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Research paper

Feasibility and tolerability of multimodal peripheral electrophysiological techniques in a cohort of patients with spinal muscular atrophy

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ABSTRACT

Objective: Electrophysiological techniques are emerging as an aid in identifying prognostic or therapeutic biomarkers in patients with spinal muscular atrophy (SMA), but electrophysiological assessments may be burdensome for patients. We, therefore, assessed feasibility and tolerability of multimodal peripheral non-invasive electrophysiological techniques in a cohort of patients with SMA.
Methods: We conducted a single center, longitudinal cohort study investigating the feasibility and tolerability of applying multimodal electrophysiological techniques to the median nerve unilaterally. Techniques consisted of the compound muscle action potential scan, motor nerve excitability tests, repetitive nerve stimulation and sensory nerve action potential. We assessed tolerability using the numeric rating scale (NRS), ranging from 0 (no pain) to 10 (worst possible pain), and defined the protocol to be tolerable if the NRS score ≤ 3. The protocol was considered feasible if it could be performed according to test and quality standards.
Results: We included 71 patients with SMA types 1–4 (median 39 years; range 13–67) and 63 patients at follow-up. The protocol was feasible in 98% of patients and was well-tolerated in up to 90% of patients. Median NRS score was 2 (range 0–6 at baseline and range 0–4 at follow-up ($p < 0.01$)). None of the patients declined follow-up assessment.
Conclusions: Multimodal, peripheral, non-invasive, electrophysiological techniques applied to the median nerve are feasible and well-tolerated in adolescents and adults with SMA types 1–4.
Significance: Our study supports the use of non-invasive multimodal electrophysiological assessments in adolescents and adults with SMA types 1–4.

1. Introduction

Hereditary proximal spinal muscular atrophy (SMA or 5qSMA) is a progressive motor neuron disorder, caused by loss of function of the *Survival Motor Neuron 1* (*SMN1*) gene and the resulting intracellular deficiency of SMN protein (Lefebvre et al. 1995). SMA displays a wide range of severity, classified according to the age at onset and achieved gross motor milestones into SMA types 0–4 (Mercuri et al. 2012, Wadman et al. 2017). The variation in severity is explained at least partially by genetic modifiers of SMN protein expression and function, of which the highly homologous *SMN2* gene is most important. A crucial point mutation leads to exclusion of exon 7 in the large majority of *SMN2* mRNA and the production of only residual levels of full length SMN protein. *SMN2* copy number variation inversely correlates with severity and explains up to 60% of clinical variability (Wadman et al. 2020).

Genetic treatment for SMA aims at restoring SMN protein levels through restoring the presence of the *SMN1* gene in motor neurons (i.e. viral gene therapy: onasemnogene abeparvovec) or by skewing *SMN2* mRNA splicing towards inclusion of exon 7 and the production of full length SMN protein (i.e. *SMN2* mRNA splicing modifiers: nusinersen or risdiplam). All therapies can improve survival and motor function in infants and children with SMA if administered timely (Baranello et al. 2021, Finkel et al. 2017, Mendell et al. 2017, Mercuri et al. 2018, Mercuri et al. 2022, Scheijmans et al. 2022).

Post-marketing experience also suggests that treatment may improve motor function in subgroups of older patients, in particular with milder SMA (Coratti et al. 2021, Hagenacker et al. 2020, Maggi et al. 2020). In all age groups there is large variation in the

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response to treatment, which can be appreciated only after longer periods of time, i.e. 12 months or longer. The high cost of genetic treatment and their burden for patients and potential side effects indicate that there is a need for tools that can help to predict response to treatment shortly after its start (Arnold et al. 2014, Kariyawasam et al. 2019).

Currently used clinical instruments to assess treatment efficacy in patients with SMA are structured assessments of motor function, such as the Hammersmith Functional Motor Scale or Motor Function Measure, or muscle strength (Duong et al. 2020, Glanzman et al. 2011, Main et al. 2003, Mazzone et al. 2017, O'Hagen et al. 2007, Wijngaarde et al. 2020). Although these tools have proven invaluable for the pivotal trials that showed efficacy of *SMN2* splicing modifiers (Baranello et al. 2021, Finkel et al. 2017, Mercuri et al. 2018, Mercuri et al. 2022), they have the intrinsic limitation that they are insensitive for small but clinically relevant changes that may occur in subgroups of patients, primarily those with longer disease duration. A second limitation is that none of the available motor function scales can cover the full disease spectrum due to considerable ceiling and/or floor effects (Pera et al. 2019, Wijngaarde et al. 2020).

