed by patchy muscle paresis in the upper extremity. Recent reports have shown that incidence is much higher than previously assumed and that the majority of patients never achieve full recovery. Traditionally, the diagnosis was mainly based on clinical observations and treatment options were confined to application of corticosteroids and symptomatic management, without proven positive effects on long-term outcomes. These views, however, have been challenged in the last years. Improved imaging methods in MRI and high-resolution ultrasound have led to the identification of structural peripheral nerve pathologies in NA, most notably hourglass-like constrictions. These pathognomonic findings have paved the way for more accurate diagnosis through high-resolution imaging. Furthermore, surgery has shown to improve clinical outcomes in such cases, indicating the viability of peripheral nerve surgery as a valuable treatment option in NA. In this review, we present an update on the current knowledge on this disease, including pathophysiology and clinical presentation, moving on to diagnostic and treatment paradigms with a focus on recent radiological findings and surgical reports. Finally, we present a surgical treatment algorithm to support clinical decision making, with the aim to encourage translation into day-to-day practice.

BACKGROUND

In 1948, Parsonage *et al* were the first to present a case series of 136 patients suffering from a distinct clinical syndrome they named 'neuralgic amyotrophy' (NA).[1] Their patients presented with sudden-onset pain in the shoulder region, followed by flaccid paralysis of muscles in the shoulder and/or arm. Four years later, Kiloh and Nevin reported on a similar clinical entity, though only affecting the anterior interosseous nerve (AIN), with associated weakness of the long thumb flexor pollicis longus (FPL) and the deep flexor of the index finger (FDP II).[2] Over the years, various reports have been published on the clinical spectrum of NA. The largest comprehensive case series to date was presented by van Alfen and van Engelen, reporting on 246 patients in a tertiary care setting in the Netherlands.[3] They defined the typical clinical characteristics of NA as primary onset of strong neuropathic pain, which is then followed by patchy paresis of the limb to a very variable extent, ranging from isolated AIN palsy to bilateral severe paresis of both upper extremities. Recent reports suggest that NA is severely underdiagnosed in day-to-day clinical practice, with an actual incidence of 1/1000 per year.[4]

NA has traditionally been considered a predominantly clinical diagnosis and treatment options were confined to conservative measures, namely early administration of corticosteroids, appropriate pain management and physiotherapy to cope with muscle weakness. In recent years, however, with the advent of improved imaging methods in MRI and ultrasound, distinct structural nerve pathologies have been identified as pathognomonic in patients suffering from NA. The recognition of these structural nerve affections has had a radical impact on our approach to NA, opening the door for more accurate diagnosis, while also facilitating the establishment of nerve surgery as a viable treatment option. This review aims to give an overview on the current state of the art in diagnosis and treatment of NA, with a particular emphasis on high-resolution imaging of peripheral nerves and viability of surgical reconstruction. On this basis, we present an algorithm for surgical treatment of NA.

PATHOPHYSIOLOGY

The exact mechanism of disease in NA is still unknown. However, some indications on the underlying pathophysiological processes can be drawn from the various predisposing events and conditions which have been identified in about 50% of affected patients. These include infection, strenuous exercise, surgery, the peripartum period and vaccinations.[3] There are reports about different pathogens triggering NA.[5–7] Most notably, it was found that approximately 10% of patients have a concomitant hepatitis E virus (HEV) infection during the acute phase, thereby explaining the prior findings of elevated liver enzymes in some cases.[3 8] This subgroup of patients suffer heavier attacks which more often occur bilaterally, when compared with NA patients without HEV infection.[9]

The majority of predisposing factors point towards some sort of autoimmune process, resulting in inflammation of selected peripheral nerves. This is congruent with pathological findings from nerve biopsies in acute NA. Different studies have found lymphocytic inflammatory infiltrates in affected

nerves, accompanied by signs of axonal degeneration.[10–12] Biomechanical stress to the nerves of the brachial plexus may also play a predisposing role, as many patients report unusually strenuous physical activity of the upper body prior to onset of disease.[3] In this context, it has been hypothesised, that repeated microtrauma to the nerves of the plexus can lead to increased permeability of the blood-nerve barrier, thus opening the endoneural space to immune factors and thereby enabling the autoimmune process.[13] As the shoulder is an exceptionally mobile joint, stress on traction to the brachial plexus may be most significant, offering a possible explanation for upper limb predilection in NA.[14]

Genetic factors also need to be considered in the pathophysiology of NA. One out of 10 patients reports a positive family history and is therefore classified as suffering from hereditary NA (HNA).[3] These patients have an increased tendency to recurring attacks and more frequently show involvement of nerves outside the brachial plexus. HNA has been linked to mutations of the SEPT9 gene, located on chromosome 17q25.[15] However, this genetic alteration could only be found in 55% of North American families suffering from HNA, indicating other, yet unidentified, mutations which can cause HNA.[13] Considering that also 25% of patients without positive family history suffer from recurring attacks within 5–10 years, it has been assumed that idiopathic NA is also linked to predisposing genetic factors.[14]

All in all, there seems to be an interplay of immunological, biomechanical and genetic factors which lead to the onset of NA. This was exemplified by van Eijk *et al* with two case reports.[13] The first example involved two unrelated surfers who developed bilateral NA attacks after surfing the same beach.[8] Both surfed there in the same time period, which was between 4 and 8 weeks prior to disease onset. Investigations revealed an active HEV infection in both, which they may have acquired from the water, as it received drainage from an adjacent grazing land. Also, both performed strenuous upper body exercise (paddling the surfboard) before disease onset. The other report referred to a localised epidemic in a Czechoslovak village in 1949, initiated through a contamination of the water supply with Coxsackie A2 virus.[16] The majority of the affected population were workers in a local knitting factory. Their profession involved 8 hours of manual work per day, including repeated bending and stretching of the arm. The epidemic came to an end once the water supply was replaced. In both events described, only a subgroup of the surfers/factory workers which were exposed to the external factors actually developed NA, highlighting the differences in individual susceptibility mediated by genetic factors.

