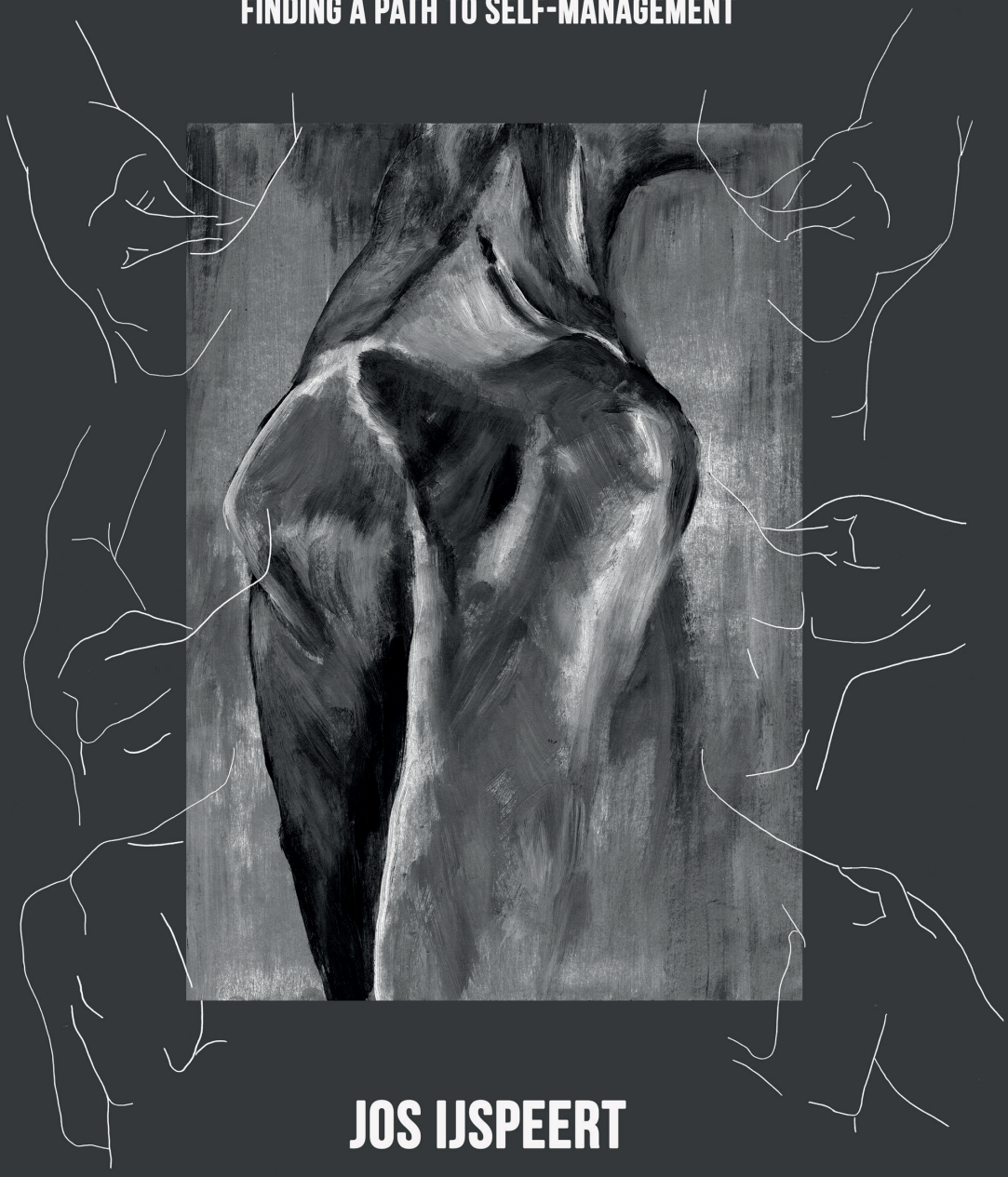
REHABILITATION AFTER NEURALGIC AMYOTROPHY

FINDING A PATH TO SELF-MANAGEMENT



JOS IJSPEERT

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Rehabilitation after neuralgic amyotrophy

Finding a path to self-management

Jos IJspeert

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Finding a path to self-management

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Table of contents

Chapter 7

Summary and General discussion

Appendix

Chapter 1

General Introduction

Imagine yourself waking up in the middle of the night due to pain in your shoulder and arm so excruciating that it's like nothing you have ever experienced before. You cannot sleep anymore, so you get out of bed trying to find a better position, but there is no way of getting comfortable. After a couple of hours, you become desperate and wake up your spouse for driving you to the emergency department. At the hospital, the doctor does a few clinical tests, but there seems to be nothing seriously wrong with you. You are told that it's probably an inflammation of the shoulder, you are given some painkillers and sent home. But the medication is not helpful. In the morning you are not able to lift your arm anymore, while your shoulder blade is sticking out and the pain is still unbearable. About ten days and a couple of doctor visits later, the pain starts to diminish and you feel somewhat relieved, but you still cannot lift your arm above shoulder height. The next couple of weeks you notice that objects keep falling out of your hand, while the excruciating pain at onset is gradually replaced by another kind of pain that is still very annoying and limiting your daily life activities. It is still hard to sleep and work seems impossible, because merely sitting upright for more than an hour is already hard to do.

You visit a physical therapist who examines you thoroughly and finds out you have an unstable shoulder blade and weakness of several arm muscles. You are advised to try to resume your work as much as possible and perform strengthening exercises. Meanwhile the physical therapist massages your shoulder muscles because they seem to be tense all the time. The strengthening exercises appear to provoke rather than relieve the pain, and after some time you are still not able to use your arm up high or lift your children to give them a hug.

During the next couple of months, the shoulder and arm pain increases again, and you have not been able to resume work, do household chores, drive a car, ride a bicycle, or wash your hair. You get extremely tired after only a limited amount of activity, and you feel unable to perform your role as a parent, partner or employee. After a while you start searching for answers on the internet and you come across some information about a condition called "neuralgic amyotrophy". It has a typical presentation that very much resembles what you have been experiencing. You consult your general practitioner, who refers you to a specialized outpatient clinic. After a substantial waiting list period, the diagnosis neuralgic amyotrophy is confirmed, and suddenly your complaints and symptoms make sense. The multidisciplinary team at the clinic tells you that you have had an acute inflammatory disorder of the brachial plexus nerves. You learn that you might have been treated with medication to suppress the

inflammation if the diagnosis had been made at onset, but now it is too late for this type of pharmacological intervention. But the health professionals at the clinic do offer an approach to decrease your symptoms based on appropriate physical and occupational therapy. It may take you another 6 to 12 months to make the pain and fatigue manageable, but you still feel relieved because at least now you have an idea of what is going on and what can be done.

The case described above is typical of people who visit the weekly plexus clinic of the muscle disease center at the Radboud university medical center. This plexus clinic is an interdisciplinary outpatient facility for patients with neuralgic amyotrophy (NA) that was initiated in 2009 through a collaboration of the departments of Neurology and Rehabilitation. At that time, it was probably the first NA- focused interdisciplinary outpatient clinic worldwide. Currently, our plexus clinic and its spin-off in San Francisco ran by dr. Ann Poncelet are serving as international reference centers for this disease. At our plexus clinic, all patients are seen by a neurologist, rehabilitation specialist, physical therapist and occupational therapist. They are provided with a diagnosis of NA (or an alternative diagnosis for their symptoms) and an individualized treatment plan. Patients usually have questions about several topics that need to be addressed: 1) *diagnosis*; confirming that the problems they experience are in fact typical of NA or can be related to NA, 2) *awareness*; identifying behavioral aspects in their disease management that can be improved, 3) *partnership*; shared decision-making with the treatment team regarding the optimal intervention strategy, 4*) interprofessional collaboration*; integrating scopes of practice between different healthcare disciplines involved, 5) *self-management*; coping independently with the disease and its functional consequences (1).

This thesis aims to contribute to the understanding, functional diagnosis, and rehabilitation of patients with NA addressing each of the aforementioned areas. The following first chapter of this thesis is designed to provide background information and results in a research objective and outline.

Neuralgic amyotrophy

NA is typically a monophasic neuropathy which is divided in two variants, idiopatic NA (INA) of hereditary NA (HNA) (2). The initial phase of the disease, which typically lasts for three to four weeks but can range from a few days to three months, is primarily marked by neuropathic pain (3, 4). The severity of pain indicated on a numerical rating scale (NRS; range 0-10) is often ≥7 (4). Concurrently, there is a noticeable decline in motor function of the shoulder girdle and/or upper extremity. Following the acute phase, patients enter a sub-acute phase marked by (partial) recovery. Previously, it has been reported that 80-90% of all patients with NA experience complete motor recovery within two to three years (5), but numerous, more recent studies have reported the persistence of residual symptoms with a profound impact on daily life in over 50% of patients (4, 6-8).

In addition, the previously existing idea of NA being a rare condition has been replaced by evidence of NA being relatively common with an incidence of 1:1000 individuals per year in the general community (9). This knowledge emphasizes the need for improving general awareness, diagnostic accuracy, and effective interventions for NA. The identification of different phenotypical presentations of NA adds another layer of complexity to clinical management. The "classic" form, characterized by involvement of the brachial plexus nerves, represents the most common manifestation, accounting for approximately 70% of all cases (4, 10). NA can also involve the lumbosacral plexus nerves, leading to pain and muscle weakness in the lower extremities, observed in about 10% of all cases (11, 12). A small proportion (8%) of all patients experience phrenic nerve involvement, resulting in diaphragm dysfunction, while another rare presentation includes the "distal" variant primarily affecting the truncus inferior of the brachial plexus (12-14).

Although most cases are characterized by severe neuropathic pain in the initial phase, about 5% of all cases exhibit a painless onset, which makes diagnosing these patients more challenging (2, 4).

Long term complaints

A comprehensive cohort study conducted by van Alfen and van Engelen (2006) and Cup et al. (2013) shed light on the long-term implications of NA. Their studies followed 246 patients for three years or more and revealed that a substantial proportion of these patients, roughly two-thirds, experienced enduring pain and paresis (4, 8). Muscle atrophy and/or residual paresis were

observed in 60% of the patients leading to movement restrictions, enhanced muscle fatigability, and discoordination of humero-scapulo-thoracic movement ("scapular dyskinesis") and scapular winging ("scapula alata") (8). From a clinical perspective, it is important to acknowledge both the true prevalence of NA and its long-term functional impact on patients' lives. Indeed, by elucidating the chronic nature and persistence of symptoms beyond the acute phase, recent research has highlighted the significance of considering long-term management strategies for NA (8, 15); notwithstanding the fact that there is still unclarity about the course of recovery after NA and the effects that different complaints have on the daily lives of those who are affected (15).

Compensatory movement after neuralgic amyotrophy

Abnormal motor patterns commonly associated with NA, such as scapular dyskinesis and scapula alata, have been extensively documented (4, 16-21). It is evident that many individuals affected by NA encounter challenges in effectively recruiting the scapular musculature to stabilize the scapula along the thoracic wall when using the affected arm (15, 21, 22). In approximately 70% of patients affected by long thoracic nerve damage, weakness of the serratus anterior muscle, a crucial scapular stabilizer, develops. While clinical experience suggests that this nerve typically recovers over time, persisting pain and fatigue caused by scapular instability usually do not resolve (8). In about 70% of the patients the long thoracic nerve is damaged causing initial weakness of the serratus anterior muscle, which is one of the most important scapular stabilizers (4). In our clinical experience with over 5000 patients, this nerve typically recovers over time but the related scapular instability usually does not improve in parallel (8). The persistent scapular instability leads to various symptoms, including pain in the compensatory muscles (e.g., levator scapulae and minor pectoral muscles), subacromial pain, complaints due to entrapment neuropathies, increased muscle fatigue, and limited active range of motion during various daily activities (7). Clinical observations at our plexus clinic have revealed an important phenomenon in a large subset of patients with NA who exhibit normal serratus anterior and trapezius muscle strength yet still demonstrate scapular instability during arm movement. This observation suggests that coordination deficits, rather than muscle weakness, play a primary role in the loss of scapular stability in NA. Recent research from our group by Lustenhouwer et al. suggests that the observed cortical reorganization after NA may contribute to the persisting scapular dyskinesis (23, 24). Their study revealed maladaptive alterations in the cortical organization related to visuomotor functions among patients diagnosed with NA (25). This notion supports the potential for (physical) therapy interventions aimed at retraining

appropriate scapular motor control. The potential for improving scapular instability and related symptoms through therapy is supported by the observation that compensatory rigid scapular positioning is a common pattern in NA patients. This rigid positioning, involving elevation, downward rotation, and anterior tilt of the scapula, is often accompanied by rigid arm stabilization through humeral adduction, internal rotation, and elbow flexion. Downward rotation of the scapula contributes to a loss of acromial height and reduced humeral head stabilization due to unfavorable positioning of the glenoid and the rotator cuff. As a result, patients frequently experience symptoms consistent with subacromial pain syndrome (SAPS), entrapment neuropathies, and muscular fatigue of the periscapular muscles.

Self-management

NA often leaves patients with persistent symptoms, turning a sudden-onset condition into a chronic one requiring long-term care. To manage the diverse challenges associated with NA, a condition marked by pain, weakness, uncertainty of recovery and functional limitations, patients need to actively reengage in self-management.

In 2003, Lorig and Holman, emphasized that patients are primarily responsible for daily care, requiring adjustments in daily habits and developing key self-management skills (26). These skills include problem-solving (e.g., finding ways to cope with pain or fatigue), decision-making (e.g., choosing exercise programs, organizing day-to-day activities), utilizing resources (e.g., finding help from family members or colleagues; changing work environments or tasks), collaborating with medical professionals, taking initiative to prevent problems (e.g., adapting activities to avoid excessive complaints), and strengthening self-belief in managing their condition (26).

Successful self-management interventions hinge on recognizing a patient's stage of change, assessing their readiness for change, and using motivational interviewing techniques (27-33). A crucial factor influencing behavior change and its sustainability is self-efficacy, the belief in one's ability to succeed (32, 33). Effective interventions empower patients with necessary knowledge, skills, and confidence to manage all aspects of NA, including physical, psychological, and social dimensions. While most self-management programs focus on the medical aspects of NA, some interventions, particularly those developed and tested by occupational therapists, go further to address both behavioral and emotional aspects (28, 29).

Specific rehabilitation approach

In 2009 no literature about the rehabilitation of patients after NA was available yet. Thus, our group started treating these patients – based on self-developed insights – with a combination of physical and occupational therapy. A treatment approach was formulated in which physical therapy focuses on coordination training of periscapular and humeral movement during practical activities and occupational therapy focuses on preventive posturing, proper activity dosing and execution, and energy conservation through behavioral strategies. This resulted in an interdisciplinary low-frequency treatment program emphasizing self-management, in which patients apply appropriate coordination and behavioral strategies during daily activities as much as possible.

Objectives and outline of this thesis

This thesis aims to advance the understanding and management of long-term complaints and limitations due to NA and reflects the development of a specific, NA-oriented rehabilitation program at the plexus clinic of Radboud university medical center.

The overarching objectives are:

a. to identify persistent difficulties in the daily lives of people with NA and to determine treatable factors for improved recovery.

b. to develop and pilot test a new interdisciplinary rehabilitation program for people with long-term complaints after NA;

c. to develop and test reliable clinimetric tools to systematically assess functional limitations faced by people with NA.

By pursuing these objectives, This research is expected to contribute to the growing body of knowledge in this field, inform clinical practice, and ultimately enhance the quality of care provided to patients affected by NA.

Chapter 2 reports a prospective cohort study aimed to develop recommendations for rehabilitation after NA by identifying the functions and activities associated with persistent pain and fatigue, such as muscle weakness and discoordination. **Chapter 3** is a pilot study presenting and evaluating a treatment approach for secondary complaints and limitations after NA, combining occupational and physical therapy. **Chapter 4** is a clinimetric study that assesses the validity and reliability of a new procedure for hand-held dynamometry to evaluate the strength of the serratus anterior muscle. **Chapter 5** is a clinimetric study that evaluates the effectiveness of a three-dimensional measurement method for upper extremity range of motion in people with NA. **Chapter 6** presents a review that offers an up-to-date overview of NA. It addresses phenotype, pathophysiology, genetics, epidemiology, and advancements in nerve imaging. Additionally, it provides a state-of-the-art for interventions used during the acute and subsequent, more chronic phases of NA.

Chapter 7 is the general discussion that highlights the importance of identifying individual needs of people with NA in terms of diagnosis, self-management, and shared decision-making, as well as the significance of an interdisciplinary treatment approach in combination with adequate movement control combined with self-management. This chapter also addresses methodological considerations and provides recommendations for further research to improve the clinical management and societal perspective of people with NA.

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Chapter 2

Residual complaints after Neuralgic Amyotrophy

Edith HC Cup, Jos IJspeert, Renske JM Janssen, Chaska Bussemaker Beumer, Joost Jacobs, Allan J Pieterse, Harmen van der Linde, Nens van Alfen

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Abstract

Objective
To develop recommendations regarding outcome measures and topics to be addressed in rehabilitation for persons with neuralgic amyotrophy (NA), this study explored which functions and activities are related to persisting pain in NA and which questionnaires best capture these factors.

Design
A questionnaire-based survey from 2 cross-sectional cohorts, one of patients visiting the neurology outpatient clinic and a cohort seen at a multidisciplinary plexus clinic.

Setting
Two tertiary referral clinics based in the Department of Neurology and Rehabilitation from a university medical center provided the data.

Participants
A referred sample of patients (N=248) with either idiopathic or hereditary NA who fulfilled the criteria for this disorder, in whom the last episode of NA had been at least 6 months ago and included brachial plexus involvement.

Interventions
Not applicable.

Main Outcome Measures
Two custom clinical screening questionnaires were used as well as the Shoulder Rating Questionnaire Dutch Language Version, the Shoulder Pain and Disability Index (SPADI), the Shoulder Disability Questionnaire (SDQ), and Overall Disability Sum Score.

Results
The survey confirms the high prevalence of persisting pain and impairments. More than half of the patients were restricted by pain, while in those without pain 60% experienced residual paresis. Correlations show an intimate relation between pain, scapular instability, problems with overhead activities, and increased fatigability. A standard physical therapy approach was ineffective or aggravated symptoms in more than 50%.

Conclusions
Pain and fatigue are strongly correlated to persisting scapular instability and increased fatigability of the affected muscles in NA. Our results suggest that an integrated rehabilitation approach is needed in which all of these factors are addressed. We further recommend using the SPADI and SDQ in future studies to evaluate the natural course and treatment effects in NA.

Introduction

Neuralgic amyotrophy (NA), also called idiopathic brachial plexus neuropathy or Parsonage Turner syndrome, is a distinct disorder of the peripheral nervous system characterized by episodes of extreme pain at onset, rapid multifocal paresis and atrophy of upper extremity muscles and a slow and often incomplete recovery (1). Most commonly the long thoracic, suprascapular and anterior interosseous nerve are affected, although the extent and distribution of symptoms can vary widely (2). For many physicians the hallmark of the disorder is a winged shoulder blade (scapula alata), which is present in about two-thirds of patients (Figure 1). Most patients recover in the course of 1-2 years to about 70-90% of their previous physical functioning, and yet many are left with residual pain and disability which appear to be due to impaired exercise tolerance and altered shoulder biomechanics (1). While NA was usually thought to be a rare disorder with a minimum incidence of 2-3 per 100,000 per year (3,4) the disorder is also under recognized and the true incidence might be several times higher than previously assumed (5).

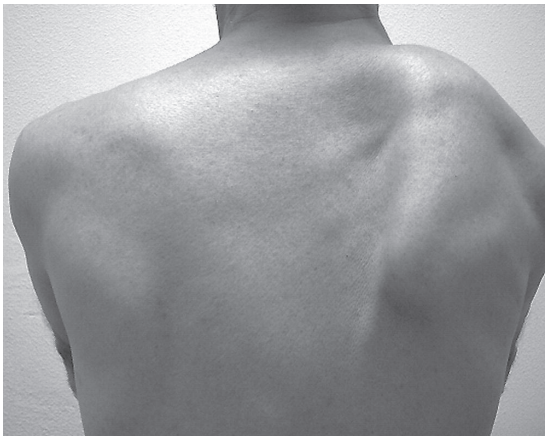

Figure 1. Winged shoulder blade or so-called scapula alata during arm elevation, which is present in about two thirds of patients with NA.

Our tertiary center has an extensive, 15-years, experience with over 900 documented neuralgic amyotrophy patients, about 10% of who have the hereditary form. Since 2009 a multidisciplinary outpatient plexus clinic, combining neurological, rehabilitation, physical therapy and occupational therapy evaluation, serves as a national referral center for the disorder. Currently, no proven effective treatment is available for NA in either the acute or later phase of the disorder (6). To develop an evidence-based treatment strategy it is necessary to first gain knowledge of the prevalence, nature and severity of residual complaints of NA patients and obtain insight into the determinants of those complaints and their severity. In addition, meaningful and valid outcome measures are needed to evaluate the natural course and effect of treatment.

In this study we take a first step by describing the residual complaints and their correlations in a large group of NA patients consisting of two cross-sectional patient cohorts from our center. The main aim of the study is to provide information that may help shape an optimal rehabilitation strategy for this group of patients. As persisting pain seems to be a key symptom for persons with NA who have difficulties regaining balance in their daily life, the current study specifically explored which factors (functions and activities) are related to the persisting pain and which questionnaires best capture these factors. These findings will result in recommendations regarding outcome measures and topics to be addressed in rehabilitation for persons with NA and this might be a starting point to develop an ICF core set for NA.

Methods

Participants

To gather information from a large group of patients with NA, 2 cross-sectional cohorts of patients visiting the Radboud University Nijmegen Medical Center were included. Cohort 1 consisted of patients with NA who had visited the neurology outpatient department from 2003 through 2007 and who had participated in a smaller scale research project on NA and persisting pain (unpublished data). Cohort 2 consisted of patients who had been referred to our multidisciplinary plexus clinic for expert rehabilitation advice from January 2009 to March 2011. Patients of both cohorts were included if 1) they fulfilled the (modified) criteria for idiopathic or hereditary NA,(7) 2) their last episode of NA included involvement of the brachial plexus, 3) their last episode of

NA had been at least 6 months ago, and 4) they had given written informed consent. If patients were seen at both the neurology outpatient department and the plexus clinic, they were arbitrarily included in cohort 2 to prevent data overlap.

Procedure and measurement instruments

As no specific or validated measurement instruments are available for NA, we explored residual complaints using a combination of 2 custom-made clinical screening questionnaires and questionnaires that have been validated in patients with other disorders affecting the shoulder and arm. To explore whether the various questionnaires on pain and disabilities were representative and thus appropriate for the population with NA, we performed correlations between our clinical variables from the clinical screening questionnaires with the questionnaires validated in other patient groups.

All patients of cohort 1 received a Questionnaire on NA and Pain (QNAP). A selection of these patients consisting of those who reported persisting pain received the following additional questionnaires: Questionnaire on Functional Abilities and Therapy (QFAT), Shoulder Rating Questionnaire–Dutch Language Version (SRQ-DLV) (8, 9), Shoulder Pain and Disability Index (SPADI) (10), Shoulder Disability Questionnaire (SDQ) (9,11), and Overall Disability Sum Score (ODSS) (12). Patients included in cohort 2 received 3 questionnaires identical to cohort 1 (QNAP, QFAT, SRQ-DLV) and also the Checklist Individual Strength 20 (CIS-20) (13,14). The properties of the custom-made screening questionnaires are discussed below.

Clinical variables: Questionnaire on NA and Pain (QNAP)

This custom-made screening questionnaire for patients with NA included questions on type of NA, arm involved, and hand dominance, with multiple choice options. Onset date of NA and number of episodes are recorded with open-ended questions. Prevalence of other shoulder complaints or diseases, including rheumatic diseases or history of shoulder surgery, was recorded with yes/no options. Also, the presence of (shoulder) pain at rest, when moving the arm, when lying on the shoulder, when lifting the arm, or when reaching backward was evaluated with yes/no options, as was the type of pain. If radiation was confirmed, the direction was asked (toward thumb or little finger). Severity of pain was evaluated with a numeric rating scale from 0 to 10 for pain at this moment and the worst and best moment of the week. Additional yes/no questions were asked regarding the relation of pain with

time of day and type of activities performed. Other consequences regarding functions (8 items) and activities and participation (3 items) were evaluated with yes/no options. Finally, the use of pain medication was evaluated (yes/no), and the patient was asked to record the type, dose, and frequency of pain medication.

Clinical variables: Questionnaire on Functional Abilities and Therapy (QFAT)

The QFAT is also a custom made instrument that explores impairments in mobility and strength of the shoulder and arm and the ability to perform specific activities such as computer work, opening pots and writing in NA patients. The type of former treatments (e.g. medication, injections, exercise therapy, surgical intervention) were explored in a yes/no manner. For analgesics the patients was further asked about type and dose. For physical therapy a number of subsequent yes/no questions were asked about treatment types (e.g. massage, weight training, stretching exercises, electrostimulation), whether the patient had found the therapy helpful, neither helpful nor harmful or harmful and whether they also performed exercises at home.

Statistics

Standard descriptive statistics were used. Pearson correlation coefficients were used to explore correlations between residual complaints and items from the validated questionnaires. P values were set at < 0.001 because of multiple comparisons. For the given sample size in this study (with N for most items ≥ 70), Pearson correlation coefficients ≥ 0.3 are considered statistically significant at the $p < 0.001$ level (15). The strength of the correlation was considered moderate between 0.3 and 0.7 and high when> 0.7. Statistical analyses were performed using SPSS 18 (IBM PASW Statistics, IBM Corporation, Somers, NY).

Results

Data collection

Details of the inclusion are shown in the flowchart shown in figure 2.

Demographics

Demographic data for the whole study population are shown in table 1. The ratio of idiopathic versus hereditary NA was about 9:1, and 60% of the patients had experienced only 1 attack, while the remainder had had 2 or more.