Quantitative instruments to assess the condition of motor units and muscle tissue constitute potential biomarkers for early treatment effects in patients with SMA. For example, quantitative muscle MRI may be sufficiently sensitive to detect year-to-year changes in muscle quality in patients with SMA (Otto et al. 2020). Electrophysiological and nerve conduction techniques have been used for the assessment of motor unit quality and may have potential to be used as prognostic or therapeutic biomarkers for treatment efficacy. Specific techniques that have been studied for biomarker qualities include compound muscle action potential (CMAP) amplitude (Swoboda et al. 2005, Wijngaarde et al. 2020), motor unit number estimation (MUNE) techniques (Bromberg and Swoboda 2002, Farrar et al. 2011, Gawel et al. 2015, Swoboda et al. 2005), CMAP scan for assessment of motor unit loss (Kariyawasam et al. 2020, Sleutjes et al. 2020) and repetitive nerve stimulation to assess neuromuscular junction function (Arnold et al. 2021, Wadman et al. 2012). Other studies have explored involvement of sensory nerves (Fletcher et al. 2017, Gogliotti et al. 2012, Rudnik-Schoneborn et al. 2003, Shorrock et al. 2019, Yonekawa et al. 2013, Yuan and Jiang 2015) and integrity of the combination of afferent and efferent fibers including H-reflex (Chiriboga et al. 2014, Pro et al. 2021, Yonekawa et al. 2013). Recent studies showed that some of these techniques are indeed sufficiently sensitive for detection of early treatment response in patients with SMA (Arnold et al. 2021, Kariyawasam et al. 2020, Kariyawasam et al. 2022, Schneider et al. 2021).

All previously published studies focused on single electrophysiological techniques and there have been no attempts to study the biomarker value of combinations of electrophysiological tests that would allow a more comprehensive evaluation of motor unit function (Ros et al. 2023). However, motor function impairments and contractures may limit the reliable execution of combinations of nerve conduction techniques and the required prolonged exposure to stimulation techniques may exceed patients' limits of what is tolerable. Therefore, we assessed feasibility and tolerability of a standardized multimodal electrophysiological protocol, including compound muscle action potential (CMAP) scan, motor nerve excitability tests, repetitive nerve stimulation (RNS), and the sensory nerve action potential (SNAP), in a prospective longitudinal cohort study in adolescents and adults with SMA.

2. Methods

2.1. Design and participants

We conducted a prospective, longitudinal cohort study to assess the feasibility and tolerability of a protocol consisting of multimodal peripheral non-invasive electrophysiological techniques. All patients aged $\geq$ 12 years (n = 237), screened for Survival Motor Neuron (SMN) modulating therapies, nusinersen or risdiplam, between May 2020 and October 2021, were invited to participate (Fig. 1) (Ros et al. 2023). All patients were seen at the Netherlands SMA center at the University Medical Center Utrecht. Inclusion criteria included confirmed loss of function of the survival *SMN1* gene and determined *SMN2* copy number using Multiplex Ligand-dependent Probe Amplification (SALSA MLPA-kit PO21-B1, MRC Holland). SMA type was defined by the highest achieved motor milestone (e.g. independent sitting or independent walking) (Mercuri et al. 2012, Wijngaarde et al. 2020). In case of discrepancies between age at symptom onset and highest achieved motor milestones, the latter determined classification. As SMN augmenting treatments, patients received either intrathecal nusinersen (injections at baseline, at two, four, and eight weeks, followed by injections every four months, with motor function assessments at two months and every four months thereafter, as part of the requirements for conditional reimbursement) or risdiplam (oral administration with motor function assessments at baseline, after two months and every eight months). Contractures were assessed during the motor function assessments. If participants consented for the follow-up part of this study and started treatment, they received a follow-up assessment two months after start of treatment combined with scheduled hospital visits.

Due to COVID-19 regulations in the Netherlands during the conduct of this study, we were not able to perform the scheduled, repeated assessments to assess reproducibility of our protocol.

We recruited age-matched controls through our website (https://www.smaonderzoek.nl), the newsletter for patients with SMA and their relatives and the newsletter of the patient organization, Spierziekten Nederland. Disease controls were all patients with Amyotrophic Lateral Sclerosis (ALS) (randomly selected), diagnosed according to the El Escorial Criteria and with no signs of frontotemporal dementia or behavioral changes. None of the disease controls received invasive or intrathecal treatment. Disease controls participated in another ongoing electrophysiological study protocol (including CMAP scan and motor nerve excitability tests) (approved by the local Medical Ethics Committee of the University Medical Center Utrecht (No. 19–550) and registered in the Dutch clinical trials registry (https://www.toetsingonline.nl - NL69267.041.19). Both healthy controls and disease controls underwent only one assessment.