Hourglass-like constriction and fascicular entwinement

In 1976, Englert was the first to intraoperatively identify nerve constrictions in patients suffering from spontaneous AIN palsy.[17] Nagano *et al* reported similar findings for eight patients in 1996, describing hourglass-like constrictions (HLCs) of the fascicles forming the AIN within the main trunk of the median nerve.[18] This structural pathology has since then been reported in numerous cases of spontaneous peripheral nerve palsy in the upper extremity, affecting various different nerves.[19–24] The occurrence of multiple constrictions has been observed frequently, which can appear on the same nerve but may also afflict more than one nerve. The symptoms of affected patients generally fit the clinical diagnostic criteria of NA, which is why Pan *et al* argued that this phenomenon should be included into the pathological spectrum of NA.[19 25] This notion has recently been reinforced by several reports on MRI and high-resolution ultrasound (HRUS) findings in NA patients.[26–29] They consistently demonstrated that these types of lesions are a frequent occurrence in clinically affected nerves, therefore, further supporting the association of this structural pathology with NA (see the Imaging section).

The causes for development of constrictions have, however, not been elucidated yet. The severity of nerve affection ranges from light diameter reduction of a single fascicle within a nerve to severe constriction of the whole nerve with total loss of its internal architecture and complete axonal incontinuity (Sunderland grade IV), which can be accompanied by rotational entwinement of fascicles.[26 30] There are different theories on the pathophysiological causes leading to constriction and rotation of fascicles, highlighting inflammatory and mechanical factors. As HLCs seem to occur as a pathognomonic feature in NA, the same pathophysiological considerations as described above need to be considered. Accordingly, the findings from biopsies of constricted nerves after spontaneous palsy show similar results as in prior reports of NA-associated biopsies, reinforcing the immune-mediated aspects of disease mechanism.[19 20] Nagano postulated an initial inflammation of the nerve, which leads to swelling and adhesion of fascicles, rendering them susceptible to mechanical trauma during limb movement.[31] The authors reaffirmed their argumentation by reference to an experimental study in rabbits by Tazaki *et al*, where artificial swelling of fascicles was achieved by saline injections.[32] In combination with movements of the adjacent joint, this led to a sharp kinking of the nerve and after repeated motion even resulted in local torsions at the point of kinking. This theory was supported in a comment on the pathophysiology of HLCs by Lundborg.[33] He emphasised that endoneural oedema may persist for a long time as it cannot easily drain, leading to increased stiffness of fascicles, making them less adaptable to bending forces and finally resulting in localised kinking and torsion (see figure 1). So far, this hypothesis has not been validated.

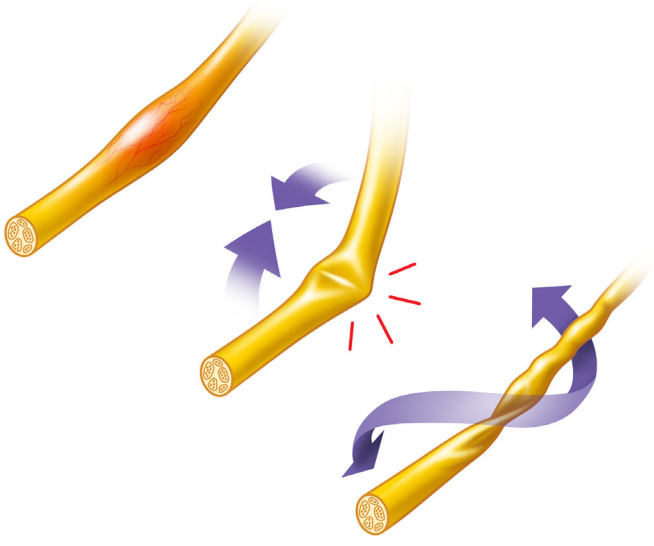

Figure 1 Schematic visualisation of the theory on constriction and torsion development in NA, as postulated by Nagano[31] and Lundborg.[33] Initial inflammation leads to intraneural oedema and swelling of the nerve. This renders the fascicles less flexible, so that motion of a nearby joint induces kinking. After repetitive kinking, rotation of the nerve can lead to constriction and fascicular entwinement. NA, neuralgic amyotrophy.

CLINICAL PICTURE

The typical patient suffering from NA will present with acute pain in the shoulder and/or arm, followed by muscle weakness in a patchy distribution after a few hours to days.[13] Clinically, muscle pareses commonly manifest as deficits in scapular fixation ('scapula alata'), shoulder external rotation and/or flexion of the thumb and index fingers. In most patients sensory symptoms occur as well, often presenting as numbness or tingling sensation in the shoulder or forearm. All in all, the clinical picture of NA is very diverse, as a large variety of nerves can be affected.[34 35] Inflammation seldomly occurs in the brachial plexus itself, but mostly in distal branches.[26 28 34] For this reason, the term 'brachial plexitis' has been largely abandoned, with authors proposing more accurate descriptions of the underlying pathology, such as mononeuropathia multiplex.[36] In rare cases, also nerves which are not related to the brachial plexus can be affected, such as the phrenic nerve, cranial nerves or even the lumbosacral plexus.[37–39]

In their case series, van Alfen and van Engelen found acute pain to be the first symptom in 90% of patients, typically reaching levels of seven and more on the Visual Analogue Scale.[3] Location of pain showed some variability, but in most cases radiated from the cervical spine or shoulder region into the arm. Over the course of the disease, the authors defined three distinct phases of pain: The initial continuous strong pain attack is often followed by stabbing or shooting neuropathic pain elicited by movement and, finally, many patients suffer from late musculoskeletal pain after long-term muscle weakness, located at the insertions of paretic or compensating muscles.

