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Compound Muscle Action Potential (CMAP) Amplitude Trajectories and Pattern in Adults with 5q-Spinal Muscular Atrophy Receiving Nusinersen Therapy: A Multicenter, Binational Observational Study

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ABSTRACT

Background: This study aimed to evaluate changes in compound muscle action potential (CMAP) amplitude in adults with spinal muscular atrophy (SMA) undergoing nusinersen treatment and its association with motor function improvements.

Methods: This multicenter study assessed median, ulnar, and peroneal CMAP over a follow-up of up to 4.5 years using linear mixed models. Motor function was measured using the Revised Upper Limb Module (RULM) and the Hammersmith Functional Motor Scale Expanded (HFMSE). Correlations between CMAP and motor function scores were analyzed.

Results: Seventy-eight patients (27 ambulatory, 51 non-ambulatory) were included. Baseline ulnar CMAP $\geq$ 2.0 mV distinguished SMA type 3 from type 2 with 91.3% sensitivity and 88.9% specificity (AUC 0.96, 95% CI 0.92–1.0), while baseline median nerve CMAP $\geq$ 6.5 mV showed 91.7% sensitivity and 77.3% specificity (AUC 0.84, 95% CI 0.72–0.96). No significant changes over time were observed in median, ulnar, and peroneal CMAP amplitudes ($p > 0.05$). CMAP trajectories did not differ between SMA types 2 and 3 ($p > 0.05$). No significant difference in the change in RULM or HFMSE at any time point was observed between SMA patients with baseline median nerve CMAP < 5 mV and those with CMAP of $\geq$ 5 mV ($p > 0.05$). No significant correlations were found between changes in median nerve CMAP and HFMSE or RULM ($p > 0.05$).

Discussion: CMAP amplitudes remained stable during nusinersen treatment, with no differences in trajectories between SMA types 2 and 3. Our findings suggest that while CMAP amplitude correlates with disease severity, it may not serve as a sensitive biomarker of treatment response in adult SMA patients.

1 | Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive inherited disease caused by mutations in the *survival of motor neuron 1* (*SMN1*) gene on chromosome 5q13.2. These lead to insufficient production of functional SMN protein and subsequent degeneration of motor neurons in the ventral horn of the spinal cord [1, 2]. In recent years, the development of disease-modifying medications for SMA has shown benefits in all SMA types, spanning from infants to adult patients [1]. Currently, approved drugs predominantly focus on two approaches: replacing the *SMN1* gene (onasemnogene abeparvovec [3, 4]) or adjusting SMN protein production through the *SMN2* gene (nusinersen [5–8], risdiplam [9–11]). Moreover, ongoing clinical trials are exploring SMN-independent approaches [12]. The evolving landscape of therapeutic strategies highlights a critical need for biomarkers to better assess patient eligibility and monitor treatment responses. Currently, no physiological, imaging-based, digital, or molecular biomarker has been validated for routine clinical use in patients with SMA [13].

Electrophysiological measurements, such as compound muscle action potential (CMAP), motor unit number estimation (MUNE), and motor unit number index (MUNIX), reflect the functional status of the motor unit, thereby offering valuable insights into disease progression [13, 14]. CMAP represents the total electrical output of the motor units innervating a single muscle or group of muscles following supramaximal nerve stimulation [14]. CMAP is recorded during standard diagnostic motor nerve conduction studies (NCS) and is a fast and straightforward measurement. A recent meta-analysis confirmed that CMAP of the upper limb distal muscles differed significantly between adult SMA patients and controls and proposed that CMAP should be further studied as a promising biomarker in SMA patients with longer disease duration [15]. In the largest natural history study on neurophysiological parameters in children with SMA, Swoboda et al. observed that subjects with SMA types 1 and 3 showed stable CMAP values over time, whereas those with SMA type 2 demonstrated a modest decline of −0.007 mV/month [16]. Based on the knowledge of the natural history of SMA, improvement of any biomarker in untreated patients is not to be expected. Thus, any improvements noticed in trials or in routine clinical monitoring are likely treatment-induced (15). However, there is a lack of studies assessing CMAP as a therapeutic biomarker in large cohorts of adults with SMA. Previous studies in small patient cohorts predominantly involving children (six to 23 participants) have already shown improvements in CMAP upon nusinersen treatment [17–20]. Hsieh et al. suggested a potential mechanism underlying electrophysiological improvements: some surviving but previously non-functional motor neurons may regain function, while some denervated neuromuscular junctions may become reinnervated following nusinersen treatment [21].

The aim of this study was to longitudinally assess the change in CMAP amplitude of ulnar, median, and peroneal nerves during a long follow-up period in a large multicentric cohort and to analyze its association with motor function in adult SMA patients treated with nusinersen.