2.2. Protocol of electrophysiological techniques

For all tests, we used QTrac-S software (Institute of Neurology, Queen Square, London, United Kingdom). We performed all tests on the median nerve unilaterally at the level of the wrist, based on the patient's dominant hand. If for any reason investigation on this side was precluded (e.g. because of severe contractures), all analyses were done on the non-dominant side. We recorded CMAP responses from the thenar muscles using surface electrodes in belly-tendon montage. The stimuli are applied with the cathode at the level of the wrist (7 cm from the active recording surface

electrode) and the anode over the radial side of the arm (10 cm proximal from the wrist) (3 M Red Dot electrodes). The optimal placement of the cathode at the level of the wrist is manually determined with a stimulation pen (Motor Point Pen, Compex, Switzerland). We checked noise levels and possible voluntary contractions. Set up and patient preparation takes approximately 5 to 10 min, depending on the mobility of the patient (e.g. contractures) and technical issues (e.g. 50 Hz noise).

The temperature of the nerve and muscle in the forearm was maintained at 37 °C degrees by wrapping the arm in a warm water blanket with a constant flow of water at 37 °C degrees (Cincinnati Sub-zero Norm-O-Temp with a Cincinnati Plastipad infant blanket) for 30 min before testing. During testing the temperature was maintained at 37 °C degrees using the same procedure (Kovalchuk et al. 2019). After warming, we rechecked noise levels, electrode placement and voluntary contractions for possible changes, and adjusted them if necessary.

All subjects underwent a standardized multimodal electrophysiological protocol that included CMAP scan, motor nerve excitability recordings, RNS and SNAP analysis (Ros et al. 2023). Each of these electrophysiological techniques has been extensively described in detail previously (Caetano et al. 2022, Jacobsen et al. 2019, Juel 2012, Kiernan et al. 2020, Kiernan et al. 2001, Shapiro and Preston 2003). For all techniques, we applied well-established and standardized tests implemented within the TRONDNF protocol, available in the Qtrac-S software (Institute of Neurology, Queen Square, London, United Kingdom). For RNS recordings we developed a 3 Hz protocol within the Qtrac-S environment, allowing to run the complete protocol in a single pack. We used the same order of tests in all patients and during all visits. All tests start with manually (re-)establishing the supramaximal stimulus levels of the maximum CMAP or SNAP amplitude.

The duration of the CMAP scan is 5 to 10 min, for which we used stimuli ranging from supramaximal to subthreshold levels (Jacobsen et al. 2019). Together with variables that reflect axon integrity and the motor unit pool (motor unit number and sizes), the CMAP scan also determines stimulus current, or thresholds, required to elicit 5%, 50% and 95% of the maximum CMAP. Subsequently motor nerve excitability was performed, which first required to run the stimulus–response (SR) test. The SR test was used to determine the threshold required to elicit the target response (at 40% of the maximum CMAP) for threshold tracking. This is standardized and automatically computed for every individual patient at the end of the SR test. The SR test is followed by the charge duration (Qt) relation (relation between stimulus charge (Q) and stimulus durations (t) of 0.2, 0.4, 0.6, 0.8 and 1.0 ms), the threshold electrotonus (time course of threshold changes during polarizing conditioning currents at ± 20% and ± 40% of the current for an unconditioned target response), the current/voltage relation (threshold changes after polarizing conditioning currents of 200 ms varying from + 50% to −100% of the current for an unconditioned target response) and the recovery cycle (threshold changes estimated at various intervals between 2 and 200 ms after a supramaximal conditioning stimulus eliciting action potentials) (Kiernan et al. 2020). If patients showed a more discrete pattern in the CMAP scan (due to a marked reduced motor unit number and enlarged motor units), we adjusted the tracking mode of motor nerve excitability tests to *single unit* for more accurate tracking. Evaluation of both tracking methods is performed in the same way and results can be analyzed together. The duration of excitability tests is 10 to 15 min. RNS consisted of a train of 10 supramaximal stimuli delivered at 3 Hz. This test was followed by comparing the maximal muscle response before and after 10 s of maximum voluntary isometric contraction (MVC) of the thenar muscles, achieved by pushing the thumb against a fixed surface/object (Lambert test) (Juel 2012, Shapiro and Preston 2003). In case of voluntary contractions during RNS, the arm was repositioned to minimize movements and the test was repeated. The duration of the RNS tests is approximately 5 min. We recorded median nerve SNAP from the third digit by placing ring electrodes positioned around the proximal and distal interphalangeal joints at the end of the protocol and performed peak-to-peak analysis (Caetano et al. 2022, Kiernan et al. 2001). We record three maximum SNAP amplitudes. Duration of the SNAP analysis is <5 min, including electrode placement.