Muscle weakness sets in within 24 hours in a third and within 2 weeks in the majority of patients.[3 40] Large reports from neurological centres show distinct 'classic' patterns of muscle weakness, commonly affecting upper plexus nerves such as the suprascapular, the long thoracic, the musculocutaneous or the axillary nerve, most frequently in some combination.[3 35 40] However, experiences from surgical units, focusing on the occurrence of HLCs, mainly report isolated palsies of nerves such as the AIN or posterior interosseous nerve (PIN).[18–21] This discrepancy might be explained via referral bias, as more classic NA manifestations have traditionally not been considered a surgically treatable pathology, while affections of the AIN or PIN are often regarded as entrapment syndromes. Accordingly, Pan *et al* suspected that patients with isolated nerve palsy are more likely to be referred to a surgical specialist, explaining the predominance of isolated palsies in their report.[19]

Depending on the quality of nerves affected, sensory symptoms in the form of numbness and/or paraesthesia are also present in the majority of cases (78.4%).[3] These are often not recognised by patient and clinician alike, since they commonly affect non-critical areas like the shoulder or the lateral arm and because pain and muscle weakness are typically the predominant concerns.

While NA was traditionally considered to have a very favourable outcome, that view has been challenged by recent reports on long-term follow-ups.[14 35 40] Two years after onset, about a quarter to a third of patients still suffer from pain and fatigue, and the majority experience impairments in daily life.[41] Over 50% of patients either need to change their profession or are unable to work at all because of NA.[3] Some degree of long-term muscle paresis affects most patients, with merely about 4% showing complete recovery. Considering that only recently structural pathologies such as nerve constriction are being associated with NA, it can be assumed that these often untreated changes in nerve structure are partly responsible for poor recovery from pain and paresis in many cases.[19 27]

DIAGNOSIS

Clinical diagnosis and differentials

Before the advent of improved imaging technologies in MRI and ultrasound, NA was considered to be a predominantly clinical diagnosis, focusing on the well-known disease characteristics as described above.[3 14] Laboratory tests may help in identifying specific infections associated with the onset of disease, such as elevated liver enzymes in HEV infection, but are otherwise of little diagnostic value.[13] Electrodiagnostic testing is widely used in peripheral nerve injury and can help support the diagnosis of NA. Needle electromyography (EMG) is a useful but invasive tool to detect and confirm muscle denervation. Since it may take up to 4 weeks for denervation to be fully apparent in EMG, early measurements can thus be of limited value.[42] Nerve conduction studies (NCS) have been used to determine lesion location in NA.[34] However, in the subacute stage of disease after some reinnervation has occurred, NCS parameters of affected nerves may be within normal range, limiting sensitivity of this approach.[13] Also, on a practical note, conduction slowing or block may be technically challenging to detect in certain involved nerves, due to their anatomical location. Regarding sensory NCS, a study has shown that in 80% of clinically affected nerves no abnormalities could be found.[43] Normal results of NCS should therefore not lead to exclusion of NA as a possible diagnosis. Rather, the clinical symptoms of the patient need to be thoroughly examined and trusted to guide initial diagnosis.

Table 1 lists common differential diagnoses of NA, including incidence and clinical presentation.[4 44–51] In a primary care setting, NA is commonly misdiagnosed as a muscle strain in the shoulder region or cervical radiculopathy, likely due to insufficient knowledge of the disease.[13] This lack of diagnostic awareness was confirmed by van Alfen *et al*.[4] In their study, the authors specifically educated primary care practitioners on the clinical criteria of NA, after which they reported an incidence of 1/1000 per year for the disease, which is about 30–100-fold more than prior estimations.[52] Considering musculoskeletal differential diagnoses of the shoulder, these conditions typically do not present with very sudden onset of pain and are often associated with limited passive range of motion.[13] In cervical radiculopathy, symptoms fit the distribution of one cervical root, in contrast to NA where this is commonly not the case. Traumatic lesions of the brachial plexus or individual nerves are common, but can usually be associated to a distinct traumatic event. The possibility of a neurogenic thoracic outlet syndrome or other rarer entrapment syndromes around the shoulder, such as compression of the axillary nerve in the quadrilateral space or the suprascapular nerve in the suprascapular or spinoglenoid notch, should also be considered.[53–55] Distal entrapments of the AIN or PIN are also possible. However, recent reports are suggesting that in the majority of cases with selective AIN or PIN palsy, fascicular constrictions can be identified through imaging, without signs for external nerve compression.[56 57] If neurological deficits are gradually progressing, imaging needs to be performed in order to detect a possibly malignant peripheral nerve sheath tumour (MPNST). Hereditary neuropathy with liability to pressure palsies is typically painless and can be ruled out via genetic testing.[58] Particularly in children, transverse myelitis can present as a similar entity to NA, but symptoms are frequently bilateral and spinal cord affection can often be identified with MRI.[59]

Table 1 NA and its common differential diagnoses, including epidemiological and clinical features