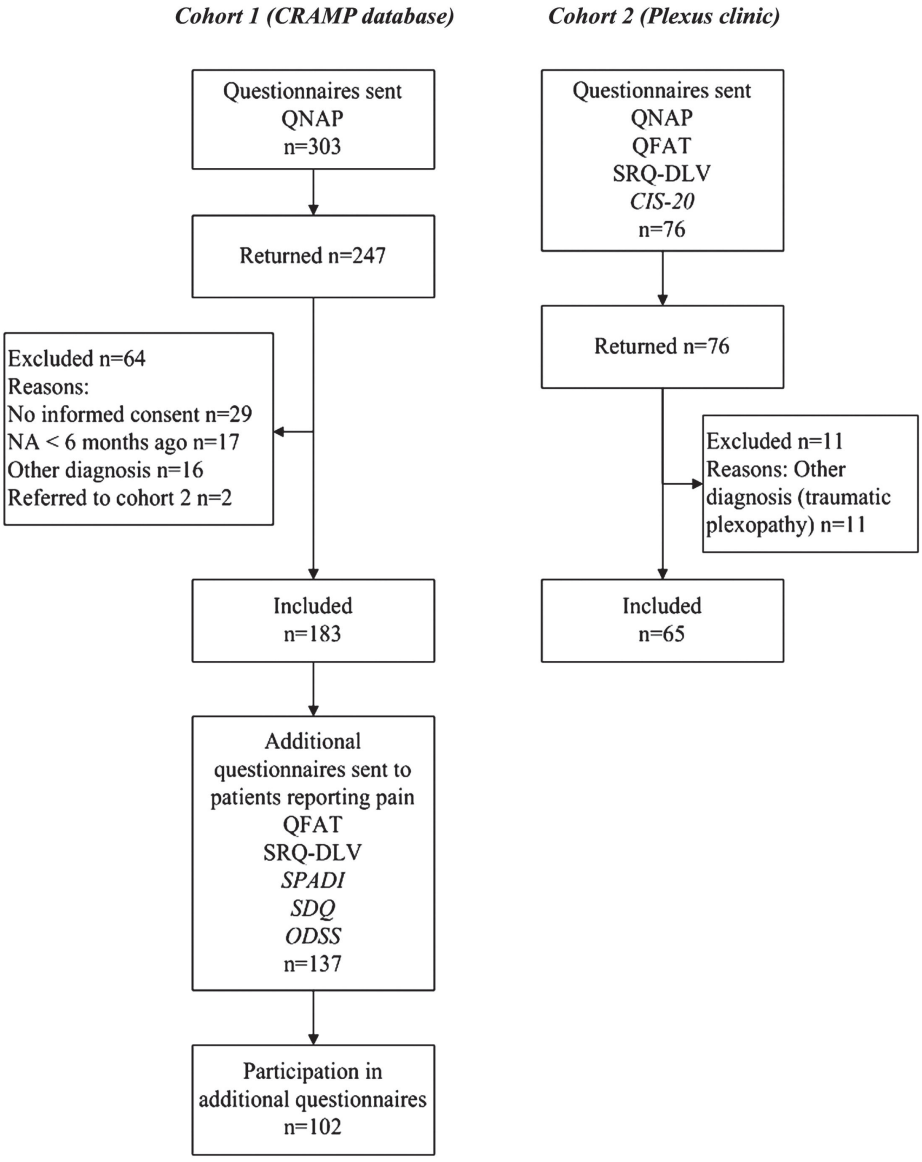

Figure 2. Flowchart showing the inclusion and questionnaires sent to cohort 1 and 2, with 3 identical questionnaires administered in both cohorts (QNAP, QFAT, SRQ-DLV), 3 questionnaires in cohort 1 only (SDQ, SPADI, ODSS), and 1 questionnaire in cohort 2 (CIS-20). Abbreviation: CRAMP, Computer Registry of All Myopathies and Polyneuropathies.

Table 1. Demographic data

Characteristic	Cohort 1 (n=183)	Cohort 2 (n=65)	*P**	Total (n=248)
Sex				
Man	63% (115)	62% (40)	.853	63% (155)
Woman	37% (68)	38% (25)		37% (93)
Age (y)	Missing n=1	Missing n=2	.022	Missing n=3
	48±11 (21–82)	44±13 (17–75)		47±12 (17–82)
Hand dominance	Missing n=1	Missing n=8	.635	Missing n=9
Right	83% (152)	89% (51)		85% (203)
Left	15% (27)	11% (6)		14% (33)
Ambidextrous	2% (3)	0% (0)		1% (3)
Side of complaints	Missing n=3	Missing n=9	.335	Missing n=12
Right	43% (78)	50% (28)		45% (106)
Left	30% (54)	32% (18)		30% (72)
Both arms	27% (48)	18% (10)		25% (58)
Months since last episode	Missing n=17	Missing n=5	.044	Missing n=22
6–12	23% (38)	63% (38)		33% (76)
13–24	34% (56)	19% (11)		30% (67)
>24	43% (72)	18% (11)		37% (83)

NOTE. Values are % (n), mean ± SD (range), or as otherwise indicated.
P values show the significance of differences between cohort 1 and 2.

Clinical data: Questionnaire on NA and Pain (QNAP)

Overall, 38% (87 from cohort 1 and 7 from cohort 2) reported no pain at all. Most, however, still had shoulder pain at rest, and nearly 60% had pain in the affected shoulder during movement and/or when lying on it. The pain was continuous in 56% and mainly described as "nagging." The severity of the pain was dependent on the type and/or duration of activities performed with the affected arm in 67%, and most (82%) found that pain was more severe in the evening. The mean visual analog scale score (0–100) for pain was 47, ranging from 33 for the best (ie, least) pain score to 64 for the worst pain score in the past week. The pain was radiating in 69%, most commonly to the radial side of the forearm and thumb (41%). Fifty-nine percent experienced paresthesia in the arm during stretching or lifting the arm, and 45% reported crepitations in the shoulder joint. The pain caused restrictions in activities of daily life in 54% of the patients. Twenty-nine percent of the patients still used analgesics for their shoulder complaints. At times when patients did not experience pain, 60% were still restricted by residual loss of strength or endurance in the affected limbs. Scapular winging was present at rest (in 44% of the patients)

and/or during lifting or reaching (in 55%), and 48% reported a lower position of the affected shoulder compared with the contralateral side. One third of the patients could not fully lift the arm overhead, and 41% indicated they needed a compensatory strategy (eg, by bending their trunk contralaterally) for this movement.

Clinical data: Questionnaire on Functional Abilities and Therapy (QFAT)

Sixty percent of the patients reported less active shoulder mobility (ie, paresis). Passively restricted range of motion was present in 37% of the patients, indicating concomitant glenohumeral joint or rotator cuff pathology. More than 80% of the patients reported difficulties with lifting the arm above shoulder height and 52% with reaching forward. Nearly two thirds of patients also reported less strength when lifting below shoulder height, opening jars and lids, and using the hand. Increased fatigability of the arm and shoulder during repeated movements or postures was present in 86% of the patients. Thirty percent reported that they could only stand or walk for a maximum of half an hour without pain, and 45% were unable to use a computer keyboard for more than 30 minutes without complaints in the affected limbs. Two thirds of patients also reported less strength in the affected hands. Just over 40% of the patients estimated that they could lift 1kg (a sugar pack) 5 times or less above shoulder height (eg, in a cupboard).

Previous therapy

The majority of patients (82% of total) have had previous physical therapy, for a median duration of 6 months (range: 1 month to 6 years). Physical therapy had involved massage of the affected region in over 70%, electrical stimulation of the affected muscles in 27% and exercises without (89%) or with weights (52%), or the use of an elastic band for resistance muscle training (49%). Two thirds of the patients also exercised at home in between therapy sessions. Over half of the patients reported either worsening (20%) or no effect (33%) of exercise therapy. Muscle stretching exercises were given to 74% of the patients and 62% of them reported this type of exercise has been effective. Thirty percent had undergone one or more injections in the shoulder joint prior to their visit and 6% had undergone previous shoulder surgery, as compared to 3% in the general population (16).

Additional questionnaires

Shoulder Rating Questionnaire–Dutch Language Version

The scores on the SRQ-DLV showed large variations in pain and limitations in daily activities, recreational/sport activities, and work. Mean scores for almost every item were approximately 40% to 60% of the maximum obtainable score, but the full range in scores from maximally limited to unlimited was obtained for every item. The most preferred areas of improvement were pain (40%) followed by the domains of activities.

The remaining questionnaires were only available for patients in either of the 2 cohorts.

Shoulder Pain and Disability Index

The mean total pain, disability, and overall scores on the SPADI (n=79) in cohort 1 indicated mild impairments, but showed significant variation between patients. Most pain was recorded for lying on the affected side, reaching on a high shelf, and pushing with the affected arm (mean subscale score, 2.6/10). Worst disability (ie, most effort required) was scored for placing an object on a high shelf (mean, 3.8/10) and carrying a heavy object of 5kg (mean, 3.6/10).

Shoulder Disability Questionnaire

The mean summary score of the SDQ in cohort 1 (n=102) was 55.5 (range, 0–100), indicating affirmative answers to more than half of the items asking about shoulder complaints in cohort 1. Problems present in more than half of the patients included shoulder pain during daily activities (53%), pain during lifting or carrying (57%), or pain when reaching above shoulder level (66%).

Overall Disability Sum Score

Generally about 75% of patients in cohort 1 reported no restrictions on the items of the ODDS (n=102). This is also represented in the mean arm grade of 1.3, which corresponds with mild to moderate symptoms, resulting in some restrictions in daily activities.

Checklist Individual Strength 20

The mean total CIS-20 score of cohort 2 (n=62) was 82, which is above the cutoff point of 76 for significant fatigue. The Checklist Individual Strength subscale fatigue showed that 63% of the patients scored ≥35, of which 50% had a score >40, indicating severe fatigue.

Correlations between variables

Among the clinical variables, the strongest correlations were found between shoulder pain, scapular winging during elevation, difficulties working above shoulder height and increased fatigability (see upper rows in table 2). Correlating clinical variables to the items and composite scores of the validated shoulder questionnaires showed that the SRQ subdomain score of how well patients were doing with respect to their daily activities and the total SDQ and SPADI scores correlated best with the clinical items above. The ODSS arm subscale was not very sensitive in this patient group and only correlated significantly with shoulder pain during arm movements (r = 0.537). all correlations are reported in table 2.

Table 2. Correlations between clinical variables and shoulder questionnaires. Correlation strength expressed as Pearsons' r with p ≤ 0.0001

Clinical items	**Correlates with**	**r**
Decreased AROM shoulder	Pain when moving arm	0.576
	Restricted without pain	0.435
	Winged scapula during activity	0.424
Winged scapula during activity	Difficulty reaching forward	0.499
Difficulty elevating arm >90°	Increased arm fatigability	0.613
	Pain when moving arm	0.546
Shoulder questionnaire item	**Correlates with clinical item**	
SRQ Daily activities	Pain when moving arm	0.715
	Decreased AROM shoulder	0.617
	Difficulty elevating arm >90°	0.594
	Increased arm fatigability	0.454
	Winged scapula during activity	0.433
SPADI total score	Difficulty reaching forward	0.649
	Pain when moving arm	0.642
	Decreased AROM shoulder	0.641
	Restricted without pain	0.462
SDQ total score	Decreased AROM shoulder	0.713
	Pain when moving arm	0.656
	Difficulty elevating arm >90°	0.642
	Difficulty reaching forward	0.600
	Increased arm fatigability	0.477
	Restricted without pain	0.421

Abbreviation: AROM, active range of motion.
Correlation strength expressed as Pearson *r* with *P*≤.0001.

Discussion

This questionnaire survey of 248 patients confirms persisting pain and impairments in about 60% of NA patients referred to a tertiary clinic during the first three years of follow up (1,5). As in other neuromuscular disorders (17), focal symptoms in NA also affect overall fitness which was shown by 63% of the patients in this study who fulfilled the criteria for severe fatigue. Most pain and impairments were reported with reaching and lifting above shoulder height as well as during prolonged or repetitive arm activities. Passively restricted range of motion of the shoulder joint was found in 1/3 of the patients.

Our finding that standard physical therapy - which for shoulder symptoms usually consists of rotator cuff muscle strength training - was ineffective or aggravated symptoms in over 50%, and our clinical experience that focusing on only one item often does not lead to successful symptom reduction, indicate the importance of a multifactorial therapy approach. In addition, the substantial percentage of patients that had received a form of treatment from which no real improvement was to be expected (e.g. massage) and the very protracted therapy sessions in some for up to 6 years are disconcerting, as they imply an unduly burden on healthcare costs and resources without concomitant benefit.

Correlation analysis confirmed the intimate relation between pain and scapular instability, problems with overhead activities and increased muscle fatigability that can lead to strain. This suggests that a treatment that improves scapular stability and periscapular muscle endurance and decreases or spreads out periscapular load over the day is most likely to reduce persisting pain . This information can be used to direct further physical and occupational therapy interventions.

We also explored which validated questionnaire items best capture the clinical problems NA patients encounter and could possible contribute to an ICF core set for NA. The best correlations with respect to this were found for the SPADI total score, the SDQ total score and the SRQ daily activities subscale. We therefore recommend to use the SPADI and SDQ questionnaires as follow up tools for future studies of the natural course and treatment effects in NA.

This study focused especially on NA patients with persisting pain, as in practice this pain seems to be a key symptom, or a "final common pathway" complaint, for people with NA who cannot regain control over and balance between their

residual complaints and the demands of daily life. Apparently, there are NA patients who are more at risk for such persistent complaints than others. We have the impression that differences in coping strategies play a major role in this. Clinically, patients with persisting pain can usally be characterized as over-users. Their coping strategy when encountering problems such as pain and impairments is to simply continue their efforts by putting more energy into it. While this may work fine as a strategy for attaining ones' goals in life, it seems to be counterproductive as an adaptation mechanism in NA. However, this assumption has not been studied formally and will need to be addressed in further studies to optimize rehabilitation for NA patients.

Study limitations

A main limitation of this study is a strong selection bias in the patients reported here, because those with a speedy and uncomplicated recovery will not likely be referred to a tertiary clinic. Another limitation relates to the patient self report about their treatment for NA. As for all patients the episode of NA is at least six months ago, there could be recall bias in the reporting of the former treatments and satisfaction with the outcomes. Also information on the adherence to former treatments is lacking which is an important issue for a treatment to be successful. In addition, the clinical and additional questionnaires were not specifically validated for this patient group. However, one of the goals was to validate these measures and to select the most appropriate clinical questions and existing questionnaires on pain and disabilities that best captured the problems in functions, activities and participation resulting from NA. Finally, this study relied on the spontaneous response of the patients visiting the neurology outpatient department (cohort 1) or the plexus clinic (cohort 2). The questionnaires were not checked for completeness. This has resulted in quite a few missing variables, especially in cohort 1 for the clinical variables in the Questionnaire on NA and Pain (QNAP). For future clinical and research purposes we aim to use a computerized / internet questionnaire which will address this issue and prevent missing values.

Conclusions

Persisting pain and disabilities are a common sequel for a proportion of NA patients. Our results indicate that a new treatment paradigm is needed that takes a multifactorial approach and addresses scapular instability and increased fatigability of the affected muscles to achieve successful

rehabilitation and prevent complications and unnecessary healthcare costs for the individual with

Supplier
A. IBM PASW Statistics; IBM Corp, 294 Route 100, Somers, NY 10589-3202.

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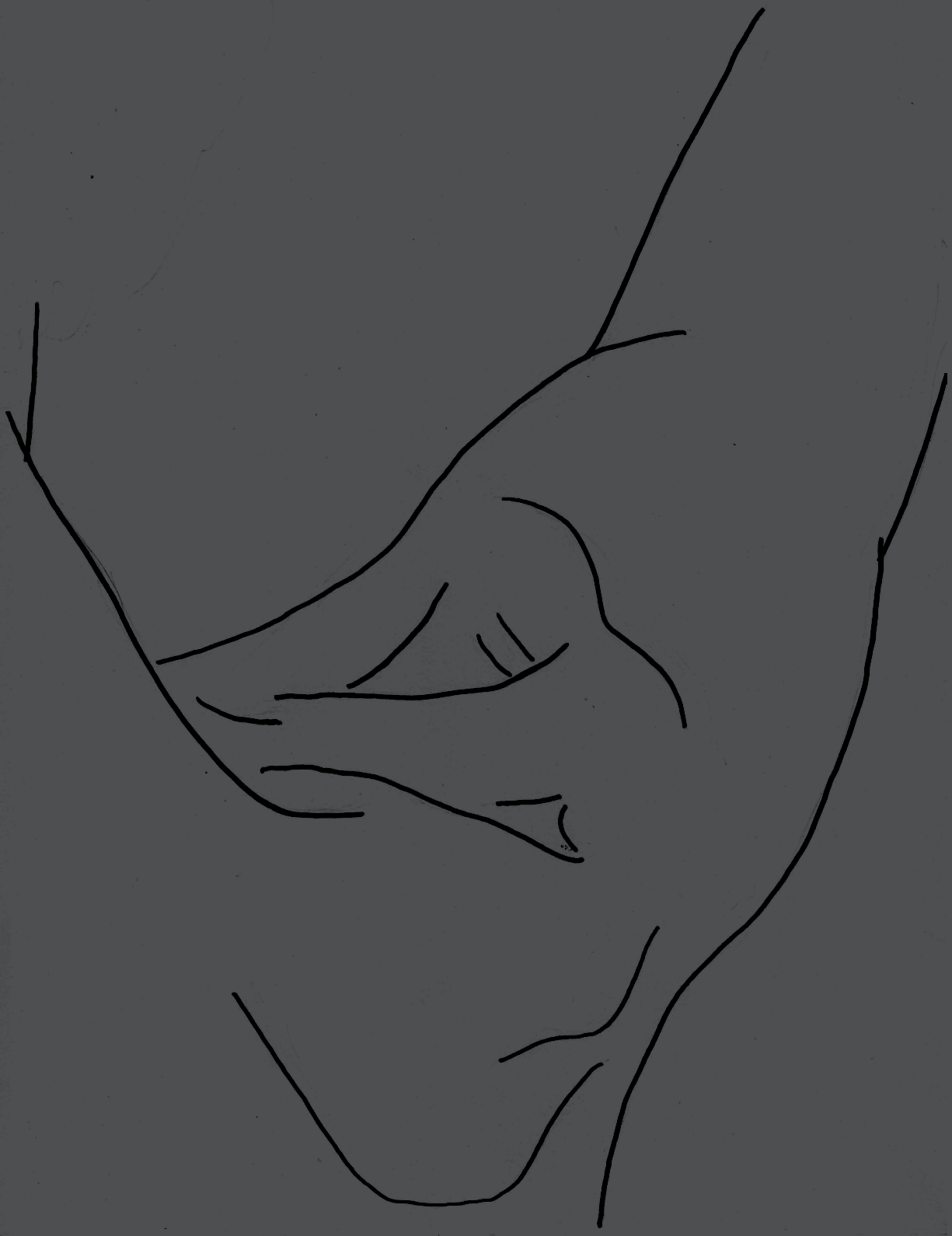

Chapter 3

Efficacy of a combined physical and occupational therapy intervention in patients with subacute neuralgic amyotrophy: a pilot study

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Abstract

Background

Neuralgic Amyotrophy (NA) is characterized by neuropathic pain, subsequent patchy paresis and possible sensory loss in the upper extremity. Many patients experience difficulties in performing activities of daily life and are unable to resume work. We developed a combined physical- and occupational therapy program for patients recovering from NA.

Objective

Evaluation of the effectiveness of a multidisciplinary intervention program for patients with subacute NA.

Methods

We performed a within subject proof-of-principle pilot study in eight patients with subacute NA. Patients followed 8 hours of physical and 8 hours of occupational therapy spread over a 16-week period. Primary outcome measures: The Canadian Occupational Performance Measure (COPM) and Shoulder Rating Questionnaire (SRQ). Secondary outcome measure: Disability of Arm Shoulder and Hand (DASH).

Results

Improvements (mean (95% CI)) were found in the performance and satisfaction scores of the COPM +2.3 (0.9–3.7) and +1.4 (0.4–2.4) points, respectively and the SRQ +14.8 (7.4–22.0) points. The majority of patients (6 out of 8) also demonstrated improvements in the DASH.

Conclusion

The proposed physical and occupational therapy program, may be effective for patients with subacute NA, as demonstrated by improvements in activity, performance and participation.

Introduction

Neuralgic Amyotrophy (NA; Parsonage Turner Syndrome, brachial plexus neuritis) is a peripheral nerve disorder which affects the brachial plexus (1). In about 10% of cases the lumbar plexus is also affected, resulting in pain and loss of neurological function of the lower extremity (2). The onset of NA is usually characterized by severe neuropathic pain (numeric rating scale (NRS) 8-10), which on average lasts three to four weeks. Generally it is accompanied by loss of neurological function of the upper extremities and shoulder girdle. This acute phase is followed by a chronic phase, in which the primary neuropathic pain is replaced by both neuropathic stretching pain of affected nerves and musculoskeletal pain localized to the origin and/or insertion of paretic and compensating muscles (3).

NA can be either idiopathic (INA) or hereditary (HNA) (4,5). INA is the most common variant with a reported incidence of 2-3 per 100,000 per year and a median onset in the fourth decade. HNA is about 10 times less common and has a median onset in the second decade. In general NA is under-recognized (3). The etiology of NA is still not fully understood, but the current assumption is that the disease is caused by a combination of genetic, mechanical, auto-immune and environmental factors (1).

The primary consequences of NA are paresis, muscle atrophy, movement restrictions, fatigue, impaired humero-scapulo-thoracic coordination and scapula alata (winging of the shoulder blade) (6,7). These impairments lead to difficulties over time, when performing activities above shoulder height, reaching, lifting below shoulder height, maintaining body positions and, in the majority of patients, when performing sustained or repetitive movements (8). In addition, shoulder exorotation, pinch grip and pronation strength are also often affected (3). Eighty-two percent of patients become impaired in performing activities of daily living (ADL) such as self care, household, work-related activities, hobbies and sport for years after onset of symptoms (8). A correlation between coping strategies and persistent complaints has been suggested (8).

Although there are promising results on the use of prednisolone treatment in the acute phase of NA (9), there is insufficient evidence to support any medical intervention to restore impairments resulting from NA (10). In addition, very little is known about rehabilitation interventions, including physical and

occupational therapy, focusing on consequences of NA in terms of functional impairments or restrictions in activities and participation (10).

Since 2009 the departments of Rehabilitation and Neurology of the Radboud University Medical Centre host a multidisciplinary outpatient clinic, which serves as a national referral center for NA in the Netherlands. In this clinic, a neurologist, rehabilitation physician, physical therapist and occupational therapist examine NA patients. The clinic has developed a multidisciplinary outpatient rehabilitation intervention program for patients in the subacute phase of NA (>6 months after onset of disease). The aim of this combined allied health care intervention is to educate patients on how to regain control over their complaints and manage their lives with the residual symptoms after NA. Physical therapy (PT) focuses on educating and training movement and position sense, coordination of the affected shoulder girdle and improving functional endurance. Occupational therapy (OT) focuses on prevention and reduction of overuse of affected and compensating muscles, body ergonomics at rest and during activities and adaptation of activities and environmental changes. From our clinical experience this approach seems to be effective, but this has not yet been formally established. Therefore, this pilot study aims to evaluate the effectiveness of the proposed multidisciplinary intervention program in patients with subacute NA.

Methods

Design

A within subject proof-of-principle pilot study was performed. Measurements were carried out during a baseline period (three months prior to intervention), at start, and at completion of the multidisciplinary intervention program. Patients were recruited by the neurologist or rehabilitation physician from our outpatient clinic.

Participants

Ten patients were invited to participate in the study from November 2011 to February 2012. Eight patients were included and all completed the intervention program (Figure 1). They all fulfilled the following inclusion criteria: 1) diagnosed with NA by an experienced neurologist (NvA); 2) uni- or bilateral complaints with a NRS pain score >5; 3) NA >6 months after onset; 4) aged >18 years; 5) understanding Dutch written and spoken language.

Patients were excluded if they had: 1) previous surgery of the affected neck and or shoulder.; 2) history of other central neurological disease; 3) a Beck Depression Inventory (BDI) score >20 (11). Two patients were excluded from the study for the following reasons; one patient had a recurrent attack of NA and was therefore no longer in de subacute phase of the disease, the second patient scored >20 points on the BDI. The study was approved by the medical ethics committee of the Radboud University Medical Centre and written informed consent was obtained from all patients.

InterventionThe aim of the multidisciplinary intervention program was to support patients in their self-management strategies to regain control over their complaints. The program teaches problem solving skills as described in the model of D'Zurilla (12), combined with role management skills (13). We developed a model, shown in figure 1, that gains insight into different components that need to be addressed during the intervention program (Figure 1).

Figure 1. Model showing treatment components.This model can be used as a checklist during treatment; it shows possible components that might be addressed and which may vary for each patient. For instance, in some patients improvement of body functions may be more important than adaptation of behavior. Optimally, the intervention focuses on all aspects of the model. Which results in a decrease in pain and fatigue, an improvement of body functions and activity levels, performance and participation. This may also lead to increased self-efficacy and ultimately self-management.

OT focuses mainly on issues in the outer two circles (activity, participation and external factors) and PT mainly addresses improvement of body functions. Both, PT and OT, address adaptation of behavior and the conveying of knowledge about NA related to functioning in daily life. Self-efficacy was improved by increasing self-control over complaints. Motivational interviewing techniques were used for behavioral changes and changes in coping style (14).

The program consisted of a 16-week treatment period during which patients were treated weekly in week 1-4, once every two weeks in week 5-8 and monthly in week 9-16. Each treatment session involved one hour PT and one hour OT.

Physical therapy interventions

PT included training to regain scapular muscular balance and progressive resistance training of rotator cuff muscles; the latter only after scapular muscular balance was achieved since scapular stability is essential for the function of arm muscles that control position (15-17). All exercises were carried out without or only with minimal pain during and after exercises. If patients did experience (excessive) pain during or after the exercises, intensity of the program was adjusted accordingly.

If patients had difficulty in implementing the scapular control movements in daily life, scapular proprioceptive taping was used to increase awareness of their scapular position during posture and movement (18). Some patients with NA experience neural stretching pains of the brachial plexus, which are likely caused by neural entrapment in case of a habitually protracted and adducted scapula because of serratus anterior weakness and compensatory activation of the pectoralis and trapezius muscles. When present, this complication was treated by increasing scapular control as described above and by using neural mobilisation techniques (19), using movements designed for the upper limb tension test (20). These involved patients to grab hold of the doorframe and stretch out their arm until they experienced mild neurological sensations such as tingling or radiating pain. They were instructed to perform this stretching exercise three times a day in three repetitions, lasting 20 to 30 seconds. Patients who lacked control of their primary cervical stabilizing muscles, tested using the cranio-cervical flexion test with pressure biofeedback (21), received sensomotory cervical stability training (22). When increased muscle tone and/or myofacial trigger points were found in the neck or shoulder region patients were treated with muscular relaxation exercises and trigger point releases as pre-conditioning for sensomotory scapular and cervical training (23).

Occupational therapy interventions

The focus of the OT intervention lied on enabling daily occupations. Patients gained insight into activities that provoked pain and into strategies focussed on preventing and reducing pain caused by overuse of affected and compensating muscles. To this end, energy conservation strategies were taught including taking mini-breaks, practicing optimal body ergonomics during rest and action, and analysing and adapting activities or the environment with or without use of aids and adaptations (24). Patients learned self-management strategies to reduce stress and physical strain and to find a balanced distribution of activities during the day/week. As readiness and willingness to change are needed to implement these strategies in daily life, motivational interviewing techniques were used (14, 25).

Outcome measures

Several domains of the international classification of functioning (ICF) were assessed (26). Outcome parameters were used at the level of

1) *Body functions:* strength of rotator cuff musculature was evaluated by using Hand Held Dynamometry (HHD) (Microfet2®), handgrip was measured using handgrip dynamometry (Takei Grip dynamometer®) and pinch grip was measured using pinch grip dynamometry (B&L systems pinchgauge)

2) *Activities and function:* Shoulder Rating Questionnaire (SRQ) and Disabilities of Arm Shoulder and Hand (DASH) questionnaire, in the Dutch language version, were used to measure activity performance and to quantify disability. The SRQ is used in combination with the DASH because SRQ scores showed high correlation with functioning in patients with NA, although the DASH is reported more sensitive to change and has higher reliability and validity in general shoulder populations (8, 27).

3) *Participation:* the Canadian Occupational Performance Measure (COPM) was used to evaluate occupational performance and satisfaction with performance of the most important daily occupations identified as a problem by the patients (28).

4) *Quality of life:* The short form 36 questionnaire (SF-36) was used to measure health-related quality of life (29).

5) Personal factors: The Checklist Individual Strength 20 (CIS-20) was used to measure fatigue. The CIS-20 (30) was also used at the time the patient was referred to the outpatient clinic and was checked for changes in perceived fatigue before patients entered the program (31). In addition, the Self Efficacy for Performing Energy Conservation Strategies Assessment (SEPECSA) was used (30). Primary outcome measures were the SRQ and the COPM with the DASH as a secondary outcome measure. All instruments used are reported sensitive to change, valid and reliable in various shoulder populations (8, 27). An assessment schedule is presented in Figure 2.