We performed the entire protocol, including set up and 30 min warming time, in approximately 60 to 75 min per subject.

2.3. Feasibility assessment

We performed the protocol with patients either seated (wheelchair bound patients) or in supine position (ambulant patients). To avoid any unwanted movement or (postural) tremor, we instructed patients to keep their arm in a comfortable position that they could maintain, to ensure optimal muscle relaxation (Fig. 2). Feasibility of longitudinal assessments depends on reliable electrode placement and position of the arm. If patients consented to participate in the follow-up study, we took photographs of the arm, hand, and electrode placement to ensure the same position at follow-up. We recorded the tracking mode of motor nerve excitability tests and maximum CMAP amplitudes to determine the lowest amplitude that resulted in meaningful data. The protocol was considered feasible if all techniques could be performed according to test standards (with limited technical factors e.g. 50 Hz noise) and with limited voluntary activity from the patient.

2.4. Tolerability assessment

We assessed tolerability of the full protocol with an established pain perception scale, the Numeric Rating Scale (NRS) (Karcioglu et al. 2018). Patients rated pain from 0 (no pain) to 10 (worst possible pain) to score the overall experience of the protocol (Karcioglu et al. 2018). The NRS does not state string rating to the individual numbers and only reports on the '0' and '10' (Karcioglu et al. 2018). Patients were not instructed to use a specific score to describe minimal pain sensation. Although this scale was developed for pain assessment, it is also used to assess other dimensions, like pruritus, disease activity and discomfort (Reich et al. 2012). We considered the test tolerable with scores ≤ 3 or when patients consented to follow-up assessment despite a higher NRS score (Boonstra et al. 2016, Hirschfeld and Zernikow 2013).

2.5. Adverse events

Adverse events related to the electrophysiological assessments were systematically assessed or registered when mentioned spontaneously by the participant.

2.6. Statistical analysis

We used descriptive statistics to present the baseline characteristics of our cohort. The effect of patient characteristics (age, gender, SMA types, therapy, ambulatory status and contracture status) was assessed at baseline on the NRS scores with the Mann-Whitney U Test, the Kruskal Wallis Test and Spearman's Rank correlation. We used the Wilcoxon signed rank Test to compare NRS scores of baseline and follow-up assessments in patients with SMA. P-values < 0.05 were considered statistically significant. For the statistical analyses, we used R software (R-version 4.0.2 for Windows) with RStudio (version 1.1.463).

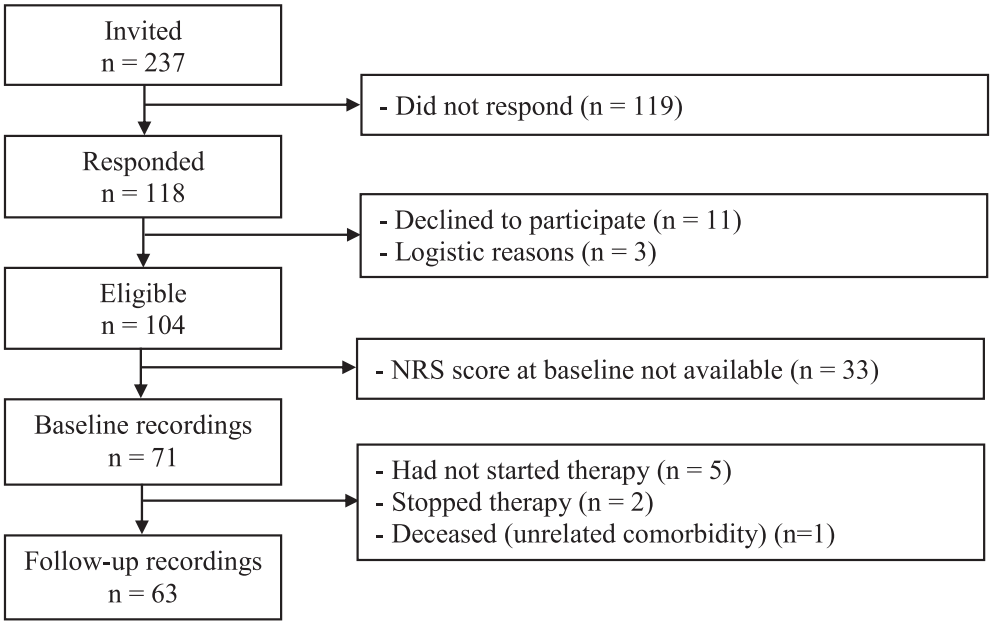

Fig. 1. Flow diagram of patient inclusion. Logistic reasons included having started therapy, no follow-up after the initial response to our invitation, and a personal situation precluding study entry.