Diagnosis	Pathophysiology	Epidemiology	Typical clinical features
NA	Spontaneous nerve palsy, frequently involving constrictions	100/100.000 per year[4]*	Acute painful attack in the shoulder or arm, followed by motor and sensory deficits in irregular distribution
Musculoskeletal shoulder pain	Different degenerative, rheumatic or traumatic causes, for example, rotator cuff tendinopathy	87/100.000 per year[44] (rotator cuff disease)	Pain chronic or after trauma, may radiate into arm, no distinct sensorimotor deficits, range of motion may be passively inhibited
Cervical radiculopathy	Compression of a cervical nerve root due to disc herniation, spinal canal stenosis, or facet joint degeneration	832/100 000 per year[45]	Chronic neck and possibly arm pain, sensory and/or motor deficits confined to a root distribution
Traumatic nerve lesion	Injury to a peripheral nerve, due to trauma or iatrogenic damage	139/100 000 per year[46]	Pain and neurological deficits in the respective innervation area of the injured nerve, presenting immediately after injury
Nerve compression	Entrapment of nerves at different anatomical locations, for example, thoracic outlet syndrome	380/100 000 per year[47] (thoracic outlet syndrome)	Chronically increasing pain and sensory symptoms, followed by motor deficits at a later stage
Peripheral nerve tumour	Spontaneous proliferation of nerve sheath tissue, can be malignant	01/100 000 per year[48] (MPNST)	Progressive pain and sensorimotor deficits
HNPP	Genetic susceptibility (autosomal dominant) to peripheral nerve entrapment	16/100 000 (prevalence)[49]	Recurring focal compression neuropathies and positive family history
Transverse myelitis	Inflammation of the spinal cord associated with prior infection or immune disorder	31/100 000 per year[50]	Sensimotor and autonomic deficits attributable to spinal cord level, frequently bilateral
NSVN/diabetic radiculoplexus neuropathy	Vasculitis affecting peripheral nerves, involving different clinical subtypes, for example, LRPN	416/100 000 per year[51] (LRPN)	Pain and sensimotor deficits, frequently affecting both lower limbs and associated with weight loss (LRPN)

Where a diagnosis encompasses multiple clinical entities, incidence data is presented for one relevant subtype.
*These numbers originate from a study, where primary care practitioners where specifically educated on the diagnostic criteria of NA.
HNPP, hereditary neuropathy with liability to pressure palsies; LRPN, lumbosacral radiculoplexus neuropathy; MPNST, malignant peripheral nerve sheath tumour; NA, neuralgic amyotrophy; NSVN, non-systemic vasculitic neuropathy.

Some authors have included NA into the spectrum of non-systemic vasculitic neuropathies (NSVN), which represents a group of inflammatory peripheral nerve afflictions characterised by histopathological evidence of vasculitis (ie, vessel wall inflammation and vascular damage) without signs for systemic vasculitis.[60 61] Well-described subtypes of NSVN are diabetic and non-diabetic lumbosacral radiculoplexus neuropathy (LRPN), both of which present clinically with initial focal pain in the lower extremity, evolving into widespread, bilateral paralytic disorders, frequently associated with weight loss.[62] A similar diabetic neuropathy affecting the upper limb has also been described, which shares many clinical features with NA.[63] However, compared with NA, fewer patients suffer painful attacks, while lower limb involvement, autonomic dysfunction and affection of nerves outside the plexus are more common. While the clinical presentation of NSVN can certainly be similar to NA, it is currently not clear whether NA fits the histopathological criteria to be regarded as a subtype of this entity.[64] Among the 246 patients reported by van Alfen and van Engelen, the prevalence of diabetes was slightly lower than in the general population, pointing towards a diagnostic distinction between NA and diabetes-associated plexopathies.[3]

Imaging

High-resolution peripheral nerve imaging greatly expanded diagnostic possibilities in NA. In earlier reports, MRI scans revealed nerve affections in only a small minority of patients and its diagnostic relevance was often confined to identifying muscular atrophy.[3 65] In one of the first studies focusing on peripheral nerve imaging in NA patients, Lieba-Samal *et al* described alterations in all clinically affected nerves, presenting as segmental swelling in HRUS and hyperintensity in MRI.[66] Furthermore, there are some earlier reports on findings of HLCs in AIN and PIN palsy through ultrasound as well as MRI.[67–69] More recently, Sneag *et al* described MRI findings from six patients with NA who showed little to no recovery, identifying 23 sites of nerve constriction in 10 individual nerves.[27] They later confirmed their findings in a larger cohort, where focal constrictions were seen in 32 of 38 affected nerves.[28] Using HRUS to evaluate patients with NA, ArÁnyi *et al* were able to consistently identify structural nerve pathologies ranging from nerve or fascicle enlargement to severe constriction and torsion, presenting in the clinically affected distal nerves rather than the brachial plexus itself.[26 70] They also demonstrated that in cases with complete constriction and rotational phenomena, there was insufficient spontaneous recovery, indicating the necessity for surgical intervention. Various reports have recently validated the possibility of detecting nerve constrictions through imaging.[24 57 71–73] Altogether, these findings suggest that in NA structural nerve alterations are the norm rather than the exception. Therefore, MRI and/or HRUS should now be considered valuable tools for confirming the diagnosis of NA. Furthermore, high-resolution imaging allows for determining the extent of individual structural pathologies and can therefore be helpful for evaluating surgical necessity. Radiological investigations should focus on the peripheral nerves which clinically present impaired and image resolution needs to allow the visualisation of individual fascicles. For some nerves, there are known locations where these lesions frequently occur. In AIN palsy, fascicular constrictions are generally found within the main trunk of the median nerve between 2.5 and 7 cm proximal to the medial epicondyle.[18] In PIN affections, constrictions frequently occur between 0.2 and 5.2 cm proximal to supinator arcade.[21] Reports on lesion location in other commonly affected nerves, such as the suprascapular, are so far limited to few cases.[24 27 74] Figures 2 and 3 present two examples of typical clinical presentations in NA with concurrent findings in MRI and HRUS.