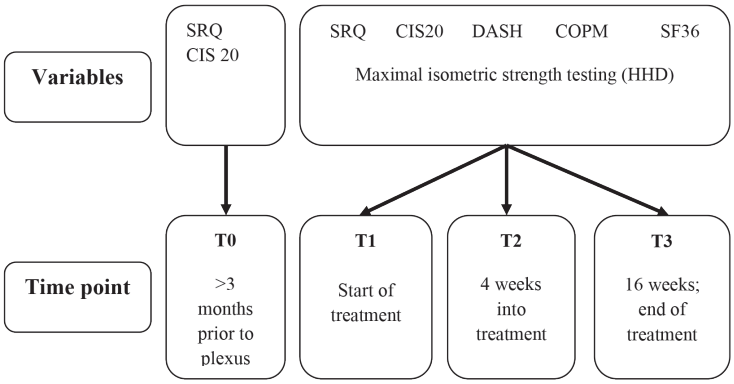

Figure 2. Study procedures timeline.COPM: Canadian Occupational Performance Measure, DASH: Disabilities of the Arm, Shoulder and Hand, CIS: Checklist Individual Strength, SEPECSA: Self Efficacy for Performing Energy Conservation Strategies Assessment, SF-36: Short Form (36) health survey

Procedure

As standard screening procedure, patients received several questionnaires (including SRQ and CIS) at the moment they were referred to the outpatient clinic, on average three months prior to the outpatient clinic visit. Therefore the SRQ and the CIS were used to control for changes in functional ability during the waiting list period. Afterwards, questionnaires were completed by the patients at the start, during, and after the intervention program. The patients' therapist carried out COPM, and HHD measurements.

Statistical methods

Descriptive statistics were used; results were presented by use of mean, standard deviation (SD) and 95% confidence intervals. Pre- to post-treatment within subject difference scores were checked for normality by use of

descriptive statistics (skewness and kurtosis) and quantile probability plots (QQ-plots). Pre and post measurements were compared and tested by use of the paired samples *t*-test and Wilcoxon signed-rank test. Significance level was set at 0.05. Statistical analyses were performed using SPSS 18 (IBM PASW Statistics, IBM Corporation, Somers).

Results

The mean ± SD age of the 8 patients (6 males) who completed the program was 46 ± 10 years (range 34-58). Mean duration of complaints until start of treatment was 35 ± 50 months (range 7-156). In 6 patients their dominant arm was affected. Pre- to post-treatment within subject difference scores were normally distributed.

During the program 2 patients developed therapy resistant glenohumeral capsular inflammation, which was treated with steroid infiltration. This decreased the symptoms, after which the intervention program was resumed. Another patient experienced prolonged nerve irritation of the middle plexus with radiating sensory symptoms in the distribution territory of the pectoral nerves, median and radial nerve. This was treated with a short course of oral prednisolone (60mg daily for one week, tapering over the next week), which decreased paresthesia and hypesthesia and reduced muscle tone in the pectoralis minor muscle. The outcome for these patients was not different from the other patients on outcome measures used. Figure 3 shows an overview of inclusion and interventions.

Two patients experienced neural stretching pains, that slowly diminished over the course of eight weeks using neural stretching exercises. All patients had myofacial triggerpoints in the neck extension muscles, trapezius descendens, levator scapulae, pectoralis minor or rhomboid muscles. Trigger point releases reduced muscle tone and increased of range of motion for up to three days. Four patients carried out cervical stabilizing exercises, which lead to a diminished muscle tone and increased activity in secondary cervical stabilizers. All eight patients received scapular sensomotory facilitation taping, which helped them to implement scapular positioning in ADL.

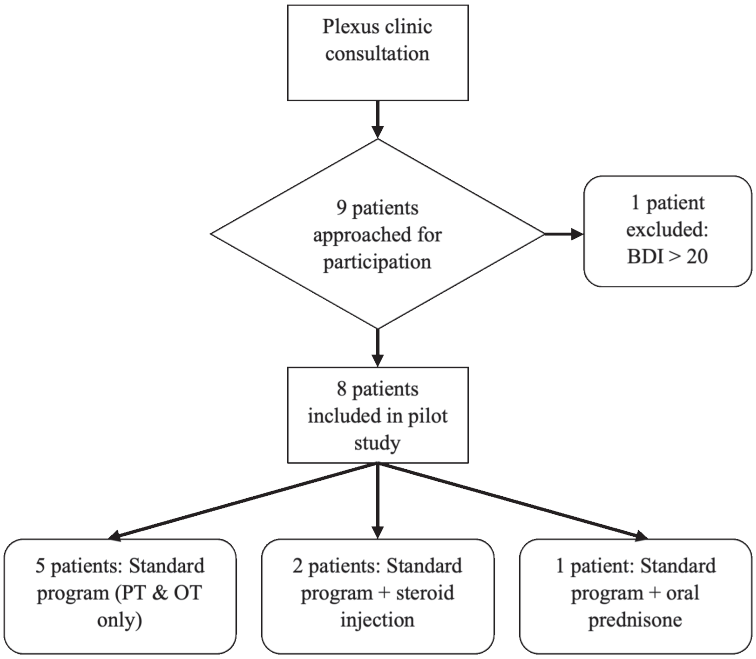

Figure 3. Flowchart procedure of the study. BDI: Beck depression inventory, OT: Occupational Therapy, PT: Physiotherapy

Outcome measures

During the 3-month baseline period before the start of the intervention program none of the patients demonstrated any change in scores of SRQ total, SRQ global or CIS-fatigue subscales.

After intervention, the (mean ± SD) change in SRQ Total score 14.8 ± 8.6, SRQ Global 3.5 ± 1.8, SRQ Pain 4.0 ± 4.9 and SRQ ADL 2.4 ± 2.4 improved significantly. The SRQ total improvement of 30.4% from baseline exceeds the reported minimal clinically important difference (MCID) of 13.5% (32). Seven patients improved on the COPM performance subscale (range) 0.2 to 3.2 points. One patient demonstrated a decrease in COPM performance score of -0.3 points. COPM satisfaction scores demonstrated improvement in all patients (range) 0.2-4.8 points. COPM group scores demonstrated a mean improvement of 1.4 ± 1.2 points in performance and 2.3 ± 1.4 points in satisfaction and the mean difference score for satisfaction also exceeded the reported MCID of 2 points (33). CIS-fatigue scores demonstrated a tendency to improve (i.e. lower scores) in six patients (range) 9.0-12.0, but this was not

significant (p=0.263). Two patients demonstrated an increase in fatigue scores with 3 and 12 points respectively. Six patients demonstrated an improvement >10 points on the DASH score, exceeding the reported MCID (34). DASH results demonstrated a tendency to improve, with a drop of 11.3 ± 14.5 points (0.9-23.4) (p=0.069). Mean SF-36 scores decreased for health change (-37.5 ± 23.1 points (p=0.003)) domains, but not on the other domains. This indicates that, compared to the judgment before treatment, patients found their health state (after the intervention) had more resemblance, compared to their health state a year ago.

HDD measurements only demonstrated a tendency to an increase in strength of the serratus anterior muscle. Values improved in five patients (range) 49.6-187.5 Newtons. Group results for the initial and follow up measurements are shown in table 1.

Table 1. Outcome measurements results.

Outcome	Mean Baseline	Mean end of treatment	Paired Differences†				Significance†
			Mean difference	Standard deviation	95% confidence interval		
					lower	upper	
COPM performance	**4.5**	**5.9**	**1.4**	**1.2**	**0.4**	**2.4**	**.015**
COPM satisfaction	**4.3**	**6.6**	**2.3**	**1.6**	**0.9**	**3.7**	**.005**
DASH total‡	62.3	51.0	-11.3‡	14.5	-23.3	0.9	.064
CIS-20 fatigue‡	38.3	36.0	-2.3‡	6.9	-8.0	3.5	.263
SRQ total	**48.7**	**63.4**	**14.8**	**8.6**	**7.4**	**22.0**	**.002**
SRQ global	**5.9**	**9.3**	**3.5**	**1.8**	**1.9**	**5.0**	**.001**
SRQ pain	**19.5**	**26.0**	**4.0**	**4.9**	**2.4**	**10.6**	**.007**
SRQ adl	**12.2**	**14.6**	**2.4**	**2.4**	**.4**	**4.4**	**.025**
SF36 physical functioning	62.5	64.4	1.9	14.4	-10.1	13.9	.723
SF36 social functioning	16.9	25.0	8.1	10.3	-.51	16.8	.061
SF36 role physical	18.8	28.1	9.4	18.6	-6.2	24.9	.197
SF36 role emotional	100	100	0	0			1.00
SF36 mental health	66.0	75.0	-4.4	13.0	-14.7	6.0	.351
SF36 vitality	50.0	45.6	-8.9	12.4	-30.3	12.4	.355
SF36 pain	57.4	48.5	1.9	25.5	-16.3	20.0	.814
SF36 health change	**75.0**	**37.5**	**-37.5**	**23.1**	**-56.9**	**-18.2**	**.003**
SEPECSA	7.3	7.7	0.4	1.1	-.5	1.4	.263
Keygrip*	10.2	8.2	-2.0	2.6	-4.5	0.4	.084
Handgrip*	35.2	32.9	-2.3	5.8	-7.1	2.6	.313
Exorotation*	94.4	97.2	2.8	29.5	-21.8	27.5	.791
Endorotation*	108.4	116.4	8.0	42.5	-27.5	43.5	.611
Elbow flexion*	158.5	165.9	7.4	50.1	-34.5	49.3	.688
Elbow extension*	125.4	105.6	-19.8	33.1	-60.0	20.3	.260
Serratus Anterior*	162.7	210.4	47.7	75.2	-15.2	110.5	.116

** Strength measures of the affected arm †Paired statistics based on paired samples T-test*

‡ Negative scores relate to functional improvement

***Bold** scores indicate significant resultsCOPM: Canadian Occupational Performance Measure, DASH: Disabilities of the Arm, Shoulder and Hand, CIS: Checklist Individual Strength, SEPECSA: Self Efficacy for Performing Energy Conservation Strategies Assessment, SF-36: Short Form (36) health survey*

Discussion

Results of this pilot proof-of-principle study indicate the efficacy of our combined PT and OT intervention program for these patients with subacute NA. Patients, who demonstrated no improvement in more than three months prior to the intervention, improved in functioning and even more so in satisfaction with their performance. All patients demonstrated large improvement in SRQ subscales, and the majority in the DASH total score. Even the lower limits of the 95% confidence interval of the SRQ-total and SRQ-global subscales indicate a clear clinically relevant improvement of more than 30%. Strength values of upper extremities obtained by HDD demonstrated no significant change during the treatment period. The serratus anterior muscle that was specifically activated during the program was the only muscle demonstrating improvement but not statistically significant. Even though functioning and satisfaction improved, no significant improvement of experienced fatigue by patients was measured with the CIS-fatigue subscale. As fatigue is a very global indicator of how much energy people have to spend during their daily life, we hypothesize that the learning and training period during our program also cost them extra energy and hence no net effect was present in their energy balance. Further follow up of these patients beyond the treatment period will have to show if in time fatigue will decrease after completion of the intervention program and if persons manage to integrate lifestyle changes automatically.

To our knowledge, this is the first ever rehabilitation intervention described in patients with NA. Even in other peripheral nerve disorders of the shoulder complex, no therapeutic interventions have been researched until now. This makes it difficult to compare our results with other findings. The novelty of the proposed therapy approach does not lie in the therapeutic interventions used, but in the combination of these interventions in complex shoulder problems due to NA. We expect the rather large effects found to be due to the personalized character of this intervention in which problems are approached from a patients perspective.

Study limitations

This study was designed as a proof of principle pilot study and has its limitations. Although patients were controlled in a within subject design, a natural recovery tendency or other confounding may have influenced results (35). In this design patients may also have reported improvement partly due to a placebo or Hawthorne effect (36). Especially because patients have been treated in the national reference center for NA, which may have enhanced patient confidence in the treatment program. Another limitation was the group size, although rather

large and significant differences were found in this small study population, generalizability may be poor (35).

Two patients received additional treatment because of glenohumeral joint complications during the program. However, primary outcome scores for the group as a whole were no different with or without these subjects.

Conclusions

We did not find indications that our intervention program caused harm or negatively influenced physical and social functioning of our patients. On the contrary, perceived global status in the SRQ and patient satisfaction in the COPM improved extremely well during the treatment period. The relatively small change in muscle strength suggests that improvement in this population is most likely caused by functional and behavioral adaptation to nerve damage and corresponding loss of function of the affected shoulder. Therefore, patients' behavior in relation to complaints, smart alternative ways of carrying out (strenuous) activities, efficient ways of shoulder movement and control and acceptance of limitations appear to be key issues for treatment of these patients. Patients apparently learn to adapt to their limitations and achieve higher efficacy without need for improvement of body functions.

We strongly emphasize the need for a further controlled study, with a larger sample, to provide this multidisciplinary program with a firmer evidence base. Qualitative studies are also recommended to give better insight and understanding of the treatment ingredients that helped patients to deal with problems as a result of NA.

Declaration of interest

The authors declare that there is no conflict of interest.

Acknowledgements

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List of suppliers

Microfet 2 handheld dynamometer: Hoggan health industries;
P.O. BOX 488, Salt Lake City, UTAH, USA
Pinchgrip dynamometer: B&L Engineering Ltd, 11 Kennet Road, Dartford, Kent, UK
Takei Grip dynamometer: Takei Medical Optical 1-1-6 Yushima, Bunkyo-ku, Tokyo,113 113-0034, JAP

Chapter 4

Validity and reliability of serratus anterior hand held dynamometry

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Abstract

Background

Strength testing of the serratus anterior muscle with hand held dynamometry (HDD) in supine subjects has low reproducibility, and is influenced by compensatory activity of other muscles like the pectoralis major and upper trapezius. Previously, two manual maximum voluntary isometric contraction tests of the serratus anterior muscle were reported that recruited optimal surface electromyography (sEMG) activity in a sitting position. We adapted three manual muscle tests to make them suitable for HHD and investigated their validity and reliability.

Methods

Twenty-one healthy adults were examined by two assessors in one supine and two seated positions. Each test was repeated twice. Construct validity was determined by evaluating force production (assessed with HHD) in relation to sEMG of the serratus anterior, upper trapezius and pectoralis major muscles, comparing the three test positions. Intra- and interrater reliability were determined by calculating intra-class correlation coefficients (ICC) smallest detectable change (SDC) and standard error of measurement (SEM).

Results

Serratus anterior muscle sEMG activity was most isolated in a seated position with the humerus in 90° anteflexion in the scapular plane. This resulted in the lowest measured force levels in this position with a mean force of 296N (SEM 15.8N). Intrarater reliability yielded an ICC of 0.658 (95% CI 0.325; 0.846) and an interrater reliability of 0.277 (95% CI -0.089;0.605). SDC was 127 Newton, SEM 45.8 Newton.

Conclusion

The results indicate that validity for strength testing of the serratus anterior muscle is optimal with subjects in a seated position and the shoulder flexed at 90° in the scapular plane. Intrarater reliability is moderate and interrater reliability of this procedure is poor. However the high SDC values make it difficult to use the measurement in repeated measurements.

Background

The ability to stabilize the scapula against the chest wall at rest and during upper limb movement has been widely recognized as a prerequisite for optimal upper limb function and related daily activities (1,2). Scapular dyskinesis, defined as abnormal scapular position and movement that may result in e.g. 'winging' or 'tipping', has been observed in many types of shoulder pathology, such as impingement syndrome, rotator cuff and labral tears, glenohumeral instability, and secondary to central and peripheral nervous system disorders (3-6). Several authors have related scapular dyskinesis to loss of muscle strength in the scapulothoracic muscles, such as the lower and middle parts of the serratus anterior muscle (7-9). Lack of strength or endurance in this muscle can cause downward (medial) rotation of the scapula, making its lower medial border more prominent (10). Others have related scapular dyskinesis to a muscular imbalance (or discoordination) rather than muscle weakness (2, 6, 11). Yet, various rehabilitation programs promote scapular strengthening exercises in the treatment of patients with shoulder disorders (12, 13). However, reference values for serratus anterior muscle strength are not available. In addition, a strength training approach may not be beneficial for patients who have coordinative problems (14-16). In this perspective, it is important to test serratus anterior muscle strength and coordination separately in order to differentiate between patients who can and those who cannot benefit from strength training. The presence of scapular dyskinesis in the absence of strength loss would suggest that motor control therapy might be a more successful approach than strength training.

Manual muscle strength is routinely scored using a six point scale described by the Medical Research Council (MRC) (17). Although the use of the MRC scale is widespread, its usefulness and reliability is questionably, particularly around joints other than the elbow and knee (18, 19). Especially the evaluation of relatively normal muscle strength within the upper ranges of the MRC scale lacks interrater reproducibility (18), which is understandable as the definitions of the MRC grades imply that grade 3 is a fixed point ('anti-gravity strength'), but grade 4 is a wide range between grade 3 and 'normal' muscle strength (grade 5) (17). Handheld dynamometry (HHD) was demonstrated to be a reliable alternative for MRC testing of muscle strength (20-22). Reliability of HHD has been found to be high for the serratus anterior and trapezius muscles, although its validity with regard to these muscles has not been extensively studied (23).

Serratus anterior muscle strength is commonly evaluated by applying axial pressure to the humerus in the frontal plane with subjects in a supine position and their scapula protracted with 90° of anteflexion in the shoulder (24). Due to the protraction, the supine test position might be prone to recruiting muscle activity in the pectoralis muscles and therefore not suited for measuring isolated serratus anterior muscle strength (24, 25). Evaluation of serratus strength using active horizontal abduction during testing to correct for pectoralis activation is possible (26), however not feasible in clinical practice. Ekstrom et al. presented a different approach to the evaluation of maximum voluntary isometric contraction (MVIC) of the serratus anterior muscle. Their subjects were sitting upright with lumbar support, the arm positioned in the scapular plane and in 90° or 125° anteflexion of the shoulder (27). In these two positions resistance was applied in the scapular plane at the olecranon and at the inferior angle of the scapula attempting to rotate the scapula downward (medially) (27). They reported significantly higher surface electromyography (sEMG) activity of the serratus anterior muscle during MVIC testing in both seated positions compared to the supine position (27). However, the two seated testing positions presented might also lack validity. The force needed for the serratus test above 90° in the scapular plane can produce co-contraction of the trapezius descendens muscle (25, 28). Therefore, the strength found in these positions is most likely not produced by the serratus anterior muscle alone.

To allow valid and reliable strength testing of the serratus anterior muscle with HHD, we modified both seated test positions described by Ekstrom et al. (27). This modification was needed because the original tests required two points of contact, whereas HHD is only possible with one point of contact. Because of the lack of reference values it was not possible to compute a reasonable force production expected for these test positions. Therefore, construct validity was determined in healthy adult subjects, during MVIC testing, by evaluating sEMG activity of the serratus anterior, upper trapezius and pectoralis major muscles for the two modified seated positions compared to the supine position. We hypothesize that the position with the most isolated serratus anterior muscle EMG activity constitutes the most valid test for serratus anterior strength. In addition, for force measurements with HHD, intra- and interrater reliability of each test position were evaluated by comparing repeated measurements by two assessors.

Methods

This study was approved by the medical ethical committee of the Radboud University Medical Center and complied with the declaration of Helsinki. Written informed consent was obtained from each subject before inclusion in this study.

Subjects

Twenty-one healthy subjects were recruited by convenience sampling from physical therapy students of the University of Applied Sciences in Nijmegen, the Netherlands.

Inclusion criteria were: age 18 years or older and sufficient knowledge of the Dutch or English language to understand written and spoken instructions. Exclusion criteria were: rotator cuff tendinopathy or tears, other glenohumeral or subacromial deficits, rheumatic diseases, central or peripheral nervous system disorders, acute shoulder pain before or during the experiment. All above criteria related to the tested arm (right side), if applicable.

Experimental protocol

We examined three different positions (A, B and C) to test the muscle strength of the serratus anterior. Test position A is a frequently used evaluation of serratus anterior muscle strength described by Michener et al. (24). In supine position, subjects are required to resist strength applied by the HHD placed just below the olecranon, while placing the elbow and the shoulder in 90° flexion in the frontal plane. Test positions B and C have been derived from Ekstrom et al. and adapted for use with HHD(27). Subjects are seated in a stable chair with lumbar support, but without scapular support. They are instructed to elevate the tested arm in the scapular plane to respectively 90° and 125° shoulder flexion, with the elbow in 90° of flexion. Angles were checked with a standard goniometer. Axial pressure was applied with the HDD on the olecranon in the scapular plane. In test positions B and C, assessors placed themselves against a wall for extra stability and strength, in contrast to position A (see Figure 1).

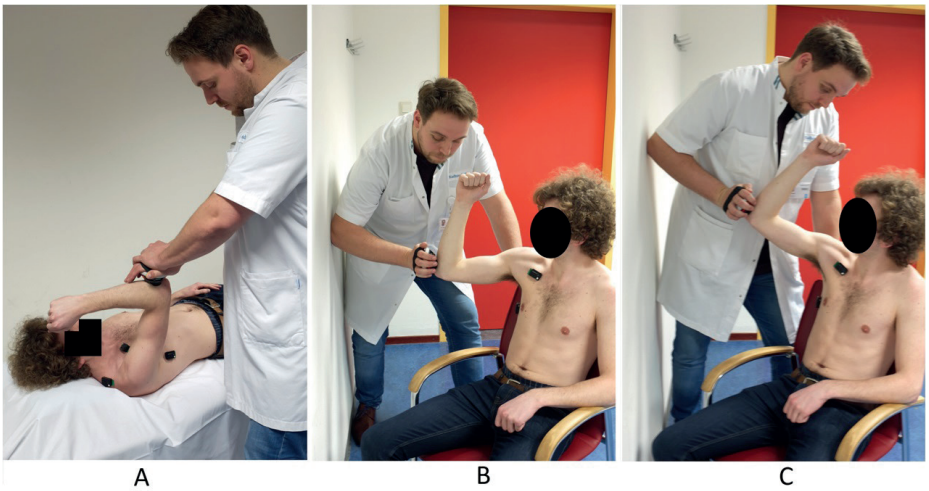


Figure 1. Test positions and surface electromyography placements for serratus anterior muscle testing, note; depicted angles differ from actual goniometry angles measured while testing.

Measurements

Subjects were tested during one day in the morning and afternoon. All subjects refrained from any sports activity on the day of testing.

For strength and sEMG measurements the 'make method' for strength testing was used (29). MVIC testing was carried out by two assessors, both experienced physical therapists (JI, 30 yrs,115 kg,192cm; and HK, 40 yrs,76 kg,183cm). Calibrated Microfet II™ HHDs were used for the collection of strength data. A test assistant stored the sEMG output as well as the strength data in Newton on a computer. The assessors were not able to read out strength data or sEMG signals during testing. Per test position, each contraction lasted 3 seconds with a ramp up of 4 seconds and a ramp down of 4 seconds. Starting cues for timing of the tests were given by the test assistant. The assessors instructed subjects as follows: after the given cue for start of measurement, they counted down from 4 to 0, after which the subject was asked to "push-push-push" for 3 seconds and then asked to gradually release strength while counting down from 4 to zero. Each contraction was repeated twice per test position, with at least one-minute rest between trials. Every subject was tested twice by each assessor, with a two-minute resting period in between, in test positions A, B and C.

EMG setup

Surface EMG signals were collected from the serratus anterior, upper trapezius and pectoralis major muscles by applying wireless sensors (W4p-SP-W01, Delsys Inc., Boston, USA) to the skin with Delsys Adhesive Sensor Interface. Prior to electrode placement, the skin was carefully shaved, degreased with alcohol and rubbed with sanding paper. The sEMG sensors were placed at the following locations: for serratus anterior muscle measurement at the 6th to 8th rib in the mid-axillary line anterior to the fibers of the latissimus dorsi muscle (27); for upper trapezius muscle measurement at 50% on the line from the acromion to the C7 spinous process, following SENIAM guidelines (30); and for the pectoralis major muscle measurement electrodes were placed approximately 2 cm medial to the coracoid process (Figure 1) (28, 30).Data analysisThe sEMG signals were filtered and rectified (low cut-off filter 10 Hz, high-cut off filter 1000 Hz, notch filter at 50 Hz), digitized at a sampling rate of 2000 Hz with a common mode rejection ratio of > 80dB (W4p-SP-W02, Delsys Inc., Boston, USA), and were stored on a laboratory computer for offline analysis. During offline analysis, the root mean square (RMS) of the sEMG signals during the three second maximum for each contraction were calculated using EMG Works® (Delsys Inc., Boston, USA). Subsequently, the signals of the 2 contractions per test position were averaged per assessor. Strength data was recorded in Newtons.

Statistical analysis

Validity: Statistical analysis was performed using Statistical Analysis System 9.2 (SAS Institute Inc, Cary, USA). Inspection of sEMG data revealed a non-normal distribution. Therefore, a logarithmic transformation was performed to correct for skewness. A linear mixed model for repeated measurements was used to assess the differences between the three test positions for each muscle, separately. The model reference point was set at test position C, as it was estimated that this test position would produce most serratus anterior muscle activity based on the study by Ekstrom et al. (27). The dependent variable was the logarithmically transformed RMS-value of EMG activity during the 3-second maximum contraction. The estimated values of the sEMG activity for each position and the relative differences between the positions with 95% confidence intervals (CIs) were calculated by use of the anti-logarithmic transformation.

Reliability: Strength data was also inspected for normality. The difference in muscle force (N) between the test and the retest measured by JIJ, and

between tester JIJ and HK was calculated. Reproducibility (test-retest) was divided into assessment of reliability and agreement parameters (31). Reliability was analysed using the intraclass correlation coefficient (ICC). ICC's were calculated using a two-way mixed effect model (ICC3.1agreement) with 95% confidence intervals (CI). ICC values were interpreted as follows in terms of reliability: < 0.5 as "poor", 0.5-0.75 as "moderate", 0.75-0.9 as "good", and > 0.9 as "excellent' (32). To assess agreement, the standard error of measurement (SEM agreement) and the smallest detectable change (SDC agreement) were calculated. Both were expressed in the unit of the measurement, Newton. The SEM was calculated as SEM agreement = pσ2 error = p(σ2 o+ σ2 residual) (33). The variance due to systematic differences between the observers (σ2 o) and the residual variance (σ2 residual) were obtained through a varcomp analysis (33). The SEM agreement was used to calculate the SDC agreement = 1.96 pn SEM (30). In this formula 'n' refers to the number of measurements, which is two in our study for test-retest reliability and inter-tester reliability (30). Bland-Altman plots were constructed to determine if there was bias in measurement error (34,35).This plot shows the rater difference against the mean muscle force. The plot visualizes the relationship between the measurement error and the observed value including the presence of systematic bias and bias related to the magnitude of serratus anterior strength. The 95% limits of agreement (95% LoA) were shown in the plot (mean difference ± 1.96 SD). All analyses were performed using IBM SPSS Statistics v22 (SPSS Inc., Chicago, Illinois, United States).

Results

We included 21 subjects (15 males; 19 right-handed) with a mean age of 21 years (range 19-32) and a mean (± SD) BMI of 22.7 ± 2.1 kg/m^2. Mean forces (± SEM) measured per test position were: position A 369.8 ± 18.3N; position B 296.0 ± 15.8N; and position C 313.0 ± 19.8N.

sEMG activity of the serratus anterior muscle was very similar between the three different test positions. However, the pectoralis major muscle showed significantly more activity in position A compared to B and C, and the upper trapezius muscle showed significantly more activity in position C compared to A and B (see Table 1, Figure 2).

Table 1. linear mixed models of electromyography activity difference estimations.