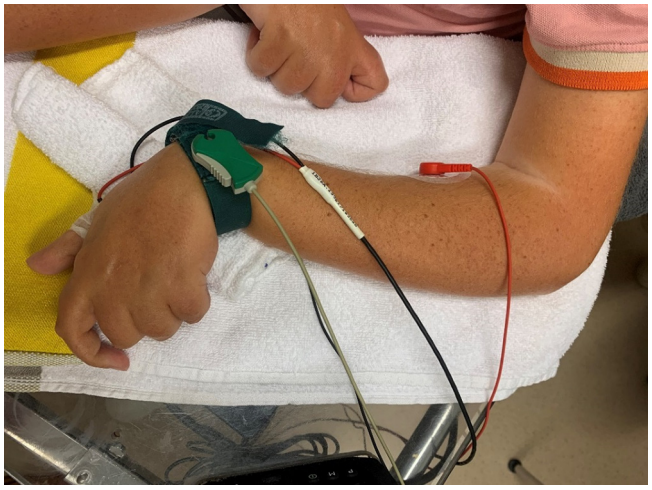

Fig. 2. Example of set up for electrophysiological assessment. Photograph of patient with SMA type 2 with severe contractures in the elbow and wrist. We used a facecloth to ensure maximum support of the wrist and relaxation of the hand muscles.

2.7. Standard protocol approvals, registrations and patient consent

This study was approved by the local Medical Ethics Committee of the University Medical Center Utrecht (No. 20–143/NL72562.041.20) and registered in the Dutch clinical studies trials registry (https://www.toetsingonline.nl). Written informed consent was obtained from all participants and/or their parents or legal guardians in case of minors. We report this study in accordance with the STROBE statement (von Elm et al. 2008).

2.8. Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

3. Results

3.1. Feasibility and clinical features

We included 71 patients with SMA types 1–4, 17 age-matched healthy controls and 65 disease controls. Baseline characteristics are shown in Table 1. Sixty-six patients started treatment with nusinersen or risdiplam, two of whom stopped with therapy before follow-up assessment. One patient died after baseline analysis due to SMA unrelated comorbidity, resulting in 63 patients with SMA available for follow-up analyses. The median time interval between baseline and follow-up measurements was 14 weeks (range 8–41 weeks). The median time interval between start of treatment and follow-up measurements was 8 weeks (range 7–13 weeks). We found a mean maximum CMAP of 4.9 mV (range 0.3 – 13.2 mV). Three of the 71 patients (4%) were tracked in *single unit* mode. The lowest maximum CMAP that resulted in meaningful data was 0.3 mV. We performed the entire protocol according to test standards in 62 of the 63 patients (98%) who underwent both baseline and follow-up measurements. Only one patient refused to finish excitability tests (but not the CMAP scan, RNS and SNAP) due to discomfort.

3.2. Tolerability

At baseline, the median NRS score was 2 (range 0–6) in patients with SMA (Fig. 3). Fifty-four (76%) patients scored 3 or lower. NRS scores did not differ between SMA types, gender, age, ambulatory status, presence of contractures or type of therapy (all $p > 0.05$). Three adolescents (one aged 13 and two aged 18 years) reported a score of 4, 2 and 2, respectively. Sixteen (24%) adult patients reported a NRS score of 4 or higher at baseline. The NRS score of the patient who did not complete the entire protocol was 4 at the end of the baseline measurements. The discomfort was only temporary and was not a reason to decline participation in the follow-up assessment. Median NRS score was 0 (range 0–4) and 2 (range 0–7) in healthy and disease controls, respectively. NRS scores did not differ with age or gender ($p > 0.05$). Median NRS

Table 1
Baseline characteristics.