TREATMENT

It has been widely argued, that treatment options in NA are very limited and no proven approaches are available to improve the prognosis of affected patients.[13 14 75] Corticosteroids are believed to have some positive effect on the duration of pain and recovery, but evidence is inconclusive and there are no reports

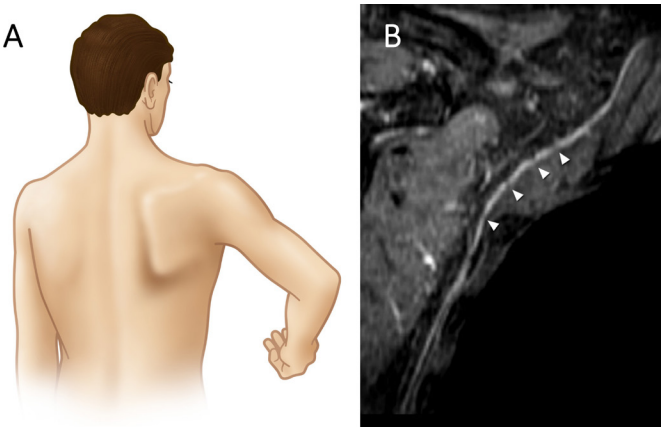

Figure 2 The typical clinical presentation of NA involves lesions of the upper plexus nerves, commonly affecting the supracapular and the long thoracic nerve. In such cases, patients characteristically present with scapular instability ('scapula alata') and a weakness of shoulder external rotation (A). 3D MR neurography was performed in such a case, including a curved multiplanar reconstruction of the long thoracic nerve from a highly T2 weighted fat suppressed isovoxel dataset (B), which revealed a hyperintense, thickened nerve with multiple hour-glass like constrictions (arrowheads). 3D, three-dimensional; NA, neuralgic amyotrophy.

on significant long-term improvements. A systematic Cochrane review of the available literature on conservative treatment in NA has concluded that there is no evidence from randomised trials to support any particular form of treatment.[76] One retrospective study has suggested that early administration of oral prednisone may shorten pain intervals and lead to accelerated recovery in some patients.[3] Otherwise, evidence is largely anecdotal. Aside from corticosteroid treatment, traditional recommendations on how to deal with NA include appropriate pain management, thorough patient education and physiotherapy to support coping with muscular weakness.[13] However, our recent understanding of structural pathological changes at the level of individual nerves or fascicles has suggested the viability

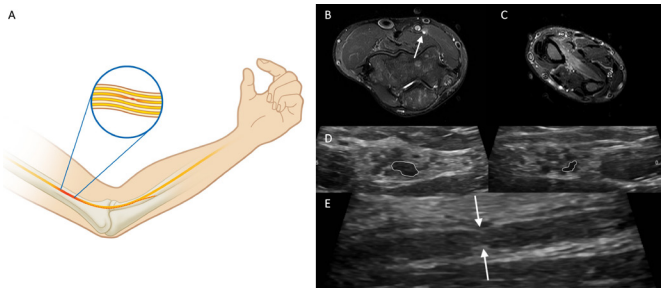

Figure 3 (A) In anterior interosseous syndrome, constrictions are most often found approximately 5 cm proximal to the elbow. Clinically, patients present with weak flexion of the distal phalanges of the first two fingers (A). Both MRI and HRUS were performed in a patient with idiopathic palsy of the anterior interosseous nerve. (B) Shows the hyperintense fascicle of the AIN within the median nerve at the upper arm (arrow) and (C) The concurring atrophy of the pronator quadratus muscle at the distal forearm. In (D) the fascicle of the AIN within the median nerve is visualised in HRUS, presenting enlarged on the right side (encircled in white), and in a longitudinal section of the same nerve (E) a constriction was detected (arrows). AIN, anterior interosseous nerve; HRUS, high-resolution ultrasound.