Model	Effect	Estimate	95% CI	
			LL	UL
Serratus anterior	Intercept (mV)	239.54	173.78	330.13
	Pos A	1.09	.78	1.38
	Pos B	1.02	.81	1.24
	Pos C	1	-	-
Pectoralis major	Intercept (mV)	33.04	23.23	45.04
	Pos A	2.94	2.13	4.05
	Pos B	1.32	.96	1.83
	Pos C	1	-	-
Trapezius descendens	Intercept (mV)	89.88	28.34	53.82
	Pos A	.43	.29	.65
	Pos B	.63	.42	.95
	Pos C	1	-	-

Legend: 95%CI, 95% confidence interval; LL, Lower limit; UL, upper limit; mV, microvolts; Pos A, test position A; Pos B, test position B; Pos C, test position C (reference).

ICC values and agreement parameters for test-retest and interrater reliability of test positions A, B and C are reported in table 2.

Paired samples t-tests for the difference scores between HK en JIJ, were significantly different ($p>0.05$), showing no agreement between these different raters. Therefore Bland-Altman plots were only presented for the test-retest data.

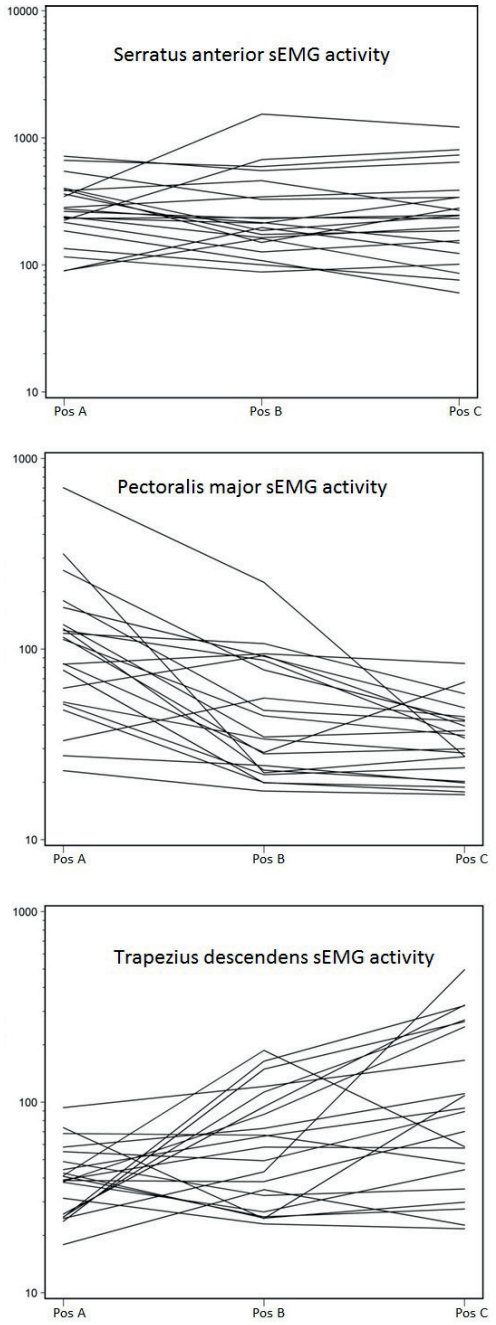


Figure 2. Linear mixed models analysis of EMG activity in micro Volts.

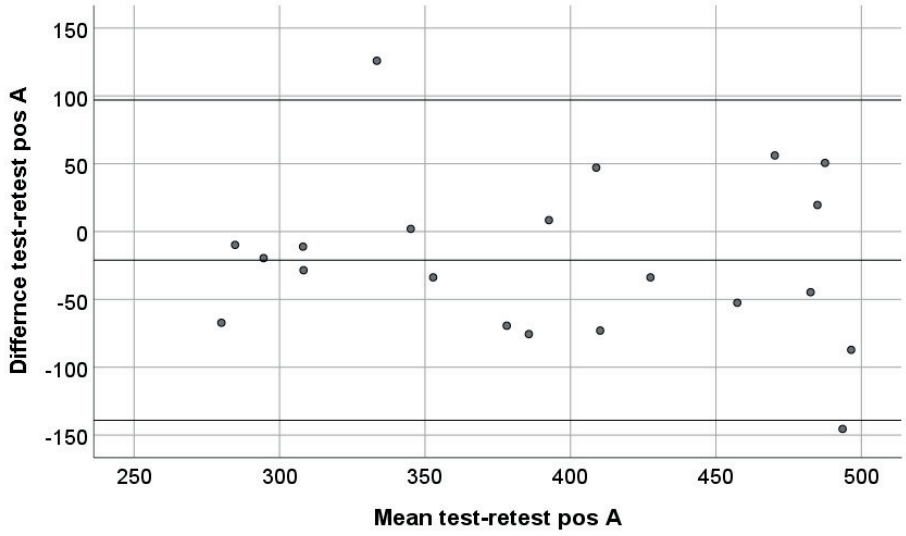
Legend: EMG, electromyography; Pos A, test position A; Pos B, test position B; Pos C, test position C. Note: the scaling for serratus anterior sEMG activity is different.

Table 2. test-retest and interrater reproducibility of serratus anterior hand held dynamometer strength testing

	Test (N) mean (SD)	*Retest (N) mean (SD)*	*Diff test-retest (N) mean (SD)*	*95% LoA (N)*	*ICC3.1 $_{agreement}$ (95 % CI)*	*SEM $_{agreement}$ (N)*	*SDC $_{agreement}$ (N)*
test-retest							
Pos A	383.88 (77.65)	404.92 (84.96)	-21.05 (60.22)	-139.08; 96.98	0.712 (0.420; 0.871)	44,10	122,40
Pos B	314.43 (75.1)	322.34 (82.34)	-7.90 (65.90)	-137.06; 121.26	0.658 (0.324; 0.846)	45,80	127,00
Pos C	351,54 (100.36)	376.16 (93.55)	-24.62 (59.37)	-140.99; 91.75	0.794 (0.490; 0.916)	44,52	123,40
Interrater	*Tester JI mean (SD)*	*Tester HK mean (SD)*	*Diff Tester JI VS HK mean (SD)*				
Pos A	383.88 (77.65)	340.44 (82.95)	43.43* (92.74)	-138.34; 225.20	0.794; (0.552; 0.912)	55,80	196,80
Pos B	314.43 (75.10)	264.21 (61.76)	50.21* (78.85)	-104.34; 204.76	0.277 (-0.089; 0.605)	55,80	154,50
Pos C	351.54 (100.36)	265.10 (40,0))	86.48* (86.21)	-82.49; 255.45	0.226 (-0.107; 559)	85,31	236,47

N: Newton; SD: Standard deviation; Diff: Difference; LoA: limits of agreement; ICC: Intraclass correlation coefficient; CI: Confidence interval; SEM: Standard error of measurement; SDC: Smallest detectable change; %: percentage; *: p<0.001

Legend: ICC 3.1, intraclass correlation coefficient model 3.1; 95%CI, 95% confidence interval; LL, Lower limit; UL, upper limit.


Differnce test-retest pos A
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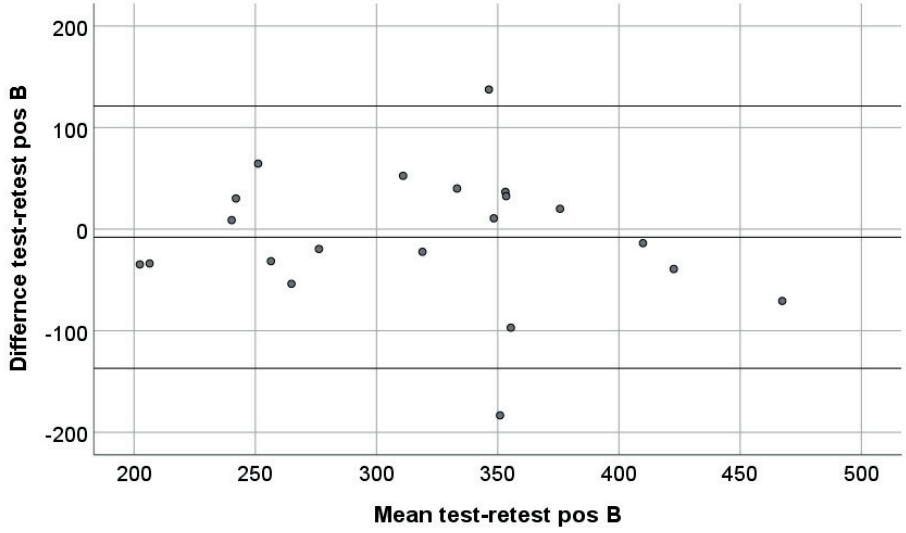
100
50
0
-50
-100
-150
250
300
350
400
450
500
Mean test-retest pos A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500
Mean test-retest pos B

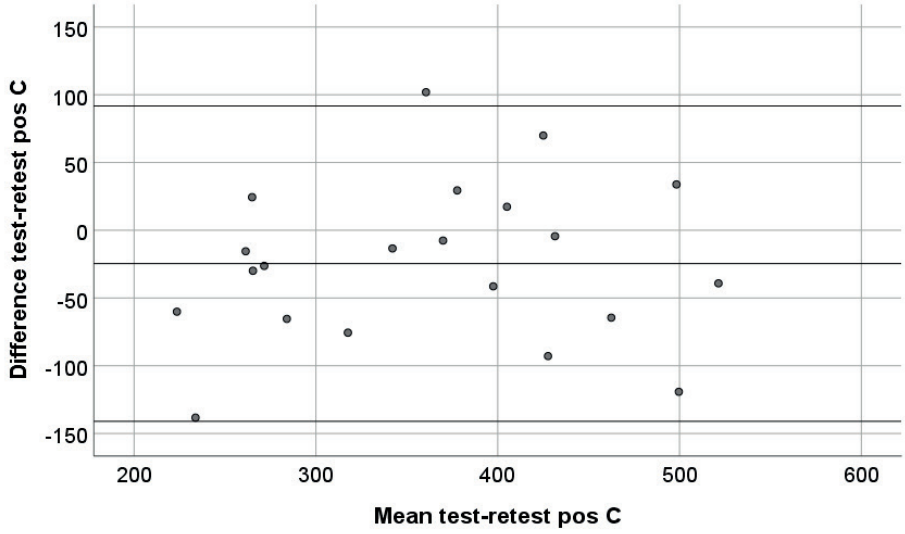

Figure 3. Bland Altman plots for test-retest differences and their relation to the magnitude of strength measured with HHD in Newtons

Discussion

By using sEMG of the serratus anterior, upper trapezius and pectoralis major muscles we were able to demonstrate that the serratus anterior muscle was equally activated in three test positions, but most selectively in the seated position with the arm placed in 90° of flexion in the scapular plane (position B, figure 1). Position B produced less maximum strength compared to position A (-74N) and C (-17N), suggesting less co-contraction by the upper trapezius or pectoralis major muscles. Therefore, test position B seems to be the most valid position for isolated assessment of serratus anterior muscle strength measured with HDD. We found similar sEMG activity in all test positions, although we expected to measure most serratus anterior muscle activity in position C based on the previous study by Ekstrom et al.(27). An important difference with the present study is that the original test provides the opportunity to apply resistance to the arm as well as the scapula using two hands. We used only one point of contact at the arm without scapular fixation, which can explain more similar serratus anterior muscle activity among test positions in our study. The idea of testing in the scapular plane is supported by a recent cadaver study, which has shown that the serratus anterior muscle fascicles from the 4^{th} to 9^{th} rib are attached to the inferior angle of the scapula (36). The inferior angle of the scapula shows more movement when the arm moves in the scapular plane than in the frontal plane (37). This confirms that serratus anterior muscle strength should be tested in the scapular plane.We observed a moderate intrarater reliability (ICC3.1 agreement). Intrarater reliability of test position B was moderate, although somewhat lower than of position A, with an ICC of .658. Interrater reliability was poor with an ICC of .277. However, the SDC agreement and SEM agreement are rather large. The apparent contradiction between a moderate ICC 3.1 agreement and high SDC agreement and SEM agreement is likely to be caused by the high heterogeneity in the population variance, which makes the random error and systematic error relatively lower. However, and SDC agreement of 127N for the most valid test position (position B) makes it less fit for use in test-retest settings.

The interrater reliability shows low ICC 3.1 agreement. Moreover, the T-test difference in measurements done by HK and JI was significant (P>0.05), so there is no agreement in these measurements (supported by even higher SDC agreement and SEM agreement scores).

The Bland-Altman plots did not show any systematic error in measurement, but did show increased difference scores in the high strength measurements.

We found relatively low intra- and interrater agreement in all our tests. Our subjects produced strength values exceeding 290N. Although we tried to compensate for this by placing the assessor's arm holding the HHD against a wall in positions B and C, our approach may still have led to variation between raters resulting in only fair to moderate ICC values . Another factor may have been the different physical characteristics of the two assessors in our study, who had a substantial difference in body size and weight and therefore, possibly, a different ability to provide resistance to the subject's force production. When compared to the data reported by Michener et al., the ICC values found in the present study are relatively low (24), but the strength values are much higher (exceeding 290N compared to around 150N (24)). This may be caused by the fact that Michener et al. included subjects with shoulder pain, whereas we tested healthy young volunteers. It has previously been reported that the reliability of HHD decreases with strength testing levels above 120N (38). This may be due to the fact that assessors do not have sufficient strength to resist the force produced by the subject.

Translating our results to patients with shoulder problems, the reliability of the measurements is likely to improve in impaired subjects, because smaller amounts of strength are required from the assessor to counteract the serratus anterior muscle forces. Using a stabilization device, as was done in a study by Kolber et al., might also improve reliability, but will decrease the feasibility of the proposed testing protocol in clinical practice (39).

Our study had some limitations. First, we used sEMG instead of finewire-needle EMG signals, to avoid subject discomfort and for medical-ethical reasons. Although sEMG captures a larger number of motor units compared to finewire needle EMG, the use of surface electrodes might have resulted in cross-talk (40). For instance, for the upper trapezius muscle, cross-talk might occur from the underlying supraspinatus muscle, and for the serratus anterior muscle from the intercostal muscles. Yet, studies by Fuglevand et al. and Winters et al. indicated that 90% of the sEMG signal is recorded from within 10-12 mm of the surface electrodes when an electrode spacing of 20 to 25 mm is used (40,41). In our setup this approach should have provided sufficient confidence to measure relatively isolated sEMG data from the serratus anterior, pectoralis major and trapezius descendens muscles, because the musculature possibly causing cross-talk was located well away from this distance. Another limitation may have been the difference in physical characteristics between the two assessors in this study. However, such variations will also occur in

regular clinical practice. Finally, the study group of 21 subjects falls short of the proposed 30 subjects or more by cosmin standards (42). We feel that the validity part of the study has not suffered from the lower number of subjects.

Conclusion

We recommend to assess serratus anterior muscle strength manually, applying axial pressure to the humerus, with subjects in a seated position and with the shoulder flexed at 90° in the scapular plane. Given the relatively low agreement parameters, evaluation of treatment with HHD should preferably be done by the same assessor.

Although further research validating this test procedure in patients with shoulder complaints and pathologies is needed, we expect it to be more feasible in populations with shoulder problems because of limited strength values in those groups.

Acknowledgements
We would like to thank all participants. HAN university of applied sciences kindly provided measurement equipment and logistic support.

Suppliers
a) Microfet II™ hand held dynamometers: HOGGAN Scientific, LLC
b) Wireless electromyogram sensors: Delsys Inc., Boston, USA)

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Chapter 5

Reachable workspace analysis is a potential measurement for impairment of the upper extremity in neuralgic amyotrophy

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Abstract

Introduction

Neuralgic amyotrophy (NA) is a common multifocal neuropathy involving the nerves of the upper extremity, limiting functional capability and reducing range of motion. The reachable workspace is a computerized 3D analysis system that evaluates the relative surface area (RSA) of an individual's arm reachability and has shown usability in several neuromuscular disorders.

Objective

To examine the ability of the reachable workspace to quantitatively detect limitations in upper extremity active range of motion in patients with NA. RSAs of patients with NA were compared to healthy controls and correlated to other upper extremity function outcome measures.

Methods

47 patients with NA and 25 healthy age- and sex-matched controls were measured with the RWS. The study participant's RSAs were correlated to the scores of the Shoulder Rating Questionnaire (SRQ), the Disabilities of Arm Shoulder and Hand (DASH) questionnaire and upper extremity strength measurements using hand-held dynamometry.

Results

Patients with NA showed significantly lower values in the affected arm for all quadrants (except for the ipsilateral lower quadrant) and total RSA compared to controls ($p<0.001$). We found moderate correlations between the reachable workspace, the DASH questionnaire ($r= -0.415$) and serratus anterior muscle strength ($r= 0.414$).

Discussion and conclusions

Reachable workspace is able to detect limitations in active range of motion of the affected arm in patients with NA, and is moderately correlated to upper extremity functional measures. RWS can demonstrate functional limitations of the affected upper extremity in NA, and is a potential functional clinical outcome measure.

Introduction

Neuralgic amyotrophy (NA) is a relatively common multifocal mononeuropathy, with a yearly incidence of 1:1000, that often involves brachial plexus nerves (1, 2). The large majority of patients with NA will have residual symptoms and functional limitations even long after nerve recovery. They usually experience limitations in upper extremity active range of motion (AROM) that impact reaching and overhead activities (3). Physical and occupational therapy, targeting motor control of the scapula and arm, can improve scapular motor control during daily activities using the upper extremities (6). An appropriate therapy program can thus result in an increase in functional capacity, due to more efficient movements that enable patients to use their upper extremity more frequently and with a larger AROM (2, 4). This AROM is typically assessed with goniometry, which is time consuming and has suboptimal reproducibility due to considerable influence of training and experience (5). Moreover, goniometry provides degrees of movement for a specific joint in a single plane, whereas decreased functional capacity is usually related to multiple movement restrictions in multiple joints and planes.

As an alternative to goniometry, a sensor-based reachable workspace (RWS) measure to evaluate the proximal upper extremity AROM and arm reachability has been developed (9-12). The RWS allows simultaneous tracking of multiple joints of the upper extremity in a series of protocolized movements, which has shown correlation to activities of daily living (6). The system shows sufficient accuracy and robustness in tracking upper extremity movement when compared to more complex and expensive motion capture systems (7, 8). As previously published, the RWS outcomes are shown as total and quadrant envelope relative surface areas (RSAs) between 0 and 1. Increasing values indicate more arm mobility (see figure 1 for the quadrant division of RSAs). The RWS produces a visual representation of the RSAs (approximately as hemispherical shape) that provides patients and clinicians with objective information about the functional AROM. The RWS has shown to be a valid and reliable outcome measure in other neuromuscular diseases and musculoskeletal conditions of the upper extremity (9-12).

The aim of this study is to examine the ability of the RWS to quantitatively detect limitations in upper extremity AROM in patients with NA and correlate RSAs with patient reported outcomes for functional capacity and hand-held dynamometry of the upper extremity.

Methods

All data was collected as part of the NA-CONTROL study (13), a randomized controlled trial investigating the effects of an outpatient rehabilitation program for patients with NA in the Netherlands. For the current study we performed a cross-sectional analysis of baseline RWS data collected from the participants in the NA-CONTROL study.

Patients with diagnosed NA who were referred to the muscle center of the Radboudumc with were included during the timeframe between dd-dd. Inclusion criteria were: right hand dominance, right-sided symptoms that included scapular dyskinesia, aged 18 years or older, and not being in the acute phase of NA (>2 months after onset). age- and sex-matched healthy controls, were recruited through the university healthy participants database, with right hand dominance without current or previous shoulder complaints or other comorbidities (e.g. muscular or neurological disorders) were included for comparison. Hand dominance was confirmed using the Edinburgh Handedness Inventory by a score ≥ 40 (14).

The sample size was based on a power analysis for the primary outcome measure of the NA-CONTROL study (i.e. functional capacity of the upper extremity as measured with the Shoulder Rating Questionnaire, Dutch Language Version (SRQ-DLV)) (7). Previous RWS studies in patients with neuromuscular disorders had similar or smaller sample sizes (6,9,11,15). Patients were recruited from the Neurology and Rehabilitation outpatient clinics at the Radboud university medical center, Nijmegen, the Netherlands. Healthy controls were recruited through the university's healthy subject databases. A detailed description of recruitment procedures and a full list of inclusion and exclusion criteria can be found in the design paper of the NA-CONTROL study (7).

Written informed consent was obtained from all study participants prior to participation, and the study was approved by the accredited regional medical ethical committee of Arnhem-Nijmegen (2017-3740,v3.0, NL63327.091.17). This study was registered at ClinicalTrials.gov under NCT03441347.

The RWS system utilizes 3D motion tracking by a sensor to provide arm movement trajectory data that can be used to reconstruct an individual's reachable workspace. We used a relatively inexpensive and portable sensor

system, i.e. the commercially-available Kinect 2sensor (Microsoft, Redmond WA, USA), which has demonstrated excellent reliability and clinical utility (9-12). RWS measurements were performed according to a previously published standardized protocol (8). Briefly, subjects followed a video movement protocol, which covered shoulder movements within cardinal planes, while subjects were seated in front of the 3D sensor (Microsoft corp., Redmond, WA, USA), under the supervision of one of the investigators (RL). Subjects were instructed to reach as far as they could with their arm in several vertical and horizontal sweeps, while keeping the elbow extended and without twisting the body or leaning forward. RSAs were reported as a total of all quadrant data summated or as individual quadrant data, split into 4 frontal quadrants: the (Q1) upper medial, (Q2) lower medial, (Q3) upper lateral, and (Q4) lower lateral quadrant (10). We also calculated an above-shoulder RSA, consisting of the sum score of Q1 and Q3. See figure 1 for a schematic representation of the measurement protocol, the RSA quadrants and a visual hemispherical representation of frontal reachable workspace RSA.

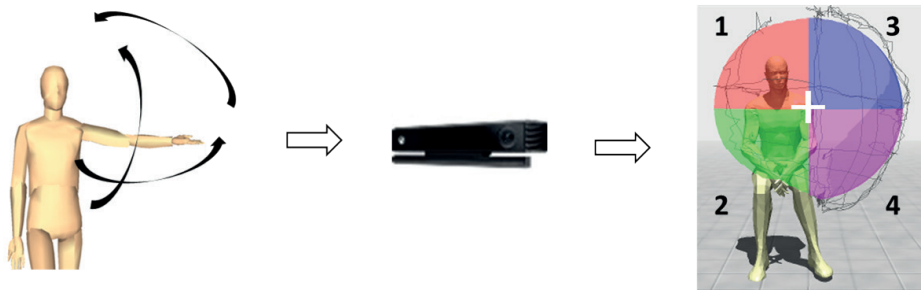

Figure 1. Movement of the arm is detected by the movement sensor and frontal hemispheric reachable workspace (RSA) is reconstructed and graphically represented, with division into four quadrants where the shoulder serves as the origin (left shoulder RSA is shown).

For patients with NA, patient-reported limitations in functional capacity of the upper extremity were evaluated using the SRQ-DLV and Disabilities of Arm Shoulder and Hand (DASH) questionnaire (16, 17). Both questionnaires measure functional capacity of the upper extremity and have shown adequate reproducibility in various populations with shoulder pathology (18). Patients with NA additionally underwent muscle strength measurements. Hand grip strength was measured with a hand-held dynamometer (Jamar®, Sammons Preston Rolyan, Bolingbrook, IL). Maximal force exerted during internal and external humerus rotation and for the serratus anterior muscle, while resisting scapular movement in the scapular plane in 90 degrees of shoulder flexion, were measured with a digital manual muscle dynamometer as described in

a previous study by IJspeert et al.(MicroFET2®, Hoggan Scientific, Salt Lake City, UT, USA)(19-21).

Individual participants underwent all physical measurements during a single day, in a fixed order. They were all tested by the same investigator (RL).

Data was analysed using IBM SPSS statistics (SPSS v 25 (IBM, Armonk, NY). Descriptive statistics were used to evaluate baseline data. RSA data, strength measures and patient reported outcomes were evaluated for normality, visually through histograms, and with the Shapiro Wilk's test. BMI differences between patients and controls were evaluated with an independent samples T-test. Due to non-normality, differences in total and quadrant RSA values of the affected and dominant right side between patients with NA and healthy controls were evaluated using the Kruskal Wallis test. Differences in total and quadrant RSA between the left (unaffected) and right (affected) side within the patients with NA were evaluated with a Wilcoxon signed rank test.

Spearman correlations were calculated for the total RSA and the combined above shoulder RSA (Q1+Q3) of the affected and dominant right arm with functional capacity of the upper extremity (SRQ-DLV and DASH scores) and strength measurements of ipsilateral hand grip, serratus anterior, and internal and external rotation strength. Interpretation was as follows: 0.00-0.10 negigible, 0.10-0.39 weak, 0.40-0.69 moderate, 0.70-0.89 strong, 0.90-1.00 very strong (22). To correct for multiple comparisons, a Bonferroni correction for multiple testing was applied, and alpha was set to 0.005 (0.05 / 10 dependent variables) for the RSAs comparisons and to 0.008 (0.05 / 6 dependent variables) for the correlations.

Results

A total of 47 unilaterally right-side affected NA patients were measured (29 men (62%), mean age 44±12 years). Mean and median time since onset were 16 (±32) and 8 months, respectively. A total of 25 healthy age- and sex-matched control subjects were included (15 men (60%), mean age 43±8 years). One healthy control was excluded due to a pre-existing shoulder problem that was missed at initial screening, but became apparent during the assessment period. This left 24 control individuals for final analysis. One patient was excluded from the RWS analyses due to potential protocol violations. Body

mass index (BMI) did not show significant differences with a mean score of 24.63 ±3.55 for the patients and 24.80 ±2.90for the controls (P=0.31). As bodyweight and height were collected as part of the MRI examination protocol 5 subjects (4 patients with NA and 1 healthy subject) who didn't undergo MRI examination were missing for BMI analysis.

RWS measurements

Patients with NA had a significantly lower total RSA score compared to healthy controls. Quadrants 1, 2 and 3, were each significantly lower in patients with NA compared to healthy controls with the largest difference found for Q1 (upper medial quadrant). Mean differences for each quadrant are shown in Table 1. For a visual representation of the differences see Figure 2.