Characteristic	Total SMA	SMA type 1	SMA type 2	SMA type 3/4	Healthy controls	Disease controls
Count	71	4	40	27	17	65
Age in years, median (range)	39 (13–67)	38 (18–49)	30 (13–52)	49 (20–67)	37 (13–69)	63 (39–78)
Sex (F:M), n	37:34	2:2	24:16	11:16	8:9	29:36
SMN2 copy number, n						
2	2		1[†]	1[‡]		
3	45	4	34	7	NA	NA
4	24		5	19		
Age at onset in years, median (range)	1 (0.3–19.0)	0.5 (0.3–0.5)	0.8 (0.3–2.0)	3.0 (1.0–19.0)	NA	62 (37–78)
Disease duration in years, median (range)	38 (5–63)	38 (18–49)	30 (13–51)	44 (5, 63)	NA	0.9 (0.1–3.2)
SMA therapy, n						
None	5			5	17	65
Nusinersen	28		6	22		
Risdiplam	38	4	34			
Ambulatory (Y:N), n	10:61	0:4	0:40	10:17	17:0	65:0
Contractures*, n	44	4	32	8	0	0

SMA Spinal Muscular Atrophy; *n* number; *F* female; *M* male; *SMN2* survival motor neuron 2 gene; *NA* not applicable; *Y* yes; *N* no.
Disease controls are all patients with Amyotrophic Lateral Sclerosis (ALS).
[†] Patient with point mutation in *SMN2* exon 7 (c.859G > C).
[‡] Patient with heterozygous *SMN1* deletion and point mutation in exon 4 (c.542A > G) on the other allele.
* Contractures present in investigated arm.

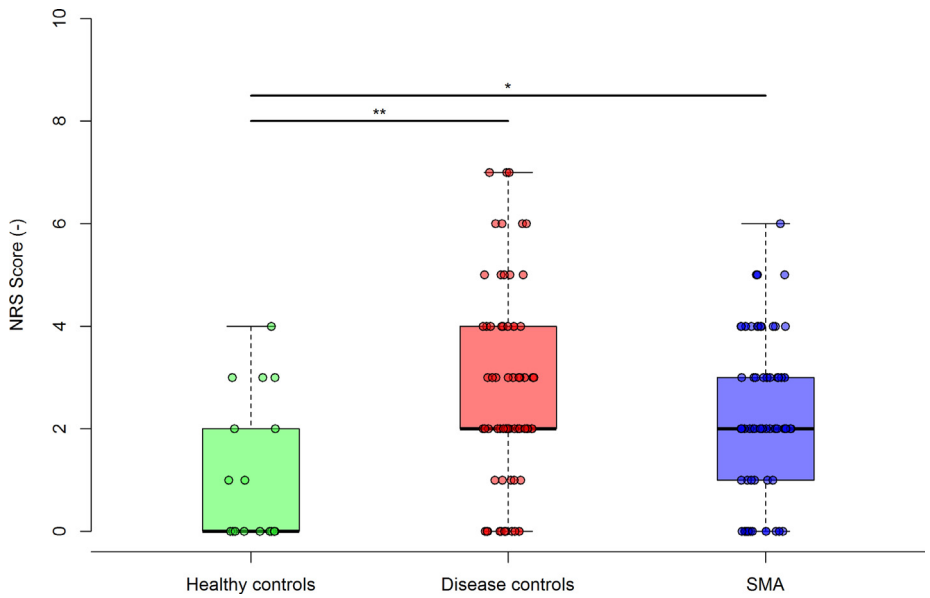

Fig. 3. NRS scores at baseline of healthy and disease controls, and patients with SMA. Boxplots of NRS scores in healthy (n = 17) and disease controls (n = 65), and patients with SMA (n = 71). * P < 0.05, ** P < 0.01. *SMA* Spinal Muscular Atrophy. Disease controls are all patients with Amyotrophic Lateral Sclerosis (ALS).

score was lower in healthy controls compared to patients with SMA and disease controls (p = 0.01). Baseline scores of SMA patients and disease controls did not differ (p > 0.05).

All patients with SMA agreed to undergo the protocol at follow-up irrespective of the NRS score at baseline. At follow-up, median NRS score was 2 (range 0–4) (Fig. 4). 90% of the patients (57 of 63) had a score of 3 or lower. NRS scores were lower at follow-up compared to baseline (p < 0.01). Twenty-eight (44%) improved, twenty-six (41%) reported the same and nine patients (14%) had a worse NRS score at follow-up compared to baseline (Fig. 4). Female patients reported less favorable NRS scores at follow-up than male patients (median 2.5 vs. 1; p < 0.05).