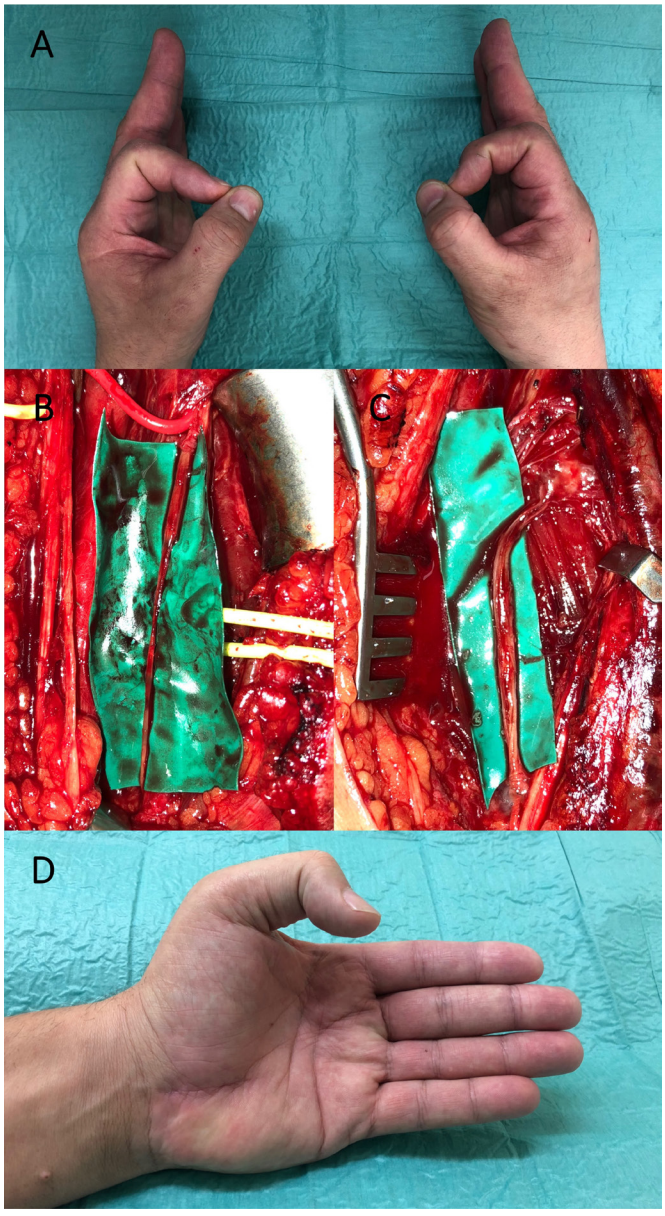

Figure 4 A middle age patient presented with spontaneous AIN palsy of the left hand. Cinical examination revealed a complete loss of function of FDP II and a weakness of FPL (A). Oral cortisone treatment for 2 weeks did not lead to any improvements. Six months after symptom onset, surgical exploration was performed, uncovering a constriction of the AIN fascicle within the median nerve (B). Given the severity of the constriction, lesion resection and sural nerve grafting was performed (C). Six months after surgery the patient had regained good FPL activity (M4) and moderate FDP II function (M3) (D). AIN, anterior interosseous nerve; FDP, flexor of the index finger; FPL, flexor pollicis longus.

of surgical nerve decompression or reconstruction for selected cases.

For selective AIN/PIN palsy there have been several reports on surgical treatment options. The 1996 manuscript by Nagano *et al* includes eight patients suffering from HLC of AIN fascicles, for which the authors reported resection of the constriction and subsequent nerve grafting in one patient while the others received intrafascicular neurolysis alone.[18] All patients available to long-term follow-up regained FPL and FDP II strength of M3 and higher (Medical Research Council Muscle Scale). Figure 4

Table 2 A summary of available reports on surgically treated HLCs, which include three patients or more and present functional results with MRC grading

Publication	No of patients (nerves) with HLC	Nerves affected	No of surgically treated nerves and methods	Average age of surgically treated patients (range)	Average time from onset to surgery (range)	Outcomes after surgery (MRC scale)
Kotani *et al*[80]	4 (4)	PIN (4)	4 4IN 0NR 0NG	32.7 (20–43)	3.9 months (2–5.5)	3 M5*
Inoue and Shionoya[81]	4 (4)	PIN (4)	3† 1IN 2NR 0NG	21.3 (15–32)	3 months (2-4)	3 M5
Nagano *et al*[18]	8 (8)	AIN (8)	8 7IN 0NR 1NG	37.4 (26–57)	5.4 months (3-10)	2 M3 1 M4 3 M5*
Yasunaga *et al*[82]	3 (3)	MN (3)	3 3IN 0NR 0NG	38.3 (30–54)	2.6 months (0.75–6)	1 M3-4 2 M4-5
Guerra *201 183*[83]	5 (6)	AN (2), MCN (2), PIN (1), SSN (1)	6 3IN 3NR 0NG	45.8 (21–68)	9.3 months (3-17)	3 M4 2 M5*
Ochi *et al*[78]	12 (12)	PIN (12)	12 12IN 0NR 0NG	26.3 (17–43)	3.6 months (1-6)	1 M2-3 11 M4-5
Ochi *et al* [79]	21 (21)	AIN (21)	21 21IN 0NR 0NG	42.3 (18–73)	5.2 months (3-11)	4 M0-3 17 M4-5
Pan *et al*[19]	42 (47)	RN (19), PIN (18), AIN (3), MN (3), AN (2), MCN (1), SSN (1)	47 20IN 17NR 10NG	27.8 (8–52)	4.3 months (1-15)	7 M2-3 29 M4-5*
Wu *et al*[21]	41 (41)	PIN (41)	24‡ 10IN 8NR 6NG	34.2 (21–60)	4.9 months (3-14)	4 M0-3 20 M4-5
Sunagawa *et al*[77]	7 (7)	AIN (7)	6‡ 6IN 0NR 0NG	36.8 (19–55)	4.3 months (0.2–9)	1 M0-3 5 M4-5
Vigasio and Marcoccio[74]	6 (6)	SSN (6)	6 3IN 3NR 0NG	33.6 (23–46)	9.3 months (4-13)	1 M0 5 M4-5
Wang *et al*[20]	20 (22)	PIN (8), RN (6), MN (5), AIN (3)	22 12IN 10NR 0NG	34.8 (16–61)	2.6 months (0.3–12)	18 M4-5*

In studies with heterogeneous nerve damage, only the cases with confirmed constriction are presented. Two reports from the same institution[25 84] were omitted from this table, as their data was later presented again in a larger cohort.[19]

*Not all patients were available to long-term follow-up.

†One patient received a tendon transfer without nerve reconstruction.

‡Remaining patients were treated conservatively.

AIN, anterior interosseous nerve; AN, axillary nerve; IN, intrafascicular neurolysis; MCN, musculocutaneous nerve; MN, median nerve; NG, nerve grafting; NR, neurorrhaphy; PIN, posterior interosseous nerve; RN, radial nerve; SSN, suprascapular nerve.

presents a case of typical AIN palsy where nerve reconstruction was performed.