Table 1. Group differences in reachable workspace RSA

Quadrants	HC RSA	NA RSA	Difference	p value
Left Q1	0.226 ± 0.008	0.205 ± 0.007	-0.021 ± 0.011	0.048
Left Q2	0.181 ± 0.006	0.166 ± 0.004	-0.015 ± 0.010	0.045
Left Q3	0.225 ± 0.003	0.222 ± 0.002	-0.003 ± 0.006	0.264
Left Q4	0.221 ± 0.001	0.223 ± 0.001	0.001 ± 0.007	0.369
Left Total	0.853 ± 0.011	0.816 ± 0.010	-0.037 ± 0.003	0.015
Right Q1	**0.234 ± 0.009**	**0.114 ± 0.067***	**-0.120 ± 0.002**	**<0.001**
Right Q2	**0.172 ± 0.022**	**0.131 ± 0.033***	**-0.041 ± 0.008**	**<0.001**
Right Q3	**0.239 ± 0.011**	**0.175 ± 0.072***	**-0.064 ± 0.015**	**<0.001**
Right Q4	0.237 ± 0.001	0.228 ± 0.029*	-0.009 ± 0.006	0.006
Right Total	**0.881 ± 0.012**	**0.647 ± 0.024***	**-0.234 ± 0.034**	**<0.001**

Legend: Values are mean ± SEM. Q: quadrant, RSA: relative surface area, HC: healthy controls, NA: patients with neuralgic amyotrophy, , Sig: Significance based on Kruskal Wallis test, L: left upper extremity, R: right upper extremity. * significant differences of left and right arm within NA group, Bold results indicate statistically significant Kruskal Wallis results

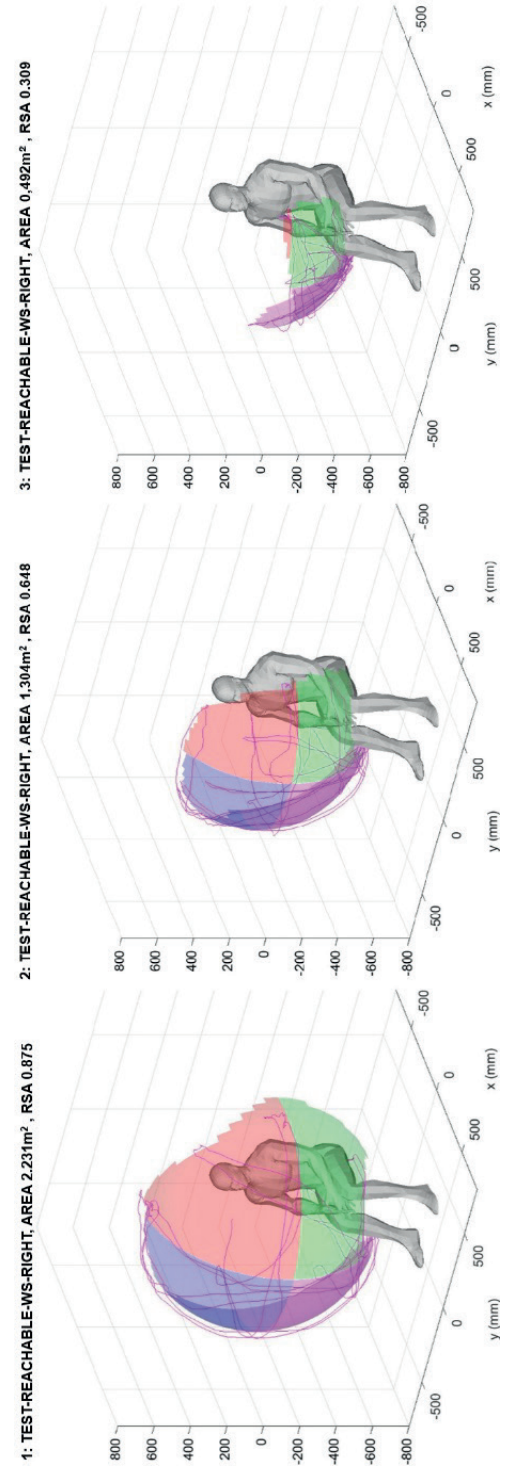

Figure 2. Visual representation of RSA in 1: healthy control, 2: moderately limited patient with NA, 3: severely limited patient with NA.

Larger total RSA and combined above shoulder RSA correlated with greater serratus anterior muscle strength . No other correlations were found between RSA and functional capacity of the upper extremity questionnaires or strength measurements. All correlations can be found in table 2.

Table 2. Spearman correlation coefficients for reachable workspace with functional capacity of upper extremity questionnaires and strength measurements in patients with NA.

	Total RSA right (affected) arm	**p value**	**Above shoulder RSA right (affected) arm**	**p value**
SRQ-DLV	0.278	0.071	0.256	0.097
DASH	**-0.415**	**0.006**	-0.394	0.009
SA strength	**0.414**	**0.006**	**0.445**	**0.003**
Grip strength	0.274	0.072	0.391	0.010
Exorotation strength	0.391	0.010	0.353	0.019
Endorotation strength	0.299	0.052	0.290	0.56

Legend: SRQ_DLV: Shoulder Rating Questionnaire-Dutch Language Version, DASH: Disabilities of Arm Shoulder and Hand questionnaire, SA: Serratus anterior, RSA: relative surface area, **Bold** results indicate statistically significant correlations

Discussion

The total reachable workspace of the affected arm in patients with NA, as measured by RSA, was significantly reduced compared to the reachable workspace of healthy controls. Most of the reduction in the NA group's reachable workspace was due to limited reachability in the upper quadrants (reaching above the shoulder level). RSAs of the affected right arm were significantly lower than the non-affected left arm within the patients with NA in Q1-3 as well. The RSA measure correlated moderately with the DASH score as well as with the affected limb's serratus anterior strength. These results indicate that the RWS can be useful for quantification of functional upper extremity limitations in patients with NA.

The lower RSA values of patients with NA compared to healthy controls in the upper shoulder quadrants (Q1 and Q3) were expected, as functional limitations during above shoulder activities of the affected upper extremity are frequently reported (2,3,23). However, interestingly, we also found that the lower contralateral quadrant RSA of the affected arm (i.e. Q2) was significantly lower in patients with NA compared to healthy controls. Whereas limitations in above shoulder level AROM are typical in NA, below shoulder level difficulties have

not yet been described (3,24,25). This novel finding indicates that impaired AROM in patients with NA and scapular dyskinesia is not limited to above shoulder level movements, but may extend to movements below shoulder level as well, impacting an individual's function. Although our patients with NA had RSAs similar to patients with facioscapulohumeral dystrophy with 'severe scapular involvement' (as indicated by Ricci clinical severity scores ≥ 5 (6,26)), similar reductions in below-shoulder level RSAs were not seen in individuals with facioscapulohumeral dystrophy (6). The fact that patients with NA did have reduced below shoulder level AROM might be explained by strain and muscle rigidity. Scapular dyskinesia in NA causes overloading of periscapular muscles such as the rhomboids and levator scapulae, and subsequent strain and rigidity in complex shoulder movements (2,4). This rigidity limits the lateral translation and internal rotation of the scapula, which are needed to position the humerus across the body, possibly resulting in a decrease in AROM for the affected arm to the contralateral side (27). This may indicate that patients with facioscapulohumeral dystrophy have less rigidity and mainly suffer from weakness of (peri)scapular muscles (6,15). However, we cannot be certain that capsular thickening or intra-articular glenohumeral problems haven't played a role in this as we did not use imaging techniques to explore these pathologies in our subjects.

Higher RSAs correlated with better functional capacity as measured by the DASH questionnaire. The moderate correlation observed (r_s -.415) might be explained by the fact that some items of the DASH questionnaire consist of activities that represent distal rather than proximal upper extremity tasks, such as cutting food, writing, or turning a key. This may also be the reason why we did not find a significant correlation for the above shoulder RSA (Q1 + Q3) and the DASH. Unexpectedly, the SRQ-DLV did not correlate significantly with the RWS measurements. In previous studies, the SRQ did show responsiveness to change in functional capacity of the upper extremity in patients with NA (4). However, the SRQ-DLV items strongly focus on complaints and activity limitations. Only 3 out of 30 SRQ-DLV items specifically relate to a larger AROM of the affected upper extremity, which might explain the lack of correlation with the RWS.

The correlation of RWS with serratus anterior muscle strength is in line with our expectations, as this muscle is the main scapular stabilizer. However, the correlation was also moderate (r_s .414). There are three possible reasons for this moderate correlation. First, the procedure used for the assessment of serratus anterior muscle strength has limited reproducibility. The

measurement error is quite substantial, with a reported SEM of 15.8N, due to considerable influence of the assessor handling the dynamometer (28). Second, 39 out of 47 patients with NA reported pain during the day of the assessments, possibly limiting the strength they were able to produce (19). Third, patients with NA also show coordinative deficits in scapular movement and positioning, possibly related to maladaptive cortical adaptation following peripheral nerve damage (29), which might have influenced serratus anterior muscle strength recruitment during testing.

We believe the RWS may become a promising tool to quantify and evaluate AROM of the upper extremity in patients with NA, both in clinical practice and in future studies. However, more research is needed to establish reproducibility, validity and responsiveness to change in RSA for functional upper extremity limitations in people with NA and other peripheral nervous system disorders affecting the upper extremity.

Conclusions

We conclude that the RWS is suitable for objective assessment of functional shoulder limitations in patients with NA. The moderate correlation of the RWS with other functional outcome measures suggests that the RWS measure reveals additional information about functional (dis)ability of the upper extremity compared to capacity questionnaires and strength measurements. Therefore, the RWS is a potentially valuable clinical outcome measure for the assessment of functional upper extremity limitations caused by NA.

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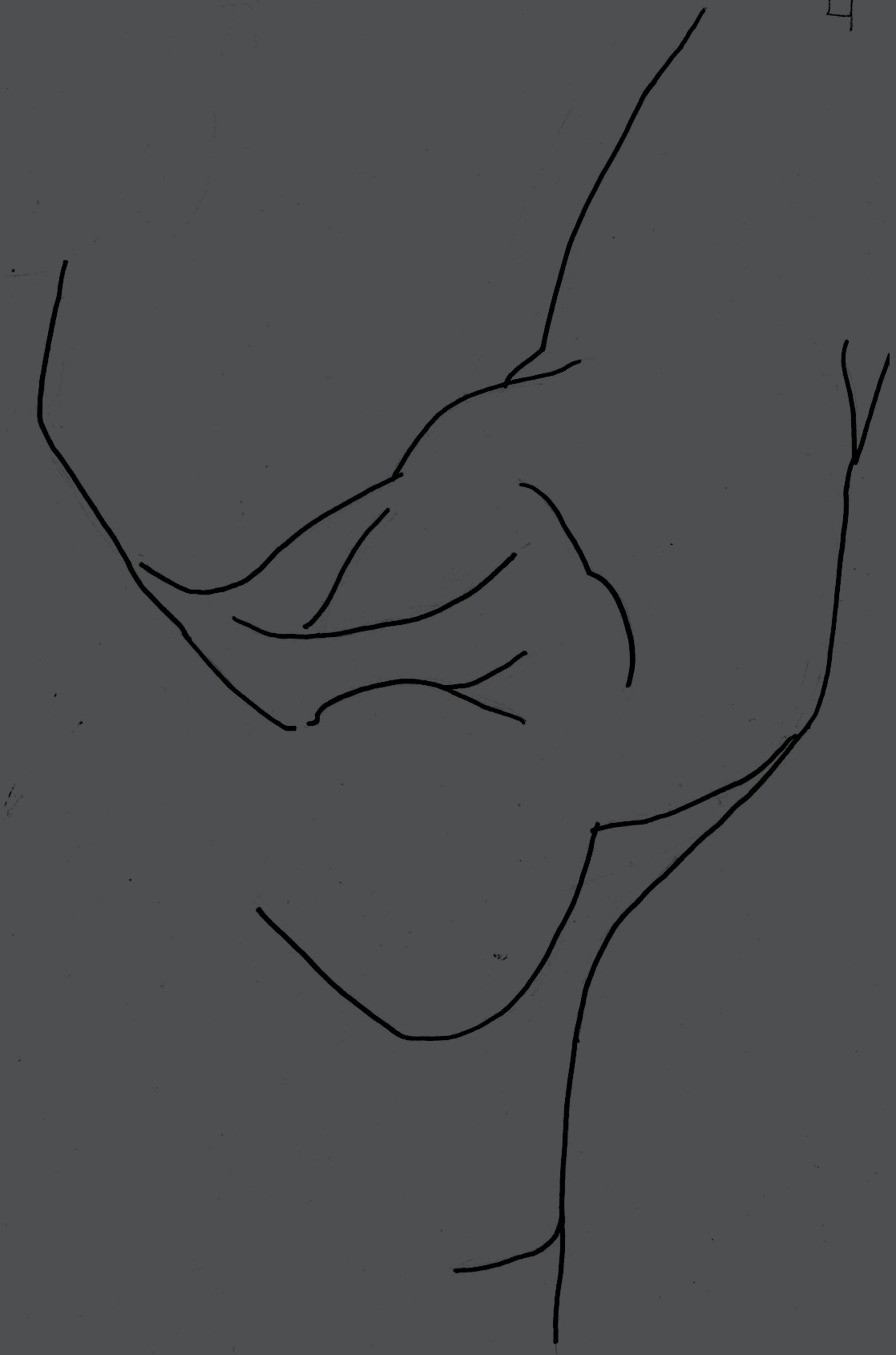

Chapter 6

Neuralgic amyotrophy

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*Jos IJspeert and Renske MJ Janssen both qualify as first authors for this paper.

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Abstract

Purpose of the review

This review focuses on the current insights and developments in neuralgic amyotrophy (NA), an auto- immune multifocal peripheral nervous system disorder that leaves many patients permanently impaired if not recognized and treated properly.

Recent findings

NA is not as rare as previously thought. The phenotype is broad, and recent nerve imaging developments suggest that NA is the most common cause of acute anterior or posterior interosseous nerve palsy. Phrenic nerve involvement occurs in 8% of all NA patients, often with debilitating consequences. Acute phase treatment of NA with steroids or i.v. immunoglobulin may benefit patients. Long term consequences are the rule, and persisting symptoms are mainly caused by a combination of decreased endurance in the affected nerves and an altered posture and movement pattern, not by the axonal damage itself. Patients benefit from specific rehabilitation treatment. For nerves that do not recover, surgery may be an option.

Summary

NA is not uncommon, and has a long term impact on patients' well-being. Early immunomodulating treatment, and identifying phrenic neuropathy or complete nerve paralysis is important for optimal recovery. For persistent symptoms a specific treatment strategy aiming at regaining an energy balance and well-coordinated scapular movement are paramount.

Keywords

Neuralgic amyotrophy, brachial neuritis, phrenic neuropathy, rehabilitation treatment, nerve surgery

Introduction

Neuralgic amyotrophy (NA), also known as Parsonage Turner syndrome or idiopathic brachial plexopathy, is a multifocal inflammatory neuropathy that usually affects the upper limbs. The classic presentation is a patient with acute onset of asymmetric upper extremity symptoms, with unbearable pain in about 95% of the attacks, a swift onset of multifocal paresis that often includes a winging scapula, and a monophasic disease course (1). NA was first described in 1879 (2), and gained its eponymous name following a detailed report by Parsonage and Turner in 1948 (3). However, the phenotype is broader than this classic presentation (4). NA is also not a rare disease (5), and recovery is often not satisfactory for patients (6). This review provides an update on NA, highlighting recent development in the diagnosis, pathophysiology and treatment.

Clinical phenotypes

NA has a broad phenotypic spectrum (7,8) with the "classic" presentation found in about 70% of the patients. Classic NA most often involves the long thoracic, suprascapular, superficial radial and anterior interosseous nerves (figure 1). Other presentations include involvement of other brachial plexus nerves, a so-called "distal" variety with predominant lower trunk involvement (9), lumbosacral plexus affection in 10% (7,10), phrenic nerve involvement leading to diaphragm dysfunction in 8% (11), a pure sensory form (12,13*), and, infrequently, affection of the recurrent laryngeal nerve, a painless onset occurs in about 4% (7). Of note, while lumbosacral radiculoplexoneuropathy is common in diabetics (14), there is no association at the group level of brachial plexopathy and diabetes in our cohort of 3000+ NA patients.

Recently, detailed nerve imaging studies showed that what was often thought to be "isolated" posterior or anterior interosseous nerve palsy, is actually almost always part of the NA spectrum (15,16,17**). Another NA subtype, often found in middle-aged males with extensive, asymmetric affection of the extremities, phrenic neuropathy, and elevated liver enzymes (7), was recently found associated with a hepatitis E virus infection (18,19**). A new phenotype is that of a patient with chronic progressive pain and axonal loss, that is steroid-responsive (20). However, as the majority of NA patients will have persisting pain (6) , it is crucial to objectify progressive axonal damage to diagnose this rare phenotype, to avoid overtreating the majority of NA patients.

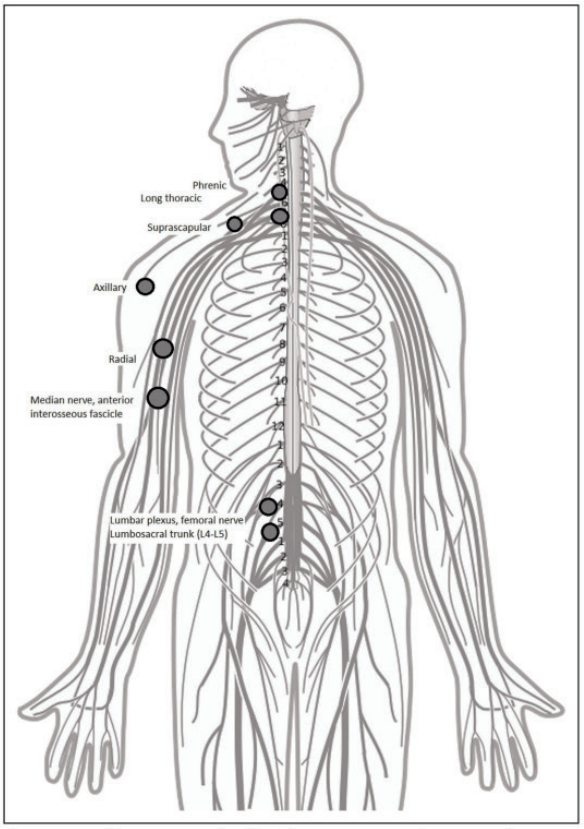

Figure 1. A graphic overview of the most commonly affected nerve sites in neuralgic amyotrophy.

Recurrences are not uncommon, and 25% experiences them the first 5-10 years after onset. Recurrences are more often seen in patients with a familial history of NA (hereditary neuralgic amyotrophy, HNA), that has a 75% recurrence rate (7). At the individual level a recurrence does not discriminate between idiopathic and hereditary NA, as in both disorders individual patients can experience just a single attack or multiple episodes. However, the number of recurrences is limited across the lifespan, and any patient who thinks they have multiple recurrences each year should be considered to suffer from exacerbations in a relapsing-remitting pattern of pain and fatigue, caused by the typical combination of an altered movement pattern and decreased endurance in the affected muscles (21).

Epidemiology

The average onset age of idiopathic NA is around 40 years, while in HNA it is around 20 years (7). The occurrence of NA across the lifespan follows a bell-shaped distribution, and it is seen in neonates and very elderly people too. Until the start of the 21st century it was generally assumed that NA was a rare disorder with an estimated incidence of 2-3 per 100,000 per year (22,23). Subsequent work indicated the diagnosis was likely underrecognized and underreported (7). A recent prospective study in the general population found a one-year incidence rate for the classic phenotype of 1 per 1000 (5), suggesting the disorder is not rare but actually 5 times more common than ulnar neuropathy at the elbow, and as frequent as cervical radiculopathies (24,25,26).

Pediatric NA

Pediatric NA is similar to the adult phenotype, but may be harder to recognize, especially in the very young who cannot verbally communicate their symptoms (27,28,29*). Painless episodes seem more common in children, and a right-sided predominance of the attacks is not yet evident in preschoolers (27,30). A particular phenotype is NA in neonates < 6 weeks old, in whom a concomitant septic osteomyelitis of the humerus is almost always present (30), and should be actively sought in this group. Overall, the impression exists that NA has a more favorable long-term prognosis in children (27), which makes sense as peripheral nerve recovery and adaptive strategies are better when people are younger (31).

Clinical examination

NA is a clinical diagnosis first and foremost. Making the diagnosis requires a sufficiently high index of suspicion combined with specific physical exam skills (5,7). To diagnose the classic phenotype, eliciting a typical history of acute onset severe, numerical rating scale (NRS) ≥7 upper extremity pain, combined with a focused exam that captures scapular movement during abduction – anteflexion and strength testing of the serratus anterior, shoulder exorotation and the long flexor of the thumb will usually suffice (5). The key features of phrenic nerve involvement in NA are orthopnea, sleep disturbance and extreme fatigue (11). A targeted workup for diaphragm dysfunction consists of a sitting versus supine vital capacity measurement, maximal inspiratory pressure measurement, and diaphragm ultrasound, which has a very high sensitivity and specificity for phrenic neuropathy (32). Both unilateral and bilateral phrenic neuropathy are symptomatic, and recovery usually takes several years (11). For the other phenotypical presentations a

tailored neurologic exam is needed, and when there is a genuine differential diagnosis to be explored additional laboratory, electrodiagnostitesting and imaging studies are warranted (1).

Following the diagnosis, the history and exam should focus on further examination of secondary complaints caused by and persisting after an NA attack. The majority of patients in the chronic phase will have persisting upper extremity pain, paresthesia, fatigue and impairments (6). This is the result of decreased muscle endurance following axonal injury, and an altered posture and scapular movement pattern, that leads to muscle strain, subacromial tendinopathy, and subpectoral impingement (1,21).

Pathophysiology and immunological triggers

Because direct access to the plexus and nerves in acute NA is unavailable, the exact onset and pathophysiology are still obscure. Most evidence points to NA being an auto-immune disorder, in which several independent predisposing factors will lead to the occurrence of an actual episode (1). With a presumed incidence rate of 1/1000/year but a recurrence in at least 1/4 with idiopathic NA, an intrinsic factor is presumed present that makes patients more vulnerable than the general population. Mechanical factors also seem to play a role as strenuous activity or local trauma can trigger an attack, and NA patients are more often physically active than the general population.

Mechanical strain is suspected to cause a focal disturbance of the fascicular perineural blood-nerve barrier (33), especially in nerve segments that routinely undergo large mechanical deformation, such as the brachial plexus and certain arm nerves. The final step leading to the onset of an attack seems to involve activation of the immune system, that in the context of a "leaky" blood-nerve barrier leads to an auto inflammatory response with subsequent damage of the nerve segments. Scant histologic evidence suggests that an attack is the result from an aspecific activation of the innate immune system at the level of the blood-nerve barrier, resulting in focal inflammatory infiltrates (4), severe pain caused by the release of inflammatory mediators and ischemia of the nervi nervorum, and acute damage to the paranodal regions of large nerve fibers, as an early conduction block has been described in proximal nerve segments in NA (34,35). If left untreated, this inflammatory response will progress into axonal loss and denervation, and perineurial and epineurial fibrosis with the formation of constrictive bands that constrict the nerve and hamper recovery (36**).

Any immune-related factor can trigger NA, including infection, vaccination, immunotherapy such as interferone or immune-checkpoint inhibitors (37,38), recovery from surgery, pregnancy or childbirth, trauma or psychological distress (7). The list with micro-organisms reported to have triggered an attack keeps expanding (39), with s. aureus and SARS-CoV2 (COVID-19) being the most recent additions (40*,41*); see table 1. A prominent antecedent infection is hepatitis E virus (HEV), which acts as a potent trigger for various peripheral nervous system disorders (42), and may be responsible > 10% of the acute NA episodes (43). HEV is commonly found in pork-derived food products, which suggests a potential role for increased vigilance from the authorities. It causes an extensive phenotype that may present with multiphasic symptoms (44**). As HEV rarely causes hepatitis and no difference in outcome was found in HEV-positive NA patients that did or did not recieve ribavirine, no specific antiviral treatment seems needed in this group (18).

Table 1. Reported antecedent infections that triggered an NA episode

Viral	Bacterial	Other
Hepatitis E virus	Borrelia burgdorferi	Aspergillus species
Parvo virus B19	Escherichia coli	
SARS-CoV2	Staphylococcus aureus	
Human immunodeficiency virus	Neisseria gonorrhoe	
Herpes simplex virus	Salmonella panama	
Epstein-Barr virus	Yersinia enterocolica	
Cytomegalovirus	Streptococcus group A	
Varicella zoster virus	Brucella species	
Vaccinia virus	Coxiella burnetti	
Coxsackie B virus	Chlamydophila pneumoniae	
West Nile virus	Leptospira species	
Hepatitis B virus	Mycoplasma pneumoniae	

NA, neuralgic amyotrophy, SARS-CoV2 severe acute respiratory syndrome coronavirus 2

Genetics

About 1 in 10 patients report a family history for the disorder (HNA), typically transmitted in an autosomal dominantly. HNA and INA are phenotypically identical, except that the underlying vulnerability to the disorder seems more pronounced in HNA, reflected by the earlier onset age, an increased affection of nerves outside the typical distribution, and the overall higher recurrence rate (4). Only one gene, SEPT9, has been implied in the transmission of an increased vulnerability to NA (45). Mutated septin-9 isoforms interfere with

intracellular microtubule bundling and impair asymmetric neurite outgrowth in cell cultures (46). How this leads to a predisposition for NA is unknown. Of note, the prevalence of a mutation or duplication in SEPT9 seems to be much lower in the Dutch population (< 5%) than in North America (around 50%), and HNA appears to be genetically heterogeneous in a significant proportion of the patients (personal communication, prof. van Engelen).

Role of EMG and imaging

With a typical history and the classic clinical phenotype, the a priori chance of having NA is so high that any further investigation will not increase the likelihood. In less typical cases, for example those without pain or with gradual progression, or when there is a genuine differential diagnosis to explore, nerve conduction studies, needle EMG and nerve imaging may help improve diagnostic certainty. Nerve conduction studies are often normal in NA (47), and paraspinal abnormalities can be found on needle EMG, making it difficult to use these tests to differentiate NA from a cervical radiculopathy. The clinical pattern will determine if weakness and sensory symptoms fit the distribution of a discrete nerve root or a multifocal mononeuropathy. Needle EMG carries a significant risk of sample error and misdiagnosis when only "routine" muscles are explored. It is therefore recommended not to rely on EMG for confirming the diagnosis (48). Obviously, the electrodiagnostic exam can assess the extent of de- and reinnervation if clinically needed, and can help in selecting patients and nerves for surgical intervention if no recovery occurs.

Recent advances in nerve imaging show focal abnormalities in the nerve roots or proximal nerve segments in 75%-80% of NA patients (17,49,50,51). This makes nerve imaging a patient-friendly option to support the diagnosis. Remarkably, abnormalities are usually not found in the brachial plexus proper, suggesting the term "brachial plexopathy" as a synonym for NA should probably be abandoned (52). Affected nerve segments in NA show focal enlargement indicating inflammation, and some nerves develop typical focal "hourglass" constrictions (53).

Acute phase treatment

Multiple case series and reports suggest that corticosteroids and intravenous immunoglobulin can be effective in the acute phase of NA (7, 18, 19, 28, 54, 55, 56, 57*, 58, 59), and the sooner the treatment can be started, the higher the chance of a positive response. In practice, a positive responder is a patient who is nearly pain-free within 24-48 hours after starting treatment. Treatment

started beyond 2 weeks has no expected effect, and chronic treatment is not warranted.

Pain in acute NA can be managed as any other nociceptive pain, using the steps of the WHO modified analgesic ladder used in proportion as the NRS pain score increases. The large majority of acute NA patients will have an NRS score of ≥7, for which a combination of NSAIDs and opioids was found most effective. The acute phase pain is usually unresponsive to co-analgesics (7). Clinically, very few NA patients will develop true chronic neuropathic pain, and in practice persistent pain is almost always caused by decreased endurance and an altered movement pattern indicated above (6).

Patients with phrenic neuropathy can benefit from non-invasive nighttime bilevel positive airway pressure ventilation and coordinative inspiratory muscle training, and may benefit from diaphragm plication when no spontaneous nerve recovery occurs (11,60*).

Chronic phase treatment and rehabilitation

The majority of NA patients is left restricted in their daily activities because of residual pain and fatigue (6,7,61). These symptoms are perpetuated by inefficient motor control of the affected shoulder/arm, loss of endurance in the affected muscles and strain of the compensating musculature. Specific outpatient rehabilitation treatment can help overcome this (21,62*,63**); see figure 2. For NA patients, important topics are an interdisciplinary approach, shared goal setting and decision making, and honest explanation and education on how NA works in relation to their complaints, and how to self-manage these complaints (64*). To support the rehabilitation process, behavioral change techniques such as motivational interviewing are recommended (65).

Physical therapy for NA focuses on regaining motor control. Patients are trained to maintain and automate scapular position in subtle posterior tilt while using the arm selectively, with supportive feedback on posture and movement control from their therapist. Initially this is practiced with relatively simple arm movements, with slow progression to more natural activity-like exercises, with supportive feedback gradually phased out. The focus is on movement technique, not on strength or endurance training (21,62). To enable muscle relaxation, manual myofascial treatment or costovertebral joint mobilization techniques can additionally be used (66,67).

Occupational therapy for NA focuses on management of pain and fatigue with use of energy conservation strategies (68). Key elements include ergonomics during activities such as self-care, household, work, education, sports and leisure and on an optimal arm and shoulder position at rest. Other strategies include activity adaptation, the use of assistive devices and planning and pacing of activities, including so-called "minibreaks" to find a balance during the day and week (69). Specific coaching is provided to facilitate return to work.