3.3. Adverse events

We recorded one adverse event. After baseline assessment, one patient complained of self-limiting stiff and painful sensations of the investigated arm, which was due to positioning of the arm during measurement. There were no other adverse events.

4. Discussion

In this prospective, longitudinal study, we assessed the feasibility and tolerability of multimodal peripheral non-invasive electrophysiological techniques in adolescents and adults with SMA. We

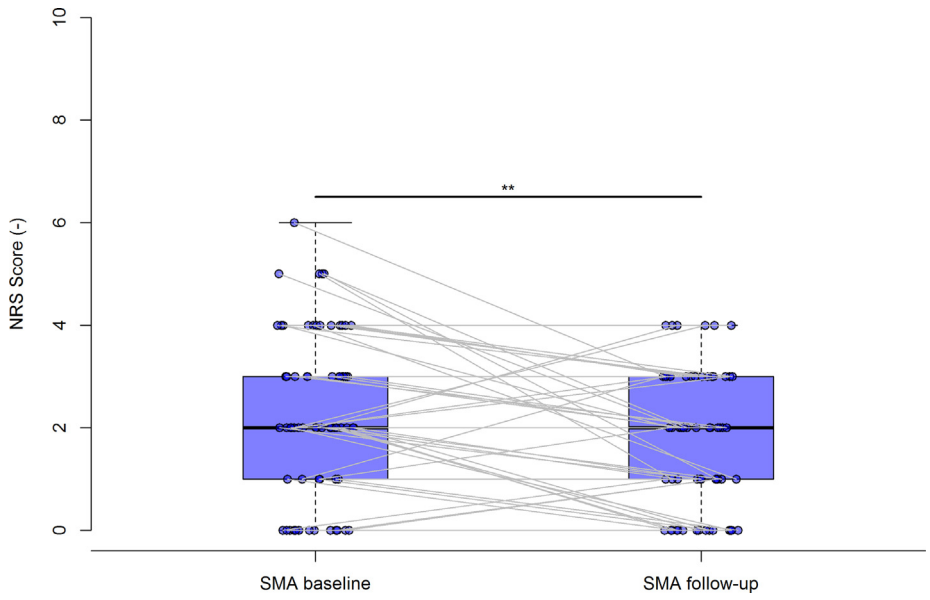

Fig. 4. NRS scores at baseline and follow-up of patients with SMA. Boxplots of NRS scores in patients with SMA (n = 63) at baseline and follow-up (±2 months after start of therapy (i.e. nusinersen or risdiplam)). ** P < 0.01. *SMA* Spinal Muscular Atrophy.

showed that our extensive protocol can be applied in the full spectrum of SMA types, including different ages, diverse levels of mobility and (severe) contractures, with 98% of participants completing the entire protocol at two time points. Importantly, we found that electrophysiological techniques were well-tolerated, with up to 90% of patients scoring acceptable tolerability (i.e. NRS score of 3 or lower). The combination of a feasible protocol in both baseline and follow-up measurements, high tolerability and the willingness of all patients to participate in follow-up assessments, regardless of their NRS score, supports the potential use of these specific techniques for clinical assessments in patients with SMA.

Electrophysiological techniques could have the potential to be used as therapeutic or prognostic biomarkers to predict (in)efficacy of SMN- augmenting treatments in patients with SMA (Arnold et al. 2014, Arnold et al. 2021, Kariyawasam et al. 2020, Kariyawasam et al. 2022, Schneider et al. 2021). These techniques have been used successfully in (pre)symptomatic infants with SMA (Finkel 2013, Kariyawasam et al. 2020, Kariyawasam et al. 2022, Swoboda et al. 2005). They may also be useful in clinical decision-making during follow-up of children, adolescents and adults with longstanding SMA. However, electrophysiological techniques can be complicated by technical, patient-related difficulties. The majority of symptomatic children, adolescents and adults with SMA have (severe) contractures due to muscle weakness (de Groot and de Witte 2005, Wang et al. 2004). We ensured feasibility of reliable longitudinal assessments by the use of photographs of position and electrode placement, even in case of considerable contractures in patients at the severe end of the SMA spectrum. The previous exploratory studies that evaluated the potential of electrophysiological techniques in symptomatic patients with SMA were mainly limited to relatively small subsets of patients (mean number of 24 patients, range 15–35) (Arnold et al. 2021, Farrar et al. 2011, Kariyawasam et al. 2020, Kariyawasam et al. 2022, Schneider et al. 2021, Sleutjes et al. 2020, Wadman et al. 2012). Moreover, these studies applied shorter protocols, often focusing on a single electrophysiological test. Our data of 71 patients showed that an extensive electrophysiological protocol is feasible in both adults and adolescents, covering the complete range of SMA severity.