Pan *et al* were the first to present a surgical case series of patients suffering from more typical NA, defined as sudden-onset pain in the shoulder region and subsequent paresis of the limb.[25] Surgical exploration was performed in severely affected nerves where regeneration was absent after a period of conservative treatment, which varied between two and eleven months. Five radial, two median and one musculocutaneous nerve were explored, all of which revealed HLCs. According to the severity of constriction, three nerves were neurolysed, two received direct neurorrhaphy and three were grafted. Good recovery (≥M4) was achieved in all but three nerves, which had received reconstruction. The authors reasoned the insufficient regeneration to be the result of late treatment in two cases (8 and 11 months delay, respectively) and an excessively long nerve graft in the third (13 cm). In a more recent, considerably larger cohort with long-term follow-up in 31 patients, the majority of nerves across all surgical treatments showed good regeneration (80.6%≥M4).[19]

Similarly, Wu *et al* reported a retrospective analysis of 41 patients suffering from spontaneous PIN palsy with HLC, who received conservative as well as surgical treatment.[21] Surgery was performed when no spontaneous recovery occurred after 3 months of conservative treatment. Severity of constriction was defined according to the percentage of nerve/fascicle thinning: ≤25% thinning was classified as mild, 25%–75% as moderate and ≥75% as severe constriction. Seven of the patients who showed no recovery after 3 months did not undergo surgery, of which only three recovered well (42.9% ≥M4). In contrast, 20 of 24 surgically treated patients showed good recovery (83.3%), indicating that surgery is more effective than conservative treatment if no recovery occurs after 3 months. Neurolysis showed good results for all mild and moderate constrictions, but failed to provide improvement in two cases with severe constrictions. The remaining patients with severe constrictions underwent either neurorrhaphy or grafting, with positive results in 12 out of 14 cases (85.7%). The notion that neurolysis may be insufficient for severe constrictions was reinforced by Sunagawa *et al*, who reported good regeneration after neurolysis in all of their patients, except for one case where the constriction was over 75%.[77] Interestingly, they also noted that after neurolysis some degree of constriction persisted in all nerves over the course of the follow-up, though less severe than before surgery and not hindering successful reinnervation.

Another recent study was published in 2019 by Wang *et al*, reporting on their surgical experience with 20 patients suffering from spontaneous nerve palsy and HLCs.[20] All of the 16 cases available for long-term follow-up showed good recovery after surgery. Nine of the affected nerves had severe constrictions, of which two received intrafascicular neurolysis and seven neurorrhaphy. The remaining nerves all showed mild to moderate constrictions and received intrafascicular neurolysis.

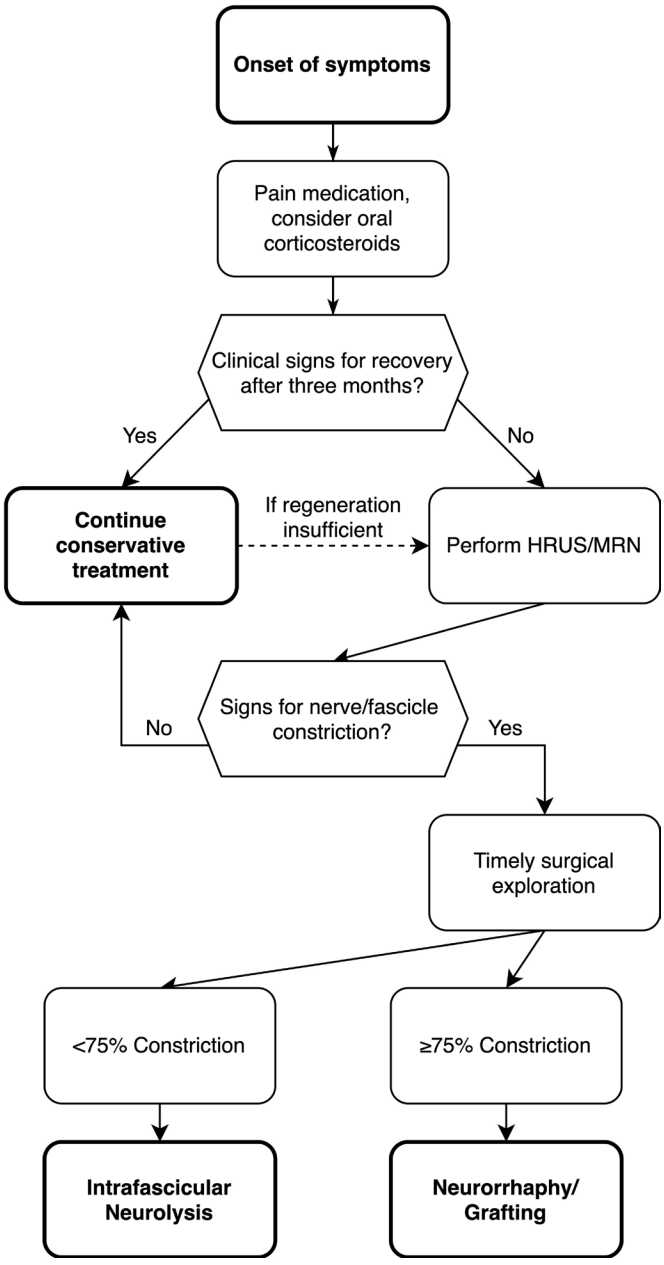

Figure 5 This treatment algorithm displays the decision-making process for nerve surgery in NA. After onset of symptoms, at least 3 months should be given to allow for any spontaneous regeneration. During this period, conservative treatment should be administered, which consists in the acute phase mainly of pain management and possibly corticosteroids. If clinical regeneration does not occur after this interval, high-resolution imaging of the affected nerves needs to be performed. Where constrictions are identified, surgical exploration is indicated. If none can be found, conservative treatment will be continued, with the possibly for a re-evaluation at a later stage. When surgery is indicated, treatment will either consist of intrafascicular neurolysis or nerve reconstruction, depending on the severity of constriction. HRUS, high-resolution ultrasound; NA, neuralgic amyotrophy.