Surgical treatment

Up to 30% of NA patients has residual motor deficits (7). Nerves that fail to recover usually exhibit focal hourglass constrictions that can lead to severe nerve narrowing (53,69). When there is a (near-)complete paralysis without recovery after 6 months, surgical neurolysis is indicated within 6-12 months to allow reinnervation (36**). With this treatment, improvement was seen in 90% of the patients (70**). In patients for whom neurolysis is not an option, but who have impairment from residual deficits, other surgical options such as nerve transfer or secondary surgery using tendon transfers should be considered (71,72).

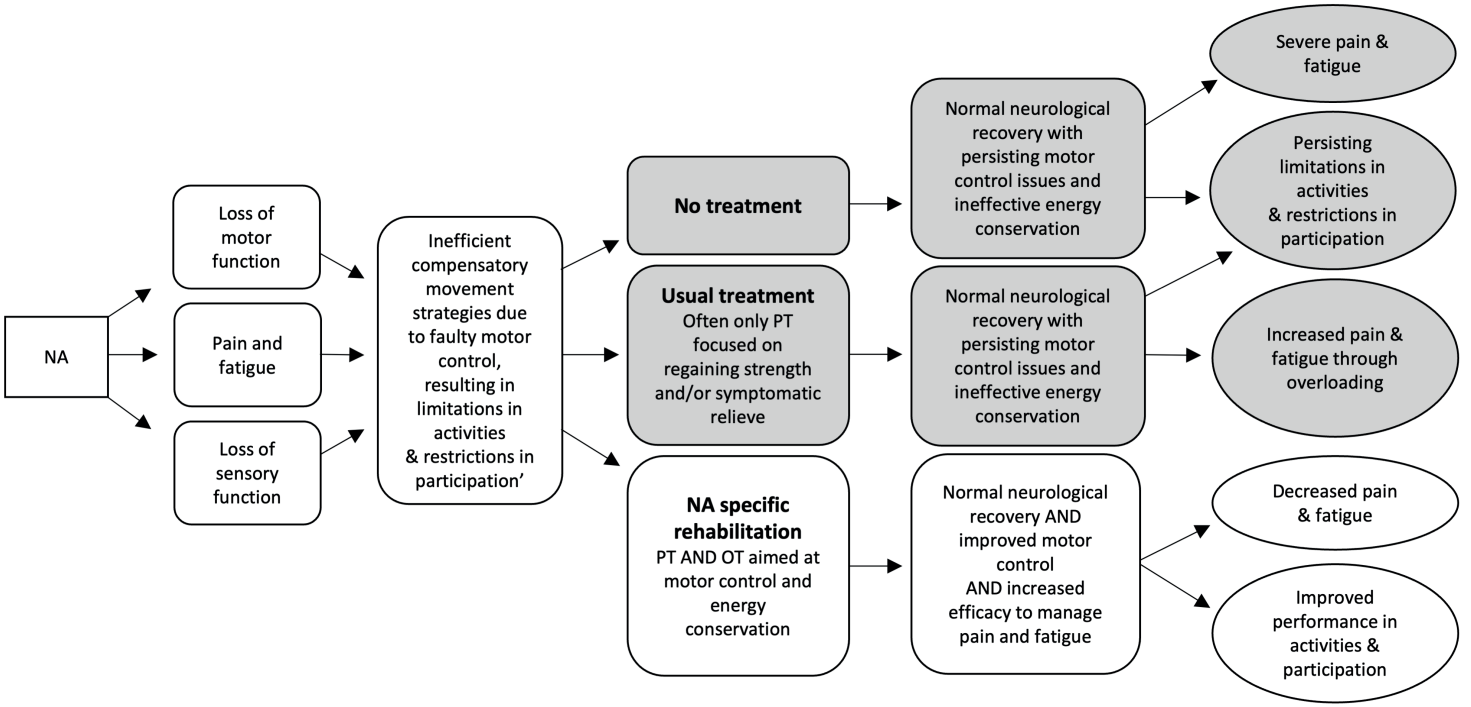

Figure 2. Persisting consequences following NA and the practice-based effect of different treatment approaches currently used for rehabilitation. NA, neuralgic amyotrophy

Conclusion

NA is not uncommon, and has a long term impact on patients' well-being. Early immunomodulating treatment, and identifying phrenic neuropathy or complete nerve paralysis is important for optimal recovery. For persistent symptoms, a specific rehabilitation strategy aimed at regaining energy balance and well-coordinated scapular movement, and identifying non-recovering nerves for surgical treatment are paramount.

Key points

Neuralgic amyotrophy is not rare, and residual deficits and impairment are common Early immunomodulating treatment may improve recovery

New nerve imaging methods may facilitate the diagnosis and help select patients for surgical treatment

Persistent symptoms need a specific rehabilitation strategy, focused on energy conservation and regaining coordinated scapular movement

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Chapter 7

Summary and General discussion

Part A: Summary

In this thesis, we outline the development of a treatment program intended to address residual complaints following neuralgic amyotrophy (NA), along with the creation of two clinimetric instruments for assessing persons throughout their NA recovery.

In chapter 1 we describe NA, characterized by sudden-onset severe pain in the shoulder and arm followed by weakness and atrophy of the affected muscles. Although the condition was considered rare, with a yearly incidence of 1:1000, this is clearly not the case anymore. Contradictory to earlier understanding of NA, many persons continue to experience residual complaints such as weakness, sensory deficits, and decreased joint range of motion. About 50% of persons find the management of their complaints through physical therapy ineffective or even aggravating their complaints. Compensating movements after NA often seem to be maladaptive, resulting in scapular instability. These maladaptations are linked to changes in the cerebral organization. Therefore, physical therapy may be more effective when focused on these maladaptations, given the plasticity of our cerebral organization, instead of focusing on less influenceable factors such as loss of muscle strength and loss of endurance as a result of axonal damage caused by NA. Loss of endurance probably needs to be addressed through behavioral adaptation.

In chapter 2 we present a cohort study aimed at developing recommendations for outcome measures and rehabilitation goals for individuals with NA. The focus was on understanding the functions and activities related to persistent pain in NA and identifying the most suitable outcome measures to capture these aspects.

Data were collected from two tertiary referral clinics associated with a university medical center's department of Neurology and Rehabilitation. The study design involved a survey based on two cross-sectional cohorts: patients from a neurology outpatient clinic and a cohort from a multidisciplinary plexus clinic.

The participants consisted of 248 patients who had either idiopathic or hereditary NA, met the criteria for this disorder, and had experienced an episode of NA involving the brachial plexus at least six months before. The study utilized two custom clinical screening questionnaires, the Shoulder

Rating Questionnaire - Dutch Language Version (SRQ-DLV), the Shoulder Pain and Disability Index (SPADI), the Shoulder Disability Questionnaire (SDQ), and the Overall Disability Sum Score.

The results confirmed a high prevalence of persistent pain and impairments after NA. Over half of the persons were limited by pain, and 60% of the people without pain still experienced residual weakness. There was a strong correlation between pain, scapular instability, difficulties with overhead activities, and increased fatigue. More than half of the persons reported that standard physical therapy was either ineffective or worsened their symptoms.

We concluded that pain and fatigue in people with NA are closely linked to persistent scapular instability and increased muscle fatigue. These findings suggest the need for a comprehensive rehabilitation approach addressing all factors involved. We also recommended using the SPADI and SDQ in future research to assess the natural progression and treatment effects in people with NA.

In chapter 3 we present a pilot study investigating the effectiveness of a novel multidisciplinary rehabilitation intervention combining physical therapy and occupational therapy for persons with NA. The intervention program consisted of 16 weeks of therapy, with a frequency of weekly sessions in the first four weeks, biweekly sessions from weeks five to eight, and monthly sessions from weeks nine to sixteen. Each therapy session included one hour of physical therapy and one hour of occupational therapy. Eight participants with NA were enrolled in the study. Assessments were conducted at three time points: a baseline assessment three months prior to the intervention, an initial assessment at the start of the intervention, and a final assessment upon completion of the intervention. Outcome measures encompassed various domains of the International Classification of Functioning, Disability and Health (ICF). The primary outcome measures were the SRQ-DLV and the Canadian Occupational Performance Measure (COPM), the latter being used to evaluate occupational performance and participants' satisfaction with performance of their most important daily activities. Secondary outcome measures included the Disabilities of Arm Shoulder and Hand (DASH) questionnaire, strength measurements, and the Self-Efficacy for Performing Energy Conservation Strategies Assessment (SEPECSA). The Short Form 36 (SF-36) questionnaire was used to assess health-related quality of life and the subscale fatigue of the Checklist Individual Strength 20 (CIS-20) to measure fatigue.

The results revealed significant improvements (mean (95% CI)) in COPM performance (+2.3 (0.9-3.7)) and satisfaction (+1.4 (0.4-2.4)) scores, as well as in SRQ-DLV (+14.8 (7.4-22.0)) and the health change subscale of the SF-36 (-37.5 (-56.9/-18.2)). Strength measurements indicated a upward trend for the serratus anterior muscle only. These findings suggest that the observed improvements can most likely be attributed to coordinative and behavioral adaptations to the nerve damage and corresponding loss of function of the affected shoulder. This pilot study provided an indication that persons with NA may experience improvements in their activity and participation levels following multidisciplinary rehabilitation.

Chapter 4 is a clinimetric study focusing on handheld dynamometry of the serratus anterior muscle (SA). The SA plays a crucial role in shoulder movement and stability, and its strength testing is of significant clinical interest to discriminate persons with and without SA weakness in relation to scapular instability. However, existing methods using handheld dynamometry (HHD) in supine subjects have shown low reproducibility and might be influenced by compensatory activity of other muscles. This highlights a clear need for more reliable and valid testing methods. In response to this need, we adapted three manual muscle tests for the SA to be suitable for HHD and investigated their validity and reliability. The commonly used method for strength testing of the SA in supine subjects using HHD has been found to have low reproducibility and might be influenced by the compensatory activity of other muscles such as the pectoralis major and upper trapezius. Two manual maximum voluntary isometric contraction tests that recruited optimal surface electromyography (sEMG) activity of the SA in a sitting position have previously been reported.

Twenty-one healthy adults were examined by two assessors in one supine and two seated positions. Each test was repeated twice. The construct validity was determined by evaluating HHD force production in relation to sEMG of the SA, upper trapezius, and pectoralis major muscles, comparing the three test positions.

Intra- and interrater reliability were determined by calculating intra-class correlation coefficients (ICC), smallest detectable change (SDC), and standard error of measurement (SEM).

The results showed that the serratus anterior (SA) muscle's sEMG activity was most isolated in a seated position with the elbow flexed 90° and the humerus

in 90° of anteflexion in the scapular plane. This position resulted in the lowest force levels measured, with a mean force of 296N (SEM 15.8N), indicating that muscle testing in this position minimizes the influence of compensatory muscles, thereby providing a more precise assessment of the serratus anterior.The intrarater reliability yielded an ICC of 0.66 (95% CI 0.33-0.85) and an interrater reliability of 0.28 (95% CI -0.10-0.61). The SDC was 127 N and the SEM was 45.8 N.

We concluded that the validity for strength testing of the SA is optimal with subjects in a seated position and the elbow and shoulder flexed at 90° in the scapular plane. However, the intrarater reliability was moderate, and the interrater reliability of this procedure poor. In addition, the high SDC values observed make it difficult to use the test in repeated measurements.

Chapter 5 explores the feasibility for reachable workspace (RWS) measurements to assess functional limitations in persons with NA. The RWS is a computerized 3D analysis system that assesses the relative surface area (RSA) of an individual's arm reachability. It has proven useful in several neuromuscular disorders.

This study aimed to explore the RWS's ability to quantitatively identify limitations in the active range of motion of the upper extremity in persons with NA. The RSAs of persons with NA were compared to healthy controls and correlated with other upper extremity functional outcome measures. We measured 47 persons with NA and 25 healthy controls matched for age and sex. The participants' RSAs were measured using the RWS and correlated with the scores of the SRQ-DLV, the DASH questionnaire, and upper extremity strength measurements using HDD.

The results showed that persons with NA had significantly lower values of the affected arm for all quadrants (except for the ipsilateral lower quadrant) and for total RSA compared to controls ($p<0.001$). Moderate correlations were found between the RSA, the DASH questionnaire ($r= -0.42$) and SA muscle strength ($r= 0.41$).

We concluded that the RWS can detect functional limitations in active range of motion of the affected arm in persons with NA and is moderately correlated with upper extremity functional measures. Therefore, the RWS can objectify functional limitations of the affected upper extremity in people with NA and has potential as a functional clinical outcome measure.

Chapter 6 is based on an invited review and provides a comprehensive overview of the current knowledge and developments in NA. We describe the clinical phenotype of NA as a multifocal neuropathy that primarily affects nerves of the brachial plexus. However, recent literature has expanded the "NA phenotype" to include conditions that were previously considered isolated nerve palsies. We discuss the epidemiology of NA, with an emphasis on its common occurrence and an annual incidence of approximately 1:1000. We explore the possible etiologies of NA, including the role of antecedent infections as disease triggers. We present a state-of-the-art approach to the clinical examination and treatment of persons suspected of NA. Treatment during the acute phase of NA typically involves the use of corticosteroids or intravenous immunoglobulin, combined with analgesic medication. We describe chronic phase treatment, which encompasses physical therapy and occupational therapy, both of which aim to assist persons in the development of more precise and energy-efficient movement coordination of the scapula and arm and achieving energy conservation through behavioral adaptations. In cases of more severe nerve damage with (near-) complete paralysis, neurolysis, nerve transfers, or muscle transfers may be considered as surgical treatment options. We conclude that NA is a relatively common and treatable condition both in its acute and chronic phases. However, it requires a specialized rehabilitation approach that prioritizes energy balance and well-coordinated scapular movement.

Part B: General discussion

This thesis describes the development of a body of knowledge leading to a new treatment and treatment evaluation approach for people with neuralgic amyotrophy (NA). We aimed to complete the following objectives:

A. To identify persistent difficulties in the daily lives of people with NA and determine treatable factors for improved functional recovery.
B. To develop and test a new interdisciplinary rehabilitation program for people with long-term complaints after NA.
C. To develop and test reliable clinimetric tools to systematically assess functional limitations in people with NA.

At the outset of this general discussion, it is important to acknowledge that NA is a condition that has been considered relatively obscure in the literature, with two significant misconceptions. Firstly, it was erroneously perceived to have a rare occurrence of 2-3:100,000 persons per year, whereas it is known now that the true incidence is 1:1000 persons per year (1). Secondly, the prevailing literature suggested that the consequences of NA would spontaneously resolve within 1-2 years in the majority of persons, whereas recent empirical evidence reveals that a substantial proportion of individuals with NA experience persistent debilitating symptoms. At the inception of this thesis, there existed no standardized treatment approach for residual symptoms after NA. Remarkably, a compelling correlation between persistent symptoms and scapular instability emerged, with evidence suggesting that scapular motor control is amenable to intervention.

This general discussion addresses:

- Residual complaints and functional limitations after NA.
- A novel multidisciplinary rehabilitation approach, integrating motor control and behavioral adaptation through self-management.
- Assessment of condition-specific constraints and treatment outcomes.
- Scapular motor control as a focus for physical therapy in NA.
- Self-management within the context of interdisciplinary rehabilitation.
- The current state-of-the-art in acute, surgical and rehabilitation management of NA.
- Recommendations for future advancement of scapular motor control treatment and interdisciplinary rehabilitation.

Residual complaints and functional limitations after NA

Our exploration in chapter two has illuminated a heightened prevalence of complaints among individuals with NA, surpassing previous assumptions (2-5). This revelation not only necessitates a recalibration of our understanding of NA recovery, but also underscores the profound impact of residual symptoms after NA on persons' lives. Indeed, localized symptoms within NA exert a pervasive influence on overall fitness, with a notable 63% of persons meeting criteria for experienced severe fatigue (6). Particularly striking is the exacerbation of pain following conventional therapies, particularly those centered on strength training, revealing a capricious paradox in treatment outcomes. Furthermore, our analysis has unveiled a robust correlation between scapular dyskinesia (SD) and the persistence of complaints, underscoring the imperative for a tailored treatment strategy targeting scapular motor control (6,7). The sudden onset of NA appears to impose significant behavioral challenges on affected persons, complicating their ability to adapt to the newfound functional limitations. Integrating behavioral interventions into the treatment framework thus emerges as essential to facilitate persons' adjustment to their altered circumstances. In light of NA's characteristic abrupt onset and gradual recovery, fostering resilience and improving coping mechanisms is of paramount importance, necessitating a new approach to patient care that extends beyond mere symptom management and helps persons manage their own situation. Obtaining knowledge of the cause of their complaints and functional limitations and learning effective strategies for energy conservation combined with improvement of scapular motor control are major components of this self-management approach (7,8).

Novel multidisciplinary rehabilitation approach, integrating motor control and behavioral adaptation through self-management

The pilot study (chapter three) of our clinically developed, novel multidisciplinary rehabilitation strategy tailored to people with NA yielded encouraging results. Patients underwent treatment focusing on enhancing scapular motor control and adapting their activity patterns to obtain a more sustainable level of energy conservation. Persons who showed a stable level of complaints and limitations in the months leading up to the treatment reported significant reductions of pain and functional improvement post rehabilitation. The development of our treatment protocol was challenging, particularly to accommodate the diverse responses of individual persons to the nerve damage characteristic of NA. A simple standardized approach would fail to address the variable and nuanced needs of persons, potentially

undermining the intervention's efficacy, and hampering self-management (9,10). Despite the study's limited small sample size, the observed treatment effects were statistically significant. This prompted a subsequent randomized controlled trial (RCT) in a larger patient group to test the effects of our new multidisciplinary rehabilitation approach, which had already been implemented in our outpatient clinic (11). In this RCT, conducted by Janssen et al. (11). persons treated with this new approach exhibited significantly greater improvements in symptom management and functional outcomes compared to those receiving conventional treatments. These findings not only corroborated the initial pilot results, but also provided robust evidence supporting the effectiveness of our new multidisciplinary rehabilitation program (11), emphasizing the rationale for adopting a personalized treatment approach that accounts for the diverse responses of persons with NA to their nerve damage.

Assessment of condition-specific constraints and treatment outcomes

Our findings highlight the intrinsic limitations and challenges associated with current clinimetrics in NA. Objectifying and quantifying scapular dyskinesis presents a formidable challenge, compounded by the absence of validated instruments for assessing shoulder kinematics, scapular posture, movement, and associated (dys)function (12,13). Clinical experience in our treatment center revealed that a significant number of persons with scapular dyskinesis could stabilize their scapula through adapted motor control strategies, suggesting that insufficient motor control might be more crucial than loss of muscle strength in this patient group. To assess whether axonal damage to the long thoracic nerve leads to excessive muscle weakness, preventing the SA from functioning as the primary scapular stabilizer, a valid and reliable clinical assessment method for this muscle is desirable. Such an evaluation can help clinicians differentiate between persons with loss of muscle strength and those primarily dealing with motor control deficits leading to scapular stability. In chapter four we investigated a novel method for hand-held dynamometry of the SA (14). This method enables clinicians to validly test SA muscle strength. Although the study was carried out in healthy subjects, we anticipate consistent validity when applied in persons with NA. In clinical practice, we employ this test to differentiate between persons with SA paresis and pseudo-paresis, related to lack of motor control. It helps to identify those who may benefit from physical therapy. Pushing from the elbow rather than with the arm fully extended seems more effective, likely because it enhances motor selectivity, prompting the brain to shift from automatic (arm-hand) control

to more conscious (elbow) motor control, thereby reducing the influence of maladaptive motor programs. During this procedure, a clinician should not be able to manipulate the position of the scapula. If the scapula yields to the tester's resistance during selective testing, the SA should be considered weak (i.e. paretic). If it only yields during the automatic, everyday movement (such as reaching forward), and not when the elbow is used, this is indicative of scapular dyskinesia or SA pseudo-paresis.

This selective approach to arm and scapular movement was also used to design the test movement for functional magnetic resonance imaging research conducted by our group, revealing distinct cerebral activation patterns in people with NA compared to healthy individuals. While the use of a dynamometer is not strictly necessary, it helps to demonstrate the significant strength of the SA muscle. It is important to note that the SA typically is so strong that it cannot be overcome by the tester, making it impossible to assess it with a "break test". Consequently, muscle strength testing with a handheld dynamometer is highly influenced by a ceiling effect due to a systematic underproduction of resistance from the tester, explaining the high SEM in our study. Hence, in clinical practice, we typically follow a rule of thumb: the scapula should not be pushed away from the thorax during selective testing (pushing from the elbow) if muscle strength is intact. Following NA, people encounter challenges in using their arms for reaching and performing overhead tasks due to limitations in multiple joints and planes of movement (9,10,15-18). These complexities render traditional assessment tools like goniometry inadequate. In our investigation outlined in chapter five, we showcased the utility of reachable workspace (RWS) analysis for a comprehensive evaluation of arm mobility limitations (19). The moderate correlations observed with established clinimetric measures such as the DASH questionnaire and SA strength indicate that RWS captures unique aspects of functional limitations in persons with NA. Our findings suggest that RWS effectively discriminates between persons with NA and healthy controls, making it potentially viable for routine clinical use, given its minimal training requirements and automated, time-efficient measurements. The RWS output intrigued participants in our study. Its visual representation of movement limitations supports discussions between clinicians and patients about potential challenges and feasible activities considering their functional limitations. While the RWS analysis did not establish significant treatment effects in the relative surface area it produces, it proved useful on an individual basis for discussing treatment effects. For clinicians, the RWS sheds light on aspects that have previously been overlooked. Heterolateral

mobility of the affected arm is notably restricted, although patients not often report this, likely because they do not fully engage their arm in activities on the heterolateral side. Nonetheless, this restriction aligns with identified limited mobility in upward rotation and lateral translation of the scapula, that is needed for proper arm elevation during functional tasks. Consequently, since we started acquiring RWS data, we have incorporated more lateral scapular facilitation exercises to increase mobility. Subsequently, we expanded the exercises within this heterolateral range to prevent patients from reverting to maladaptive patterns, such as scapular stabilization in retraction and downward rotation. Given the advantages of the RWS, we are now in the process of implementing these measurements widely in our neuromuscular center. These data will assist us in developing a more personalized and effective approach to treatment, aimed at improving functional mobility and alleviating symptoms in persons with NA and similar these conditions affecting the shoulder joint.

Nevertheless, in clinical practice we are still confronted with persistent challenges in developing a means to quantify the substantial observable improvements in scapular motor control, which limits our ability to assess treatment effectiveness. To this end, we are engaged in creating a structured clinical visual evaluation method for scapular kinematics, named "Visual Analysis of Scapular Kinematics," which aims to provide a valid and reliable approach for quantifying SD. A first study into reproducibility of results of this instrument has been submitted for publication.

Scapular motor control as a focus of physical therapy in NA

SD is a controversial construct due to inconsistent definitions and measurement techniques, the complex interplay of shoulder mechanics and motor control, variable symptom associations, and the heterogeneous nature of the condition (20-24). The general concept of altered motor control through cortical control deficiencies might not be limited to NA, as it has also been described in patients with repetitive shoulder instability (21). Scapular motor control as a focus for therapy has also been noted in people with more common shoulder problems (20). More clearly than in people with other shoulder complaints, there seems to be a high correlation between the presence of SD and reported complaints and experienced functional limitations in persons with NA (6,8). Conventional therapeutic interventions such as joint mobilization, stretching, and trigger point release, while occasionally providing temporary relief, fall short in effectively managing the secondary complications after NA, because

the cause of the problems persists is scapular motor control is not improved (7,9,25). There is only very limited efficacy of strength training, primarily due to its inability to restore the loss of muscle strength or endurance resulting from axonal damage. Notably, strength training may even exacerbate the complaints and limitations, particularly since the remaining motor units in many patients are already under considerable strain and may be overloaded by strength training (6,17).

Patients' complaints and limitations after NA largely stem from a mix of different interacting factors. Initially, loss of motor function and proprioception due to nerve damage inherently poses a challenge on the brain when using the affected limb. As a result, patients often develop a maladaptive response to the nerve damage, which is reflected in scapular motor control aberrations when using the arm, referred to as SD (26-28). This results in overloading the scapulocervical and scapulohumeral regions, causing myofascial complaints, subacromial pain and entrapment neuropathies in the affected limb.

Neuroimaging studies that were part of the NA CONTROL study, conducted by Lustenhouwer et al. (27,28), have highlighted distinct cerebral reorganization patterns in patients with NA compared to healthy individuals. These could be linked to scapular motor control problems (26,27). These findings underscore the importance of a multifaceted approach to NA rehabilitation that addresses both peripheral abnormalities and their central nervous system adaptations. Hence, there is increasing recognition that physical therapy after NA needs to focus on improving scapular motor control and behavioral adaptation during functional activities (11). This notion is rooted in a deeper understanding of cortical organization and neural plasticity. In 2019, Yokoi and Diedrichsen argued that during sequential daily-life movements cortical representations overlap in the premotor and parietal cortices, whereas isolated movements are uniquely represented in the primary motor cortex (29). This insight implies that scapular motor control training is best embedded in a training program that emphasizes functionally relevant activities that are meaningful to the individual patient.

Hence, it is important to recognize that there is not a one-size-fits-all solution when it comes to addressing scapular motor control problems after NA. Instead, therapists are encouraged to adopt an adaptive and dynamic approach, exploring various exercises, instructions, and stimuli to evoke the desired motor responses. This iterative process, devoid of rigid protocols,

allows for a personalized and adaptive therapeutic process, tailored to each patient's unique needs and responses. In box 1, I have outlined a sample with treatment topics and suggestions that provides clinicians with concrete guidance, offering practical tools to navigate the complexities of scapular motor control rehabilitation in clinical practice.

Box 1: Step by step treatment of residual complaints and functional limitations after NA

Objective treatment begins with shared goal setting between and practitioners to manage expectations and tailor treatment plans accordingly.

Education plays a pivotal role, elucidating the mechanism of nerve damage, the brain's (mal)adaptive response to peripheral nerve changes, and the correlation between residual problems and observed scapulothoracic and scapulohumeral motor control.
In the first consultations pain education supports patients in understanding pain modulation and the adaptivity of the nervous system, empowering them to manage symptoms effectively.

Ergonomics interventions focus on optimizing shoulder position during rest and while making movements in daily activities, while hands-on treatment, such as local mobilization techniques, targets muscle tension and facilitates selective movement.

Scapular motor control exercises are meticulously crafted to promote energy-efficient and relaxed scapular stability. This entails deliberately or implicitly positioning the scapula in a posterior tilt, thereby stimulating activation of the serratus anterior and trapezius muscles, while minimizing recruitment of the rhomboids, levator scapulae, and pectoralis minor muscles. The aim is to equip patients with the ability to employ their arms selectively without experiencing discomfort or tightness resulting from reverting to anterior tilt of the scapula. This should result in a comfortable way of moving without increasing pain. It takes some time to help patients find a position and a way of visualizing adaptive movement patterns, and to help them interpret how this feels and how they can use their proprioception to detect when they move more or less efficient. The goal of exercising therefore is not only to change scapular and humeral motor control, but also to help patients discriminate in which situations it is needed to adapt their motor control.

Gradually transitioning from supine to sitting or standing positions, while emphasizing tactile or visual feedback on scapular positioning and reinforcing patient responsibility for repetitions and series.
Meanwhile energy conservation strategies aim to balance activity and rest, recognizing the limited durability of muscles. When patients do not seem to be able to adjust their motor control consciously, a therapist can use implicit strategies to attain the afore-mentioned scapular control and positioning. Usually, these strategies encompass task oriented movement, combining balance reactions with arm movements in abduction, exorotation and supination.