Our results show good agreement with the previously reported tolerability of non-invasive electrophysiological techniques in non-SMA populations. Two previous studies compared pain levels experienced during needle electromyography and non-invasive electrophysiological techniques (Alshaikh et al. 2016, Wee et al. 2004). One study reported a good mean score (i.e. 3.8) in children and adolescents (4–17 years old), who underwent non-invasive electrophysiological tests and/or electromyography without the use of sedation or anesthesia (Alshaikh et al. 2016). They also showed that the protocols with solely non-invasive electrophysiological techniques, upper limb analysis and confined to one muscle, were best tolerated (Alshaikh et al. 2016). In line with this study, we found that repeated assessments produced more favorable pain scores compared to baseline (Alshaikh et al. 2016). Another study reported that adult patients generally considered non-invasive electrophysiological techniques less painful than needle electromyography (Wee et al. 2004). However, neither study specified the diagnosis, disease duration or possible presence of technical difficulties (e.g. severe contractures). Furthermore, the tolerability of the CMAP scan has been assessed previously, but only in healthy controls (respectively aged 25–67 years and 26–47 years) (Maathuis et al. 2012, Sorensen et al. 2022). Pain scores were comparable to our findings and they reported a tendency towards the median nerve to be the least painful recording site in comparison to other nerve sites (i.e. ulnar and common peroneal nerve). Our techniques are performed solely stimulating the median nerve. We even applied a more extensive protocol that was still well tolerated.

The NRS, used to assess tolerability in this study, is a validated and easy way to rate pain intensity and discomfort (Karcioglu et al. 2018, Page et al. 2012). It is used to assess pain in different settings, but has also proven its usefulness in scoring or objectifying other sensations (i.e. pruritus, nausea, arthritis, skin psoriasis and disease activity) and their intensity (Jang et al. 2020, Meek et al. 2015, Reich et al. 2012, Ye et al. 2021), making it a fast and practical method for objectifying tolerability of (new) electrophysiological techniques.

Perception of pain or discomfort during electrophysiological assessments may be influenced by several factors, such as expectation management, preparation by written and/or oral information

and experience with previous electrophysiological assessments (Lai et al. 2018, Richardson et al. 1994). Two studies reported on a positive effect on the pain perception of electrophysiological techniques if patients received written information beforehand (Lai et al. 2018, Richardson et al. 1994). Our participants (SMA patients, healthy controls and disease controls) received extensive information prior to the start of assessments, and this could have contributed to the overall good tolerability of our protocol. The higher pain scores in disease controls, compared to SMA and healthy controls, may be due to the fact that the patients underwent their examinations as part of the diagnostic work-up for ALS, not yet having received a definite diagnosis inducing more stress and discomfort.

Our study has several limitations that need to be addressed. Our study consists of a heterogeneous population that included patients with different SMA types, ages and treatment modalities. However, this diversity is in line with normal distribution in routine clinical practice and our results could therefore be applicable to the complete spectrum of SMA patients in routine clinical setting. Only half (104 out of 237) of the invited patients agreed to undergo electrophysiological measurements. The majority was reluctant to participate because they were about to start their first-ever treatment with nusinersen, which left little room for any additional visits or study participation. Consequently, potential selection bias, possibly favoring tolerability scores, should be considered. On the other hand, our large sample size, wide range of ages, inclusion of all types of SMA and treatments (nusinersen and risdiplam) are unlikely to be a skewed representation of common SMA population. Furthermore, to assess feasibility of a new protocol, performing reproducibility studies is preferred. Due to the COVID-19 regulations in the Netherlands, we were unable to perform these tests. Reproducibility of the techniques investigated in our protocol has been confirmed by previous studies, but never all techniques combined (Maathuis et al. 2011, Mogyoros et al. 2000, Sorensen et al. 2022). Our study investigates the median nerve at the abductor pollicis brevis muscle. In SMA proximal muscles are most severely affected, so analysis in distal muscles and nerves might underestimate true disease-related effects. (Kiernan et al. 2020, Song et al. 2022, Tankisi et al. 2022, Wadman et al. 2012).

5. Conclusions

Our study shows the feasibility and tolerability of an extensive protocol with multimodal peripheral non-invasive electrophysiological techniques in 71 adolescents and adults with SMA types 1–4. It supports the practical utility of multimodal electrophysiological techniques in adolescents and adults with all types of SMA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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