Table 2 gives an overview of the reports in English literature, which describe surgical treatment of HLCs in three or more patients.[18–21 74 77–84] Across all studies, 143 patients were available to long-term follow-up, of which 122 showed motor recovery of M4 or better (85.3%). Average patient age in the individual cohorts ranged from 21 to 46 years and patients between 15 and 73 years were afflicted overall. This wide age range in NA is compatible with the findings of van Alfen and van Engelen.[3] Various authors have noted that younger patients had a higher chance for good recovery, while patients aged 50 or older more frequently showed unfavourable results.[21 78 79] In the majority of reported cases, timing of surgery was between three and 6 months after symptom onset. Only nine patients (6.3%) received operation after a year or later, of which six recovered well (66.7%).

Surgical treatment algorithm

Based on the findings described above as well as our own experience, we have devised an algorithm for surgical treatment of NA (figure 5). While the initial diagnosis of NA remains clinical, high-resolution imaging can be helpful early on in order to detect possible pathognomonic constrictions or rule out differential diagnoses such as entrapment or tumour. If lesion location is not clear, it might be advisable to screen the whole neuraxis of a clinically affected nerve. After diagnosis of NA, conservative treatment measures should include appropriate pain medication and possibly oral corticosteroid administration. We recommend that, following onset of symptoms, at least 3 months should be given to await any spontaneous recovery. In peripheral nerve surgery, this is an agreed on time frame for cases where potential regeneration is unclear, as it will generally allow for some regeneration in mild nerve injury (Sunderland grade 1 and 2), while still facilitating timely surgical intervention for more severe cases.[30 85–87] Various authors have also proposed a 3-month interval of conservative treatment prior to surgery in NA, as many patients will show spontaneous recovery during that period.[18 21 78 79 83] If recovery is clinically absent at that time, HRUS and/or magnetic resonance neurography (MRN) need to be performed in order to evaluate the presence of possible constrictions. Affected nerves which present with constrictions and did not show recovery, warrant timely surgical exploration. In cases where no constrictions are found, conservative treatment should be continued. In such a situation care must be taken not to miss a possible nerve entrapment, which may mimic NA clinically and require surgical treatment. If regeneration remains insufficient or halts under conservative measures, a re-evaluation using high-resolution imaging may be useful, as it is yet unclear whether constrictions can also develop after 3 months and might thus be missed during initial screening. If imaging is not available with sufficient resolution, surgical exploration could still be considered in cases where regeneration is negligible after an appropriate time frame, given the possibility for HLCs if NA has been diagnosed. Furthermore, if severe constrictions with rotational phenomena are clearly identified through imaging prior to the 3 month interval, early intervention may be justified as spontaneous recovery is not to be expected in these cases.[26]

Intraoperatively, intrafascicular neurolysis should be performed and, depending on severity of the lesion, reconstruction considered. The decision to reconstruct will in individual cases be taken by the experienced nerve surgeon, based on the appearance and quality of fascicles as well as on intraoperative electrostimulation. However, reconstruction is generally advised when nerve/fascicle diameter at the site of constriction is one-fourth or less compared with the healthy nerve. After resection of the lesion, direct neurorrhaphy should be performed whenever possible in a tension-free manner. If this cannot be achieved, nerve grafting needs to be considered. In very proximal lesions or late presentation of the patient, distal nerve transfers can be helpful to accelerate reinnervation and prevent irreversible

degeneration of motor endplates. Where timely reinnervation of the relevant muscles cannot be achieved, secondary procedures such as tendon transfers can be used to improve shoulder, elbow and/or hand function.[88 89]

In cases where the nerve does regenerate spontaneously or after surgical intervention, the possibility of a 'double crush' should be kept in mind, meaning that the swelling accompanying a regenerating nerve can lead to distal entrapment.[90 91] If suspected clinically, HRUS should be performed at known entrapment sites, such as the supinator arch for the radial nerve or the pronator teres muscle for the median nerve. If the nerve presents entrapped and clinically the regeneration does not progress, surgical decompression is warranted.

In order to support the patient in regaining strength and/or sensory function after surgical treatment, tailored physiotherapy or occupational therapy should be considered, especially in severe cases. Postoperative rehabilitation may follow standard recommendations for sensory and motor re-education after nerve injuries.[92 93] Following nerve or tendon transfers, structured therapeutic interventions have been established to promote cortical plasticity for relearning and thereby improve surgical outcomes.[94 95] These techniques should be considered an integral component of the treatment algorithm, if such surgical interventions are chosen.

FUTURE OUTLOOK

We propose a treatment algorithm that integrates peripheral nerve surgery into the existing treatment paradigms in NA. While the presented algorithm covers today's relevant experience with this entity, further studies are needed to establish a clearer guidance on the frequency and location of structural pathologies in NA. It is yet unclear, whether severity of constrictions is the single most relevant factor for unfavourable outcome or if other, concomitant factors like multifocal constriction or amount of swelling during the early inflammatory phase influence the prognosis. Therefore, larger studies matching the extent of structural pathologies to the associated prognosis of regeneration will give a clearer guidance on the necessity of surgery and in particular on the possibility of early intervention in cases where constrictions are severe and no spontaneous recovery is to be expected. Furthermore, future investigations should seek to perform high-resolution imaging early on and in regular intervals, which will help to improve our understanding of pathophysiology and timing of constriction development. Now, more than ever, it is clear that patient management in NA will benefit greatly from an interdisciplinary approach, which includes neurologists, radiologists and surgeons.

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