Functional implementation. When scapular motor control is sufficient to allow arm movement in a range that is necessary for daily activities, exercising shifts to functional implementation of scapular motor control training during daily activities with feedback utilized for postural corrections. One can use mirror feedback, video feedback, or tactile proprioceptive feedback by placing the scapula against a surface or palpating the coracoid process. The adapted motor control should lead to less complaints during typical activities such as drinking and eating, self-care, household activities work et cetera.
Behavioral change techniques, including motivational interviewing, help patients to actively adapt their lifestyle to regain self-efficacy and optimize functioning.

Activity analysis aids in finding activities that need to be altered in terms of duration, ergonomics or motor control. When patients are able to implement scapular motor control adaptations in their daily activities, they should be able to discriminate which activities are going well and which are not. Patients should start instructing their therapist regarding which activities and movements they want to adapt next. The therapy frequency should decrease when this happens, so patients can gain experience and start getting more and more self-efficacious.

Our therapy program follows a treatment schedule comprising four one-hour weekly sessions, two sessions every two weeks, and two monthly sessions. This comprehensive approach, integrating physical and occupational therapy with education, ergonomics, hands-on treatment, energy conservation, functional implementation, activity analysis, and behavior change, reflects the holistic care necessary for effectively managing residual complaints and functional limitations.

Self-management within the context of interdisciplinary rehabilitation

The main goal of a rehabilitation program should be, if possible, that caregivers become redundant because patients achieve a state of self-management. Self-management implies empowering patients by enhancing their understanding of their condition and learning them to adjust their behavior accordingly. This enables them to effectively deal with the various symptoms, functional limitations and emotional challenges inherent in their condition (30). We have learned that a multitude of self-management tactics are helpful to enhance quality of life in individuals with NA.

Key among these tactics is *education*: empowering patients with detailed information about NA, its various symptoms and functional consequences, underlying causes, and potential treatment avenues. Such knowledge aids patients to gain a clearer understanding of their problems and to make informed choices about the healthcare they need and regarding practical day-to-day decisions. This has been underlined in a qualitative study conducted by Janssen et al. within our research group (31). Education typically entails teaching patients methods to handle the constellation of pain and fatigue associated with NA. Their spectrum of coping strategies should incorporate elements such as achieving sufficient scapular movement control during daily activities, work and sports, adopting adequate energy conservation strategies, and applying ergonomic principles. Therefore, the development of an activity blueprint tailored to individual physical limitations forms an integral part of this tactic. It encourages patients to incrementally enhance their activity level, whilst preserving their self-efficacy and autonomy.

Social support is another pivotal aspect. Fostering a strong social support network involving family, friends, and healthcare professionals allows patients to access emotional reinforcement, practical assistance, and informative resources (31).

By leveraging these self-management strategies, patients can enhance their quality of life and regain control over their condition. In our treatment approach to NA, this is achieved through a collaboration of physical and occupational therapy. The *occupational therapist* focuses on evaluating daily activities, considering which activities consume a lot of energy from the neck and shoulder region, and which activities yield energy gains. Explicit attention is needed to recognize body signals when approaching the limits of endurance. A proper distribution and duration of activities should ensure that individuals

do not consistently exceed their endurance limits, resulting in less muscle tension, pain, and fatigue. The occupational therapist helps making rest more effective by ensuring proper ergonomics and posture during mini breaks, which involves maintaining sufficient lumbar support to prevent shoulder protraction, positioning the shoulders in a neutral stance with the upper arms parallel to the body, and supporting the arms at the correct elbow height. This setup facilitates effective rest by allowing shoulder muscles to fully relax and recuperate. Symptoms caused by overload become more manageable when patients integrate effective mini breaks timely and promptly. By transforming breaks into mini breaks, symptoms show less escalation requiring less time for recovery.

The *physical therapist* first tries to construct an physiological explanation for the complaints and limitations that individual patients experience through (scapular) movement analysis and evaluation of muscle strength and endurance. This provides insight into possible underlying causes, such as subacromial pain, myogenic overuse pain, or nerve structure entrapment. In the case of excessive pain, it can be advisable to incorporate pain education into the treatment (32). Then, appropriate movement strategies are sought to reduce or avoid most of the daily complaints and limitations. When patients can apply these strategies, it enables them to regain self-control. Because of the extensive change in behavior that is often needed, most patients first show some resistance to change before they are actually able to adjust their behavior properly. Therapists play an important role in this process by employing various techniques such as motivational interviewing (33), a strength-based approach (34), or an acceptance commitment therapeutic approach (35). They can also utilize their personal qualities through "therapeutic use of self," incorporating personal behaviors, insights, and creativity (36). Delivery methods vary depending on whether patients are given direct instructions or are being coached towards self-management. Self-efficacy, a strong predictor of treatment success, can be enhanced by e.g. successfully performing a skill or by social persuasion (37). In our program, we primarily utilize motivational interviewing and acceptance and commitment therapy to enhance self-efficacy (11,38). To optimize our intervention, we may incorporate the other methods as well, as suggested by the qualitative study from our research group (31). This includes providing peer support through group interventions and addressing patient-reported challenges in creating awareness and the desire for additional psychological support.

Current state-of-the-art in acute, surgical and rehabilitation management of NA

The last chapter of this thesis provides an overview of the evidence available on the etiology, epidemiology, diagnosis and rehabilitation of NA. It also reflects on the knowledge gained by our research group since the start of this thesis. NA has evolved from a relatively rare to a common neuropathy (1,39). Early on in our clinic, we already noticed an ever increasing amount of patients presenting with neuropathic shoulder complaints, even among our own staff at Radboudumc; a frequency that was later confirmed in a formal incidence study (1). We have contributed to the development and implementation of a standard of care for the use of anti-inflammatory drugs in the acute phase of NA, as well as to the implementation of surgical approaches e.g. neurolysis or nerve transposition in patients with paralyzed muscles without signs of recovery within 3-6 months.

As already explained, our interdisciplinary rehabilitation program for NA prioritizes the enhancement of scapular motor control, alongside the training of self-management techniques aimed at mitigating pain and fatigue. Our approach has demonstrated clinical efficacy in a randomized controlled trial (11). In addition, patients have expressed their appreciation for the integrated rehabilitation approach in qualitative research (31).

In order to disseminate knowledge effectively and facilitate further implementation of our rehabilitation program, it is imperative to delineate the contents of our treatment regimen. To this end, we have developed and implemented standardized video instructions for appropriate exercise therapy in the early phases of motor control training after NA. We also made videos of patient-specific situations of coordinative adjustments of day-to-day activities that can be used in later stages, when adapted motor control needs to be implemented in daily life. Additionally, we have developed "tip sheets" focusing on three key areas: 1) education, 2) guidance on achieving balance between activities and rest, and 3) principles of ergonomics.

"One of the six core self-management skills is 'taking action' (30). Taking action may seem more like a decision than a skill, but there are skills involved in learning how to change behavior. Coping and action plans support patients in their behavioral change process and in applying their personal actions in daily life. Patients are asked to rate their confidence in reaching their goals and their action plans on a scale of 1 to 10 (40). It is commonly believed that

a confidence level of at least 7 out of 10 is necessary for effective action. If a patient rates their confidence below 7, it is recommended to set smaller goals or revise the action plan (41)."It is advisable to recalibrate goals or revise action plans if a patient's confidence level falls below this threshold.

Upon completion of our rehabilitation program, attention is gradually directed towards sustaining the achieved behavioral changes and preparing patients for potential relapses. Acknowledging the likelihood of relapse, patients are encouraged to build up resilience to manage such setbacks. A personalized retention and relapse plan, collaboratively developed with patients, can further bolster their confidence in navigating unwelcome eventualities.

Recommendations for future advancement of scapular motor control treatment and interdisciplinary treatment

Further research is required to improve diagnostic and therapeutic approaches in the rehabilitation of people with NA. Some key areas for improvement are summarized in the following textbox.

In the field of motor learning, the optimal path forward for improving training modalities is not yet clear. Emerging treatments like 3D augmented reality and immersive reality training are beginning to show promise in influencing motor control for complex conditions such as frozen shoulders (42-44). Nonetheless, the absence of consensus on scapular dyskinesis and its relevance for shoulder problems remains a significant gap in our research, possibly stemming from flawed interpretations of scapular movement (12,13). Without a generally accepted gold standard for assessing scapular movement, training therapists and physicians in scapular movement evaluation remains challenging, hindering the selection of appropriate treatment paths for individual patients. Within our research and treatment group, based on extensive clinical experience with over 5000 persons with NA, we have developed a consensus on meaningful visual characteristics of scapular dyskinesia. It provides a clear description of scapular dyskinesia that correlates with patient complaints, enabling clinicians and patients to define individually tailored movement adjustments to mitigate symptoms. This method for evaluating scapular dyskinesis was named “Visual Analysis of Scapular Kinematics” of which a first study into reproducibility of results has been submitted for review. Artificial Intelligence (AI) applications could potentially learn from clinical expertise and assist less experienced therapists and physicians through automated video scapular motion analysis. However, for practical use in prevalent

conditions like NA, such applications must be cost-effective, efficient, and compatible with existing clinical hardware.

Box2: Suggestions for future research areas in rehabilitation after NA innovative therapeutic interventions:
The most effective treatment for NA focuses on restoration of scapular motor control. Future treatment might be enhanced by new training modalities such as immersive or augmented 3D training. Further research is also warranted on the complex brain-body interactions that result in (mal)adaptive movement strategies to search for specific sensorimotor targets.

Challenges to measure scapular dyskinesia:
There is no gold standard for measuring scapular kinematics, complicating the distinction between scapular dyskinesia and normal scapular movement. This leads to a lack of consensus on who should or should not be treated and how treatment should be formed. Future studies should focus on the creation of a gold standard for measuring scapular dyskinesia that should ideally have broad applicability and bring clinicians and scientists together in adequately describing patients with neuromuscular shoulder impairments.

Artificial Intelligence (AI) for scapular analysis:
AI applications that are trained to imitate expert clinician scapular ratings could assist less experienced clinicians with augmented video scapular motion analysis, improving their diagnostic skills.

Behavioral change strategies:
Research into behavioral change strategies, such as Acceptance and Commitment Therapy (ACT) or motivational interviewing, could further benefit persons with NA. Integration of psychological concepts is essential to help persons with NA adapt to their bodily limitations more effectively.

Application to other conditions:
Scapular motor control problems are relevant to other neuromuscular diseases beyond NA, which may imply that similar therapeutic approaches could be beneficial in multiple conditions. Hence, further research into upper extremity kinematics of various neuromuscular patient groups may help to explore new pathways for managing shoulder problems that may be present in these conditions.

The self-management aspect of rehabilitation places significant demands on persons that need to cope with the consequences of NA. Further psychological or agogic research into behavioral change strategies could be beneficial, as no research has yet been conducted in this area among persons with NA. The results of this thesis and the related RCT (11) underscore the vital role of interdisciplinary collaboration in the management of people with NA, particularly in empowering their self-management (11). The research embodied in this dissertation furthered our understanding of patient needs in terms of diagnosis, self-management, and shared-decision making in the context of the functional consequences of NA. A patient-centered approach helped to address individual nuances in functional consequences, emphasizing the need to actively involve patients in their care process. The results of our studies accentuated the important role of interdisciplinary collaboration in the clinical management of people with NA, particularly for empowering self-management. The effectiveness of interdisciplinary collaboration underscores the potential benefits of integrating motor control and energy conservation strategies in rehabilitation, combining the efforts of physical and occupational therapists. Future research might be focused on the most critical elements of interdisciplinary rehabilitation and how these can be strengthened.

Recently, we have been exploring the implementation of similar therapeutic approaches across diverse patient populations within our neuromuscular disease center, including individuals with muscular dystrophies affecting scapular movement and those with complex orthopedic shoulder problems resistant to conventional forms of physical therapy or surgical interventions. In persons with orthopedic conditions, abnormal movement patterns are often less prominent compared to neuromuscular conditions, which may lead to overlooking of symptoms by less experienced therapists. Still, subtle movement deviations can significantly contribute to the perpetuation of shoulder and scapulocervical complaints (20,24). However, since orthopedic conditions typically do not entail nervous system damage and the sensorimotor system, thus, remains relatively unchanged compared to neurological ailments, subtle movement deviations in these patients seem to be more promptly corrected. Consequently, rapid symptom alleviation in daily activities is feasible, and complaints resulting from persistent strain due to maladaptive movement patterns appear to resolve within a few therapeutic sessions. In muscular dystrophies, however, scapular dyskinesis often manifests itself prominently, even more so than in patients with NA. It is recognized as a characteristic feature of specific muscle diseases, such as fascioscapular

humeral dystrophy (FSHD) (45,46) and myotonic dystrophy (or dystrophia myotonica) (47). In these latter conditions, muscle mass diminishes due to a dystrophic process within the muscle tissue. Interestingly, clear scapular dyskinesis has been observed in dystrophic patients, who may exhibit notably greater strength in specific muscle groups, e.g. the serratus anterior, than would be expected based on the severity of their scapular dyskinesis. Consequently, our neuromuscular disease center prioritizes physical therapy interventions aimed at enhancing scapular motor control in various groups of neuromuscular patients. It appears that consciously guided corrections pose great challenges on this population, yet they respond favorably to implicitly induced scapular corrections. Improvements may persist for quite a period following therapeutic exercises, leading to a reduction in SD.

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Nederlandse samenvatting

In dit proefschrift behandelen we de ontwikkeling van een behandelprogramma voor restklachten na neuralgische amyotrofie (NA) en de creatie van twee meet instrumenten om patiënten tijdens hun herstelproces na NA te evalueren.

In hoofdstuk 1 beschrijven we de aandoening NA, die wordt gekenmerkt door plotseling optredende hevige pijn als gevolg van een zenuwontsteking in de schouder en arm, gevolgd door zwakte en atrofie van de aangedane spieren. Hoewel de aandoening eerder als zeldzaam werd beschouwd, is dit nu niet meer het geval, omdat ongeveer 1 op 1000 mensen elk jaar deze aandoening krijgt. In tegenstelling tot oude opvattingen over NA blijven veel patiënten last houden van restklachten zoals spierzwakte, gevoelsstoornissen en bewegingsbeperkingen. Ongeveer 50% van de patiënten vindt de behandeling van hun klachten door fysiotherapie ineffectief of zelfs verergerend. Compenserende bewegingen na NA blijken vaak ongunstig te zijn, wat resulteert in instabiliteit van het schouderblad. Deze ongunstige compensaties gaan gepaard met veranderingen in de aansturing vanuit de hersenen. Fysiotherapie is daarom zeer waarschijnlijk effectiever als het zich richt op het verminderen van deze ongunstige compensaties, gezien het aanpassingsvermogenvan onze hersenen, in plaats van te focussen op minder beïnvloedbare factoren zoals krachtverlies en verminderd uithoudingsvermogen die door de zenuwschade worden veroorzaakt. Het verminderde uithoudingsvermogen zal door gedragsaanpassing moeten worden aangepakt.

In hoofdstuk 2 presenteren we een cohortstudie gericht op aanbevelingen voor uitkomstmaten en aangrijpingspunten voor revalidatie van mensen met NA. De focus lag op het begrijpen van stoornissen op weefselniveau en beperkingen op activiteitenniveau die samenhangen met aanhoudende symptomen na NA, en het identificeren van de meest geschikte uitkomstmaten om deze problemen vast te leggen.

De gegevens werden verzameld met een enquête gebaseerd op twee groepen: een groep patiënten van de polikliniek Neurologie en een groep van de multidisciplinaire plexuspoli van het Spierziektencentrum van het Radboudumc.

De deelnemers bestonden uit 248 patiënten die niet-erfelijke of erfelijke NA hadden doorgemaakt volgens de criteria voor deze aandoening, ten minste

zes maanden geleden, waarbij de zenuwbanen van de arm betrokken warens. Binnen de studie hebben we gebruik gemaakt van twee aangepaste klinische screeningsvragenlijsten en van de Shoulder Rating Questionnaire - Dutch Language Version, de Shoulder Pain and Disability Index (SPADI), de Shoulder Disability Questionnaire (SDQ) en de Overall Disability Sum Score.

De resultaten bevestigden dat veel mensen last houden van aanhoudende pijn en beperkingen. Meer dan de helft van de patiënten was beperkt door pijn en 60% van de patiënten zonder pijn had nog steeds last van restzwakte. Er was een sterke correlatie tussen pijn, instabiliteit van het schouderblad, moeilijkheden met activiteiten boven schouderhoogte, en toegenomen vermoeidheid. Meer dan de helft van de patiënten gaf aan dat "gewone fysiotherapie" niet effectief was of hun klachten zelfs verergerde.

We concludeerden dat pijn en vermoeidheid bij NA nauw samenhangen met voortdurende instabiliteit van het schouderblad en toegenomen spiervermoeidheid. De bevindingen onderschrijven de noodzaak van een uitgebreide revalidatieaanpak die al deze factoren aanpakt. We bevelen ook aan om de SPADI en SDQ te gebruiken in toekomstig onderzoek om de natuurlijke progressie en behandeleffecten bij NA te beoordelen.

In hoofdstuk 3 presenteren we een pilotstudie waarin de effectiviteit werd onderzocht van een nieuwe multidisciplinaire revalidatie-behandeling die fysiotherapie en ergotherapie combineert voor patiënten met NA. Het interventieprogramma bestond uit 16 weken therapie, met wekelijkse sessies tijdens de eerste vier weken, tweewekelijkse sessies van week vijf tot week acht, en maandelijkse sessies van week negen tot week zestien. Elke therapiesessie bestond uit één uur fysiotherapie en één uur ergotherapie. Acht deelnemers met NA deden mee aan het onderzoek. De metingen werden op drie tijdstippen uitgevoerd: een nulmeting drie maanden voorafgaand aan de interventie, een eerste beoordeling aan het begin van de interventie, en een eindbeoordeling na afloop van de interventie. De uitkomstmaten omvatten verschillende domeinen van de International Classification of Functioning, Disability and Health (ICF). De belangrijkste uitkomstmaten waren de Shoulder Rating Questionnaire - Dutch Language Version (SRQ-DLV) en de Canadian Occupational Performance Measure (COPM), die dienden om de uitvoerbaarheid en de tevredenheid met betrekking tot de belangrijkste dagelijkse activiteiten van de deelnemers te beoordelen. Secundaire uitkomstmaten waren onder andere de Disabilities of Arm Shoulder and

Hand (DASH) vragenlijst, krachtmetingen en de Self-Efficacy for Performing Energy Conservation Strategies Assessment (SEPECSA). De Short Form 36 (SF-36) vragenlijst werd gebruikt om de gezondheidsgerelateerde kwaliteit van leven te beoordelen en de Checklist Individual Strength 20 (CIS-20) om vermoeidheid te meten.

De resultaten lieten significante verbeteringen zien in COPM-prestatiescores (gemiddeld +2,3 punten op een 10-puntschaal) en tevredenheidsscores (gemiddeld +1,4 punten op een 10-puntschaal), evenals in SRQ-DLV (gemiddeld +14,8 op een X-puntschaal) en de subschaal voor gezondheidsverandering van de SF-36 (gemiddeld -37,5 punten op een Y-puntschaal). Krachtmetingen lieten een trend richting toegenomen kracht zien voor de serratus anterior spier. Deze bevindingen suggereren dat de waargenomen verbeteringen waarschijnlijk kunnen worden toegeschreven aan coördinatie- en gedragsaanpassingen aan zenuwbeschadiging en daardoor betere omgang met het bijbehorende functieverlies van de aangedane schouder. Deze pilotstudie geeft een indicatie dat patiënten met NA verbeteringen kunnen ervaren in hun dagelijkse en sociale activiteiten na multidisciplinaire revalidatie.

Hoofdstuk 4 is een klinimetrische studie gericht op manuele krachtmeting middels dynamometrie van de serratus anterior (SA) spier. De SA speelt een cruciale rol bij schouderbeweging en -stabiliteit. Het testen van deze kracht is van groot klinisch belang om patiënten met en zonder SA zwakte te onderscheiden in relatie tot de stabiliteit van het schouderblad. Echter, bestaande methoden met behulp van manuele dynamometrie in rugligging hebben een lage betrouwbaarheid en kunnen gemakkelijk worden beïnvloed door compensatie vanuit andere spieren. Dit onderstreept de behoefte aan meer betrouwbare en valide testmethoden. Als antwoord op die behoefte hebben we drie handmatige spiertesten voor de SA aangepast, zodat ze geschikt zijn voor manuele dynamometrie, en hun validiteit en betrouwbaarheid onderzocht. De veelgebruikte methode voor krachttesten van de SA in rugligging bleek een lage betrouwbaarheid te hebben, mogelijk beïnvloed door compensatie vanuit andere spieren zoals de pectoralis major en het bovenste deel van de trapezius. In eerder onderzoek werden twee handmatige, maximale aanspanningstesten gerapporteerd die optimale spieractiviteit van de SA in zittende houding produceerden, waarop we onze nieuwe testposities hebben gebaseerd.

Eenentwintig gezonde volwassenen werden onderzocht door twee beoordelaars in een liggende en twee zittende houdingen. Elke test werd twee keer herhaald.

De validiteit werd bepaald door de kracht bij manuele dynamometrie te evalueren in relatie tot de gemeten spieractiviteit van de SA, bovenste trapezius, en pectoralis major spieren, waarbij de drie testposities met elkaar werden vergeleken.

De betrouwbaarheid binnen en tussen beoordelaars werd bepaald door het berekenen van intra-klasse correlatiecoëfficiënten (ICC), kleinste detecteerbare verandering (SDC) en standaardmeetfout (SEM).

De resultaten toonden aan dat de activiteit van de SA spier het meest geïsoleerd te meten was in een zittende positie met de elleboog 90° gebogen en de bovenarm horizontaal naar voren wijzend. Deze positie resulteerde in de laagst gemeten krachtniveaus met een gemiddelde waarde van 296N (SEM 15,8N). De betrouwbaarheid binnen dezelfde beoordelaars leverde een ICC op van 0,66 (95% betrouwbaarheidsinterval 0,33:0,85), terwijl de betrouwbaarheid tussen verschillende beoordelaars 0,28 (95% betrouwbaarheidsinterval -0,10:0,61) betrof. De SDC was 127N en de SEM was 45,8 N.

We concludeerden dat de validiteit voor krachttesten van de SA optimaal is met proefpersonen in zittende positie en de elleboog 90° gebogen en bovenarm horizontaal naar voren wijzend. De betrouwbaarheid van deze procedure binnen beoordelaars is echter matig en de betrouwbaarheid tussen beoordelaars slecht, terwijl ook de hoge SDC-waarden het moeilijk maken om de meting te gebruiken bij herhaalde metingen.

Hoofdstuk 5 onderzoekt de haalbaarheid van reachable workspace metingen om bewegingsbeperkingen te meten bij patiënten met NA. De reachable workspace (RWS) is een gecomputeriseerd 3D-analysesysteem dat de relatieve oppervlakte (RSA) van het bereik van de arm van een individu meet. RWS is nuttig gebleken bij verschillende andere neuromusculaire aandoeningen.

In deze studie werd onderzocht of de RWS in staat is om beperkingen in het actieve bewegingsbereik van de bovenste extremiteit te kwantificeren bij patiënten met NA. De RSA's van patiënten met NA werden vergeleken met die van gezonde controles en gecorreleerd met andere maten voor het functioneren van de bovenste extremiteit. We maten 47 patiënten met NA en 25 gezonde controles, gematched voor leeftijd en geslacht. De RSA's van de deelnemers werden gemeten met de RWS en gecorreleerd met de scores van

de Shoulder Rating Questionnaire (SRQ), de Disabilities of Arm Shoulder and Hand (DASH) vragenlijst, en met krachtmetingen van de bovenste extremiteit met behulp van manuele dynamometrie.

De resultaten toonden aan dat patiënten met NA significant lagere waarden hadden voor bewegingsbereik van de aangedane arm voor alle kwadranten (behalve het onderste kwadrant aan de aangedane zijde van het lichaam) en voor de totale RSA waarde vergeleken met controles ($p<0,001$). Er werden matige correlaties gevonden van de RSA met de DASH vragenlijst ($r= -0,42$) en met de SA spierkracht ($r= 0,41$).

We concludeerden dat de RWS beperkingen in het actieve bewegingsbereik van de aangedane arm kan detecteren bij patiënten met NA en matig gecorreleerd is met functionele maten van de bovenste extremiteit. We concludeerden ook dat de RWS meerwaarde heeft voor het kwantificeren van functionele beperkingen van de aangedane bovenste extremiteit bij NA en potentieel heeft als functionele klinische uitkomstmaat.

Hoofdstuk 6 is een op uitnodiging geschreven review en geeft een uitgebreid overzicht van de huidige kennis van en ontwikkelingen bij NA. We beschrijven de klinische uitingsvorm van NA als een aandoeningen van voornamelijk de zenuwen in de zenuwbanen van de arm, die deze plexus op meerdere plaatsen kan aantasten. Recente literatuur heeft echter deze NA uitingsvorm uitgebreid met aandoeningen die voorheen werden beschouwd als geïsoleerde zenuwverlammingen. We bespreken de epidemiologie van NA, met de nadruk op een jaarlijkse incidentie van ongeveer 1:1000. We onderzoeken de mogelijke etiologie van NA, inclusief de rol van voorafgaande infecties als trigger van de aandoening. We presenteren een state-of-the-art benadering van het (poli) klinisch onderzoek en de behandeling van patiënten die verdacht worden van NA. Behandeling tijdens de acute fase van NA bestaat meestal uit het gebruik van ontstekingsremmende medicijnen, de zogenaamde corticosteroïden en eventueel intraveneus immunoglobuline, gecombineerd met pijnstillende medicatie. We beschrijven de behandeling in de chronische fase, die bestaat uit fysiotherapie en ergotherapie; beide gericht op het helpen van patiënten bij het verbeteren van energiebehoud door middel van gedragsaanpassingen en de ontwikkeling van een preciezere en efficiëntere coördinatie van het schouderblad en de arm. Bij ernstigere zenuwbeschadiging met (bijna) volledige verlamming kan het operatief vrijleggen van de zenuw, zenuwtransplantatie of spiertransplantatie overwogen worden als chirurgische behandelopties. We concluderen dat NA een relatief veel

voorkomende en behandelbare aandoening is, zowel in de acute als chronische fase, die een gespecialiseerde behandelingsaanpak nodig heeft met prioriteit voor energiebalans en coördinatie van schouderblad- en armbewegingen.

Research data management

General information about the data collection

The presented research followed the applicable laws and ethical guidelines. Research data management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics and privacy

Chapters 2, 3 and 4 and 5 were based on the results of human subject data. These chapters were conducted according to the principles of the Declaration of Helsinki (version 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The principles of Good Clinical Practice were followed throughout. Written informed consent was obtained from all study participants, prior to any study procedure.

The local Medical and Ethical Review board Committee of the region Arnhem Nijmegen, Nijmegen, The Netherlands (CMO) has given approval to conduct these studies (file numbers: chapter 2 CMO2012/456 chapter 3; CMO2011/481, chapter 4; CMO2013/177 and chapter 5; CMO2017/3740). The data used in chapter 5 was collected during a separate study: "the NA-CONTROL study" and was registered at ClinicalTrials.gov (NCT03441347).

The privacy of the participants in all studies of this thesis was warranted using encrypted and unique individual subject codes. The encrypted keys were stored separately from the research data and were only accessible to members of the project who needed access based on their role within the project.

Data collection and storage

Data were stored on a shielded part of the server of the Rehabilitation department of the Radboudumc (chapter 2, 3, 4). For the reachable workspace study (chapter 5) clinical data (questionnaires (.csv) and reachable workspace files (.mat) were stored in a Castor EDC database and on a shielded part of the server of the Rehabilitation of the Radboudumc. The paper CRF files were stored at the departments archive. Data were stored in the following formats: .XLSX (Microsoft Office Excel), .SAV and .SPS (SPSS) and .hpr (Altlas Ti). No existing data standards were used such as vocabularies, ontologies or thesauri.

Data sharing

The datasets suitable for reuse are published in the Radboud Data Repository (DOI: will follow later). Data were made reusable by adding sufficient documentation (research protocol, codebook and a 163 readme file), by using preferred and sustainable data formats and by publishing under the CC BY-NC 4.0 license. Requests for access will be checked, by the principal investigator (PI) of the department, against the conditions for sharing the data as described in the signed Informed Consent. The data not suitable for reuse will be archived for 15 years after termination of the study

Curriculum Vitae

Jos IJspeert (MSc PT) is a physical therapist and junior researcher at Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Department of Rehabilitation-Physical Therapy, The Netherlands.

In 2007, he graduated as a physical therapist from HU University of Applied Sciences Utrecht. In 2012, he earned a Master's degree in clinical health sciences, majoring in Physical Therapy Science, from Utrecht University.

Since 2009, he has worked at Radboudumc Nijmegen's neuromuscular center as a physical therapist and researcher.

Between 2014 and 2016, he lectured in the Avans+ Master's program in geriatric physical therapy. Since 2016, he has taught in the Radboudumc Plexus Management course, an interprofessional course for physical and occupational therapists treating brachial plexus problems. He regularly gives lectures at international conferences on shoulder-related issues.

His expertise includes shoulder and respiratory problems related to Neurology, specifically Neuralgic Amyotrophy (NA) and neuromuscular dystrophies. For his Master's degree, he conducted a pilot study on a combined occupational and physical therapy intervention for NA patients, developed in collaboration with the plexus clinic team, including occupational therapist Renske Janssen at Radboudumc. He co-founded the children's shoulder clinic at Amalia Children's Hospital, Radboudumc, and previously Kinos Schouders, a rehabilitation clinic for complex shoulder complaints. After January 2025, he will continue researching multifaceted and interdisciplinary approaches to shoulder and respiratory problems in NA and other neuromuscular disorders.

*

List of publications

Cup EH, IJspeert J, Janssen RJ, Bussemaker-Beumer C, Jacobs J, Pieterse AJ, van der Linde H, van Alfen N.
Residual complaints after neuralgic amyotrophy.
Arch Phys Med Rehabil. 2013 Jan;94(1):67-73. doi: 10.1016/j.apmr.2012.07.014. Epub 2012 Jul 28. PMID: 22850488.

IJspeert J, Janssen RM, Murgia A, Pisters MF, Cup EH, Groothuis JT, van Alfen N.
Efficacy of a combined physical and occupational therapy intervention in patients with subacute neuralgic amyotrophy: a pilot study.
NeuroRehabilitation. 2013;33(4):657-65. doi: 10.3233/NRE-130993. PMID: 24004606.

IJspeert J, Janssen RMJ, van Alfen N.
Neuralgic amyotrophy.
Curr Opin Neurol. 2021 Oct 1;34(5):605-612. doi: 10.1097/WCO.0000000000000968. PMID: 34054111.

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BMC Musculoskelet Disord. 2019 Aug 7;20(1):360. doi: 10.1186/s12891-019-2741-7. Erratum in: BMC Musculoskelet Disord. 2019 Sep 17;20(1):433. doi: 10.1186/s12891-019-2780-0. PMID: 31391035; PMCID: PMC6686461.

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Disabil Rehabil. 2019 Jun;41(12):1427-1434.
doi: 10.1080/09638288.2018.1430175. Epub 2018 Jan 31. PMID: 29385821.

Voermans NC, van der Bilt RC, IJspeert J, Hogrel JY, Jeanpierre M, Behin A, Laforet P, Stojkovic T, van Engelen BG, Padberg GW, Sacconi S, Lemmers RJLF, van der Maarel SM, Eymard B, Bassez G.
Scapular dyskinesis in myotonic dystrophy type 1: clinical characteristics and genetic investigations.
J Neurol. 2019 Dec;266(12):2987-2996. doi: 10.1007/s00415-019-09494-8. Epub 2019 Aug 31. PMID: 31471688; PMCID: PMC6851043.

PhD portfolio

Training activities	Hours
Courses	
- Radboudumc - Introduction day (2009)	6.00
- Radboudumc - Scientific integrity (2014)	24.00
- Motivational Interviewing, basisvaardigheden (2015) - Maartensacademie	24.00
- Donders graduate school - GS Introduction Day (2017)	7.00
- Radboudumc - eBROK course (2018)	20.00
- Basistraining kwalitatief onderzoek (2023)	12
Seminars	
- Schoudersymposium Orthopedie Amphia. Lezing "Neuralgische Amyotrofie" (2021) - Orthopedie Amphia	3.00
Conferences	
- VRA Annual Congress: Mini-symposium: Rehabilitation in PNS disorders of the shoulder: a new paradigm (2013)	8.00
- Schoudernetwerken Nederland congres (2015) 'joint togheter' lezing 'neuralgische amyotrofie'	8.00
- Schoudernetwerken Nederland congres (2017) 'Flexibility Matters' lezing: 'n. phrenicus uitval bij neuralgische amyotrofie' lezing: 'validity and reliability of serratus anterior hand held dynamometry'	8.00
- FSHD society international research conference (2019) lezing: 'Clinical examination of scapula function in patients with FSHD'	16.00
- EUSSER schouder netwerken Nederland conference (2019) 'Brain & Pain' Lezing: 'rehabilitation of neuralgic amyotrophy'	8.00
- Schoudernetwerken Nederland congres (2022) 'gluren bij de buren' Lezing: 'Kinderrevalidatie: motorisch leren en impliciet trainen van scapula coördinatie' Sessie voorzitter: Asbtracts presentations	16.00
- FSHD Society connect conference Orlando FL (2022) Lezing: 'scapular training in FSHD' Workshop: 'hands on scapular training seminar'	16.00
Other	
- Symposium: Behandeling van plexus brachialis letsel; een nieuwe aanpak (2014)	8.00
- Consulentenmiddag Spierziekten Nederland, lezing: behandeling van neuralgische amyotrofie en spierziekten (2018)	4.00
- Consulentenmiddag spierziekten Nederland (2020) lezing: behandeling van kinder schouderklachten.	6.00
- Spierziektencongres voor patiënten (online). Lezing: over Neuralgische Amyotrofie (2022)	1.00
- Oratie professor Nens van Alfen 2023	1.00
- Refereer bijeenkomsten afdeling fysiotherapie revalidatie Radboudumc wekelijks 1 uur (2013-2024)	440.00
- Oratie professor Nicol Voermans 2024	1.00

Teaching activities	
Lecturing	
- Avans+ master geriatriefysiotherapie onderwijs 'module evidence based practise' 2014-2016	72.00
- Online course 'herkennen en behandelen van spierziekten, KNGF' (2022) 4 online courses over 1 year	8.00
- Cursus plexus management (course into rehabilitation strategies for neuralgic amyotrophy for physical- and occupational therapists) twice per year 16 hours per course 2015-2024	288.00
Supervision of internships / other	
- Praktijkbegeleiding opleiding fysiotherapie: stage begeleiding (2013-2024) 11 stagiairs.	220.00
Total	**1225.00**

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Dankwoord

Dit proefschrift is het product van een reis die in 2009 begon. Als fysiotherapeut en onderzoeker heb ik het voorrecht om te werken in een centrum waar collega's, ieder op hun eigen manier, geïnspireerd raken door de vragen die we elkaar stellen. Samen vormen we een cultuur waarin het mogelijk is om die vragen te onderzoeken en antwoorden te vinden.

Mijn grootste dank gaat uit naar onze patiënten. Jullie nemen de moeite om naar ons spierziekten centrum te komen, vaak van ver, en staan open voor bijna elk onderzoek verzoek. Jullie delen waardevolle inzichten en geven eerlijke feedback op onze behandelingen, waarmee jullie de basis leggen voor alles wat ik op dit gebied doe. Dankzij jullie heb ik veel geleerd over veerkracht en ben ik geïnspireerd geraakt om diezelfde veerkracht toe te passen in mijn eigen leven en werk.

Professor Van Alfen, beste Nens, jouw bescheidenheid en inspirerende aanpak in het leven, zowel als arts en wetenschapper, hebben mij veel geleerd. Ik ken niemand zoals jij die een bijna onmenselijke productiviteit combineert met een oprechte empathie voor anderen. Sinds mijn afstudeerfase begeleid je me al, en jouw voortdurende steun tijdens mijn promotieonderzoek is van onschatbare waarde geweest. Je hebt jezelf wel eens "kwartiermaker" voor NA-zorg genoemd binnen ons centrum en het interdisciplinair zorgmodel dat daarbinnen is ontwikkeld, vormt een voorbeeld voor ons allen. Ook ben ik dankbaar voor de vriendschap die we hebben opgebouwd samen met je partner Sigrid. Ik hoop dat we zowel op professioneel als persoonlijk vlak nog lang met elkaar verbonden blijven.

Professor Groothuis, **beste Jan,** sinds 2012 zijn we aan elkaar verbonden door onze gezamenlijke patiënten en het onderzoek dat we doen. Ik waardeer jouw steun in mijn ambities en de kalme, nuchtere begeleiding die je biedt. Jij hebt me altijd ruimte gegeven om mijn ideeën te volgen zonder ze te beperken. Jouw benadering leert me veel over het behouden van rust en perspectief, zelfs bij grote uitdagingen. Ik kijk uit naar nog vele jaren van samenwerking in schouderonderzoek en zorg.

Professor Geurts, beste Sander, ik heb je leren kennen als een zeer bekwame arts en een betrokken hoogleraar. In de beginjaren stond je wat op afstand voor mij, maar door ons gezamenlijke onderzoek en patiëntencontact zijn we dichter

naar elkaar toegegroeid. Ik bewonder je brede begrip van de geneeskunde en de beschouwende wijze waarop je onderwerpen benadert. Elke keer als ik inhoudelijke feedback op mijn wetenschappelijke werk van jou kreeg, hielp dat om de inhoud te verbeteren en om mijn gedachten te ordenen en mijn begrip te verdiepen. Ik hoop dat onze samenwerking nog een tijd blijft voortduren.

Professor Van der Wees, beste Philip, onze eerste ontmoeting vond plaats tijdens mijn studie waar jij als gastdocent een werkopdracht gaf over zorgverbeteringsonderzoek. Later kwamen we elkaar weer tegen in het Radboudumc, waar je als hoogleraar paramedische wetenschappen bij onze afdeling betrokken werd. Jouw positieve houding en stimulerende begeleiding waren cruciaal in de laatste fase van mijn promotietraject. Ik hoop dat we in de toekomst de kans krijgen om samen nieuwe projecten op het gebied van schouderonderzoek te starten.

Dr. Janssen, beste Renske, de afgelopen 15 jaar zijn door jouw collegialiteit en vriendschap niet alleen leerzaam, maar ook zoveel aangenamer geweest. Samen hebben we een behandelprogramma ontwikkeld voor patiënten met neuralgische amyotrofie, een complexe aandoening die een uitdaging blijft. Ik vind dat je soms te bescheiden bent over jouw bijdrage aan de fysiotherapeutische behandeling, want ik heb veel van je geleerd over het verdiepen in wat echt betekenisvol is voor patiënten met NA. Jouw modelmatige en methodische benadering vult mijn vaak wat filosofische blik perfect aan en het paranimfschap dat we nu delen bekroont deze samenwerking op een bijzondere manier. Onze vriendschap betekent veel voor me en ik hoop dat we nog lang zullen samenwerken en elkaar blijven inspireren.

Judith van Engelen-Kanters, mijn maatje op de plexuspoli. Jij bent voor mij een belangrijk tegenwicht. Je bent organisatorisch sterk en nauwgezet, waar mijn benadering soms wat chaotischer is. Sinds 2015 werken we samen en ik waardeer de ruimte die je me geeft om mijn ideeën uit te voeren terwijl je me ook helpt om structuur aan te brengen waar nodig.

Dr. Voet, beste Nicole, in mijn beginjaren bij het Radboudumc was ik naast fysiotherapeut ook onderzoeksassistent in jouw FSHD-studies. Dit leidde tot vele waardevolle momenten samen, zowel in overleg als in gedeelde zorg voor patiënten. Ik bewonder je tomeloze energie, zowel in je werk als in je sport. Jouw activistische houding en de persoonlijke connectie die je maakt met patiënten maken jou tot een groot voorbeeld. Onze professionele klik

is uitgegroeid tot een persoonlijke vriendschap met jou en Joost die ik zeer waardeer. Het is mooi dat ik jou als paranimf aan mijn zijde heb, net zoals ik dat bij jou mocht zijn.

Dr. Van der Linde, beste Harmen, jij was de eerste revalidatiearts waarmee ik intensief samenwerkte. Ik heb veel te danken aan jouw steun in de behandeling van NA-patiënten, zoals je het vaak noemde "met al hun (eigen) aardigheden". Onze samenwerking leidde ook tot mijn deelname aan Kinos, wat specialistische schouderrevalidatie buiten het Radboudumc mogelijk maakte. Ik kijk met bewondering naar jouw vermogen om conflicten op te lossen en de rust te bewaren, zowel binnen de academie als daarbuiten. Inmiddels geniet je van een welverdiend pensioen, maar ik denk nog vaak aan onze samenwerking.

Professor Van Engelen, beste Baziel, hoewel we niet vaak direct hebben samengewerkt, ben ik je dankbaar voor de rol die je hebt gespeeld voor mijn positie binnen en buiten het Radboudumc. Je hebt me bij veel collega's en patiënten geprezen als expert op het gebied van schouderbewegingscoördinatie en fysiotherapie, wat me de ruimte heeft gegeven om me te profileren. Onze gesprekken boden verheldering over de waarden achter goede zorg en je filosofische kijk op geneeskunde is een inspiratie. Inmiddels geniet je van een welverdiend emiritaat, maar ik hoop dat we zo nu en dan nog contact houden.

Professor Voermans, beste Nicol, jouw benadering van geneeskunde, net als die van Baziel, is filosofisch en bijzonder doelmatig. Je combineert een indrukwekkende productiviteit met persoonlijke aandacht voor collega's en jouw toewijding inspireert me. Onze samenwerking, onder andere in de promotie van Maaike, biedt veel perspectief en ik kijk ernaar uit om nog veel van jou te leren.

Beste collega's van de fysiotherapie, specifiek unit 4, ik ben trots op ons team. Na een roerige periode ontstond er een hechte groep collega's met hart voor patiëntenzorg, onderwijs en wetenschap. Ik waardeer de sfeer van vertrouwen waarin we elkaar ondersteunen in zowel goede als minder goede tijden. De sinterklaasavonden en de teamuitjes zijn momenten die ik koester, en ik hoop dat we nog veel van deze waardevolle momenten samen zullen meemaken.

Marlou, dank voor je voortdurende geduld en ondersteuning.

Collega's van de plexuspoli, Judith, Jessica, Jan, Nens, Renske, Manouk, Yvonne, Edith, Jacqueline, in de afgelopen 15 jaar zijn we samen gegroeid tot een sterk team. Onze samenwerking maakt het mogelijk om niet alleen onderzoek te doen, maar ook de beste zorg te leveren. Zonder jullie zou dit onderzoek niet mogelijk zijn en zouden we niet de hulp kunnen bieden die onze patiënten verdienen.

Collega's van de kinderschouderpoli, Maaike, Hilde, Saskia en Anitha, jullie zijn geweldig in de benadering van schouderproblemen bij onze neuromusculaire kinderpopulatie. Met jullie is de olievlek van de schouders in Spierziektencentrum Nijmegen gaan uitvloeien. Ik hoop dat we daarin kunnen blijven bouwen aan bruggen tussen de volwassenen- en kinderrevalidatie.

Lieve schoonouders, Henk en Ineke, jullie steun is van onschatbare waarde. Jullie betrokkenheid bij ons gezin is voelbaar in alles wat jullie doen en ik beschouw jullie echt als bonusouders. Bedankt voor de ruimte en steun die jullie bieden, zowel praktisch als emotioneel.

Pa, fijn dat je erbij bent. Misschien had je nooit verwacht dat ik ooit een proefschrift zou afronden, maar ik ben dankbaar voor jouw steun en die van mama en de vrijheid die jullie me gaven om mijn eigen keuzes te maken.

Mam, ik had dit moment graag met je gedeeld, net zoals zoveel andere momenten. Ik hoop dat je op een of andere manier toch bij me bent.

Lieve Rob, ik waardeer onze band enorm. Wat er ook gebeurt, wij kunnen altijd op elkaar rekenen. Ik ben blij dat ik een broer heb die zo hartelijk en warm is.

Lieve Vera en Ilja, jullie zijn de kroon op mijn relatie met jullie moeder en het mooiste wat mij ooit is overkomen. Het ouderschap leert me dat alle clichés waar zijn. Ik zie jullie opgroeien tot de bijzondere kinderen die jullie zijn en ik hoop nog veel mooie momenten met jullie te mogen delen.

Lieve Eva, jij bent mijn rots in de branding. Jij bent de spil van ons gezin en hebt me het grootste geschenk gegeven: onze kinderen Vera en Ilja. Jij motiveert me om een beter mens te worden en ik ben je dankbaar voor je onvoorwaardelijke steun en geduld. Jij hebt me nooit afgeremd in mijn ambities en je leert me focussen op wat echt belangrijk is in het leven. Ik ben oneindig dankbaar voor jouw liefde en toewijding. Ik houd van jou.

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Theses Spierziekten Centrum Radboudumc

The work described in this thesis was conducted in the Neuromuscular Center of the Radboud university medical center.

Year	PhD	Title thesis	Supervisors
2002	Drs. M van Beekvelt	Quantitative near-infrared spectroscopy in human skeletal muscle. Methodological issues and clinical application	Prof. dr. RA Wevers Prof. dr. GWAM Padberg Dr. Ir. WJNM Colier Dr. BGM van Engelen
2004	Drs. J Hiel	Ataxia telangiectasia and Nijmegen Breakage syndrome, neurological, immunological and genetic aspects.	Prof. dr. FJM Gabreëls Prof. dr. BGM van Engelen Dr. CMR Weemaes Dr. LPJW van den Heuvel
2005	Drs. G Hengstman	Myositis specific autoantibodies, specificity and clinical applications.	Prof. dr. BGM van Engelen Prof. dr. WJ van Venrooij
2005	Drs. M Schillings	Fatigue in neuromuscular disorders and chronic fatigue syndr.ome, a neurophysiological approach.	Prof. dr. MJ Zwarts Prof. dr. BGM van Engelen Prof. dr. G Bleijenberg
2006	Drs. B de Swart	Speech therapy in patients with neuromuscular disorders and Parkinson's disease. Diagnosis and treatment of dysarthria and dysphagia.	Prof. dr. BGM van Engelen Prof. dr. GWAM Padberg Dr. BAM Maassen
2006	Drs. J Kalkman	From prevalence to predictors of fatigue in neuromuscular disorders. The building of a model.	Prof. dr. G Bleijenberg Prof. dr. BGM van Engelen Prof. dr. MJ Zwarts
2006	Drs. N van Alfen	Neuralgic amyotrophy.	Prof. dr. BGM van Engelen Prof. dr. FJM Gabreëls
2007	Drs. G Drost	High-density surface EMG, pathophysiological insights and clinical applications.	Prof. dr. MJ Zwarts Prof. dr. Ir. DF Stegeman Prof. dr. BGM van Engelen
2009	Drs. M van der Linden	Perturbations of gait and balance: a new experimental setup applied to patients with CMT type 1a.	Prof. dr. J Duysens Prof. dr. BGM van Engelen Dr. HT Hendricks
2010	Drs. J Trip	Redefining the non-dystrophic myotonic syndromes. Phenotypic characterization based on genetic testing.	Prof. dr. BGM van Engelen Dr. G Drost Dr. CG Faber
2010	Drs. C Horlings	A weak balance, balance and falls in patients with neuromuscular disorders.	Prof. dr. BR Bloem Prof. dr. BGM van Engelen Prof. dr. JHJ Allum
2011	Drs. E Cup	Occupational therapy, physical therapy and speech therapy for persons with neuromuscular diseases. An evidence based orientation.	Prof. dr. RAB Oostendorp Prof. dr. BGM van Engelen Prof. dr. GJ van der Wilt Dr. HT Hendr.icks
2011	Drs. A Tieleman	Myotonic dystrophy type 2, a newly diagnosed disease in the Netherlands.	Prof. dr. BGM van Engelen Dr. H Scheffer
2011	Drs. N Voermans	Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome, expanding the phenotype of inherited connective tissue disorders and investigating the role of the extracellular matrix in musle	Prof. dr. BGM van Engelen Prof. dr. BC Hamel Prof. dr. A de Haan

2012	Drs. A Pieterse	Referral and indication for occupational therapy, physical therapy and speech-language therapy for persons with neuromuscular disorders.	Prof. dr. RAB Oostendorp Prof. dr. BGM van Engelen Prof. dr. GJ van der Wilt Dr. HT Hendricks
2012	Drs. B Smits	Chronic Progressive External Ophthalmoplegia. More than meets the eye.	Prof. dr. BGM van Engelen Prof. dr. LPWJ van den Heuvel
2012	Drs. I Arts	Muscle ultrasonography in ALS.	Prof. dr. ir DF Stegeman Prof. dr. BGM van Engelen Dr. HJ Schelhaas Dr. S Overeem
2013	Drs. M Minis	Sustainability of work for persons with neuromusclar diseases.	Prof. dr. MWG Nijhuis-van der Sanden Prof. dr. BGM van Engelen Dr. YF Heerkens Dr. JA Engels
2014	Drs. W Leen	Glucose transporter-1 deficiency syndrome.	Prof. dr. M Willemsen Prof. dr. BGM van Engelen
2014	Drs. M Jansen	No use is disuse: physical training in Duchenne muscular dystrophy	Prof. dr. ACH Geurts Dr. IJM de Groot Dr. N van Alfen
2015	Drs. B Janssen	Magnetic Resonance Imaging signature of facioscapulohumeral muscular dystrophy.	Prof. dr. A Heerschap Prof. dr. BGM van Engelen
2015	Drs. N Rijken	Balance and gait in facioscapulohumeral muscular dystrophy, relations with individual muscle involvement.	Prof. dr. ACH Geurts Prof. dr. BGM van Engelen Dr. VGM Weerdesteyn
2016	Drs. F Seesing	Shared medical appointments for neuromuscular patients and their partners.	Prof. dr. BGM van Engelen Prof. dr. GJ van der Wilt Dr. G Drost
2016	Drs. A Bergsma	The upper limb in neuromuscular disorders: from basic function to daily life performance	Prof. dr. ACH Geurts Dr. IJM de Groot Dr. EHC Cup
2017	Drs. N Voet	Aerobic exercise and cognitive behavioral therapy in facioscapulohumeral muscular dystrophy: a model based approach.	Prof. dr. ACH Geurts Prof. dr. BGM van Engelen Prof. dr. G Bleijenberg
2017	Drs. B van der Sluijs	Oculopharyngeal muscular dystrophy (OPMD) in the Netherlands, beyond dysphagia and ptosis.	Prof. dr. BGM van Engelen Dr. NC Voermans
2018	Drs. S Knuijt	Prevalence of dysarthria and dysphagia in neuromuscular diseases and an assessment tool for dysarthria in adults.	Prof. dr. ACH Geurts Prof. dr. BGM van Engelen Dr. BJM de Swart Dr. JG Kalf
2018	Drs. M Wohlgemuth	A family based study of in facioscapulohumeral muscular dystrophy. Lessons learnt from mild and severe phenotype	Prof. dr. GWAM Padberg Prof. dr. BGM van Engelen Dr. NC Voermans Dr. RJ Lemmers
2019	Drs. Karlien Mul	The many faces of facioscapulohumeral muscular dystrophy: opportunities and challenges on the road to therapies	Prof. dr. BGM van Engelen Prof. dr. Ir. SM van der Maarel Dr. GC Horlings Dr. NC Voermans
2019	Drs. J van Vliet	Myotonic dystrophy type 2. The challenging diagnosis of a complex disease.	Prof. dr. BGM van Engelen Dr. A Verrips Dr. AA Tieleman

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2019	Drs. K Bhansing	Clinical aspects and muscle ultrasound in polymyositis and dermatomyositis.	Prof. dr. PLCM van Riel Prof. dr. BGM van Engelen Dr. MC Vonk
2019	Drs. L Peeters	The trunk in neuromuscular disorders: a neglected part of the chain.	Prof. dr. ACH Geurts Prof. dr. JH van Dieën Dr. IJM de Groot Dr. I Kingma
2020	Drs. L Heskamp	Quantitative muscle MRI to unravel the physiology of dystrophic and healthy muscle.	Prof. dr. A Heerschap Prof. dr. BGM van Engelen
2020	Drs. R Goselink	Growing up with FSHD. Characteristics of early-onset FSHD and childhood FSHD.	Prof. dr. BGM van Engelen Dr. CE Erasmus Dr. NC Voermans
2020	Drs. S Lassche	Contractile function in facioscapulohumeral muscular dystrophy.	Prof. dr. BGM van Engelen, Prof. dr. CAC Ottenheijm Dr. NC Voermans
2020	Drs. J van Eijk	Antecedent infections in neuralgic amyotrophy, a prominent role for hepatitis E virus.	Prof. dr. BGM van Engelen Prof. dr. B Jacobs Dr. N van Alfen
2020	Drs. N Bin Abu Bakar	Glycomics by mass spectrometry for the diagnosis of congenital disorders of glycosylation (CDG)	Prof. dr. DJ Lefeber Prof. dr. RA Wevers Dr. M van Scherpenzeel
2021	Drs. A Rietveld	Anti-cN-1A reactivity in JDM	Prof. dr. BGM van Engelen Prof. dr. GJM Pruijn Dr. CGJ Saris
2022	Drs. Y Veenhuizen	Aerobic Exercise Training and Energy Conservation Management to improve social participation in people with a neuromuscular disease. Effectiveness and cost-effectiveness of the Energetic group program.	Prof. dr. ACH Geurts Prof. dr. BGM van Engelen Dr. EHC Cup Dr. JT Groothuis
2022	Drs. C Ausems	First steps towards a pericyte-based muscle therapy for myotonic dystrophy	Prof. dr. JHLM van Bokhoven Prof. dr. BGM van Engelen Dr. DG Wansink
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2023	Drs. K Okkersen	The brain in myotonic dystrophy type 1, Hammer & Anvil.	Prof. dr. BGM van Engelen Prof. dr. JA Knoop Dr. J Raaphorst
2024	Drs. C Seijger	Respiration in myotonic dystrophy: characteristics and therapeutic interventions	Prof. dr. PJ Wijkstra Prof. dr. BGM van Engelen
2024	Drs. J Molenaar	Focus on muscle relaxation in health and disease. From in vivo to in vitro and back again.	Prof. dr. BGM van Engelen Prof. dr. NC Voermans Dr. J Doorduin

2024	Drs. K Bouman	Optimization of clinical care and trial readiness of two rare muscle diseases: LAMA2-related muscular dystrophy and SELENON-related congenital myopathy	Prof. dr. NC Voermans Prof. dr. BGM van Engelen Dr. JT Groothuis Dr. CE Erasmus
2024	Drs. R Janssen	Development and evaluation of an integrated multidisciplinary rehabilitation program for patients with neuralgic amyotrophy	Prof. dr. MJL Graff Prof. dr. ACH Geurts Prof. dr. JT Groothuis Dr. EHC Cup
2025	Drs. J IJspeert	Rehabilitation after neuralgic amyotrophy. Finding a path to self-management	Prof. dr. ACH Geurts Prof. dr. JT Groothuis Prof. dr. N van Alfen Prof. dr. PJ van de wees

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