2 | Methods

In this multicenter, longitudinal observational study, we retrospectively collected data from all adult patients with SMA who underwent nusinersen treatment at five German neuromuscular centers (Hannover Medical School, Technical University of Dresden, Technical University of Munich, University Medicine Göttingen, and University Hospital Erlangen) and one neuromuscular center in Switzerland (Kantonsspital St. Gallen) over a 6-year period (2017 to 2023). All participants provided written informed consent, and the study received approval from local ethics committees (6269; EK393122012; 16/14; 13/11/12; 63_14Bc; 2018–00289, respectively). All patients were part of the German and Swiss Networks for Motor Neuron Diseases and were enrolled in the SMArtCARE registry [22]. All participants were 17 years or older and had a genetically confirmed diagnosis of 5q-SMA (either a homozygous deletion of exon 7 and/or exon 8 of the *SMN1* gene or a compound heterozygous deletion of exon 7 and/or exon 8 of the *SMN1* gene along with a point mutation on the second gene copy). Nusinersen was administered intrathecally according to the approved protocol, starting with a loading phase (Days 0, 14, 28, and 63), followed by subsequent administrations every four months.

Data about sex, age at therapy start, disease duration, SMA type, functional status (non-sitter, sitter, walker), ambulatory status (defined as the ability to walk at least 10 m with or without assistance [23]), *SMN2* gene copy number, use of wheelchair, presence of scoliosis, use of non-invasive ventilation (NIV) and presence of percutaneous endoscopic gastrostomy (PEG) were recorded at baseline.

2.1 | Motor Function Assessments

Motor function was assessed by trained raters the day after nusinersen administration. The Revised Upper Limb Module (RULM) score [24], a disease-specific scale, evaluated upper extremity function and daily activity performance, comprising 20 items with a maximum score of 37 points (higher scores indicating better upper limb function). The Hammersmith Functional Motor Scale Expanded (HFMSE) score [25], another disease-specific scale, assessed gross motor function across 33 items, with a maximum score of 66 points, where higher scores reflect better overall motor function. Motor function worsening was defined as a decrease of ≥ 3 points in the HFMSE score or ≥ 2 points in the RULM score when compared to the baseline score. Improvement was defined as an increase of ≥ 3 points in the HFMSE or ≥ 2 points in the RULM relative to baseline.

2.2 | Nerve Conduction Studies

All participants in the study underwent routine motor NCS, consistently performed at each center and at each study time point (except at T2 and T3 (Days 14 and 28 of the loading phase)), on the day after the nusinersen administration. The technicians and supervisors at each center had extensive experience in electrodiagnostics of neuromuscular diseases, including motor neuron diseases, and were blinded to the clinical outcomes throughout the study.

Motor NCS of ulnar, median, and peroneal nerves were recorded unilaterally, maintaining consistency in the side examined during the treatment period. The dominant side was selected. Recordings were taken from the abductor pollicis brevis muscle for the median nerve, the abductor digiti minimi muscle for the ulnar nerve, and the extensor digitorum brevis muscle for the peroneal nerve. CMAPs were recorded by applying a supramaximal stimulating current to the peripheral nerves at the wrist or ankle. Total CMAP amplitudes were measured from the negative to the positive peak (peak-to-peak). For this analysis, only CMAP amplitudes generated from distal nerve electrostimulation sites were considered. Patients without a baseline CMAP measurement for at least one of the analyzed nerves were excluded.

2.3 | Statistical Analysis

The statistical analysis was performed using IBM Statistical Software Package of Social Science (SPSS, Chicago, IL, USA) version 29. Normality of data was determined using Shapiro–Wilk, Kolmogorov–Smirnov test, and graphical interpretation of histograms. Continuous variables are reported as either median and interquartile range (IQR) (or minimum and maximum) or mean and standard deviation (SD), depending on the distribution of the data. The optimal cut-off value for dichotomizing data was selected based on the highest Youden Index, and the area under the curve (AUC) was calculated to evaluate the test performance. Associations between CMAP amplitudes and baseline characteristics, as well as motor function scores, were analyzed using Spearman's rank correlation and Pearson's correlation, as appropriate. To control for Type I error due to multiple comparisons, all correlations were adjusted using the Bonferroni correction.

We assessed longitudinal changes in CMAP amplitude of the median, ulnar and peroneal nerves using linear mixed-effects models. We hypothesized an improvement in CMAP amplitudes depending on SMA type over the time of treatment. The linear mixed-effects models included time, SMA type, and their interaction as fixed effects. Dependency in the data due to repeated measures was accounted for by including a random intercept for each patient. Significance testing for CMAP improvement over time between SMA types was performed using least square means (95% confidence intervals [CI]). Estimates were derived by restricted maximum likelihood in combination with the Newton–Raphson algorithm as a computational method, and degrees of freedom were estimated using the Kenward–Roger approximation. Within-patient errors were modeled with a first-order autoregressive covariance structure (ARH1) to account for repeated CMAP measures.

3 | Results

3.1 | Patients' Characteristics at Baseline and Correlations With CMAP Amplitude

Ninety-eight patients were initially included in this study. However, 20 patients were excluded due to the absence of any CMAP measurements during the loading phase. Therefore, the final analysis included 78 SMA patients. The main sociodemographic and clinical characteristics of the examined SMA cohort at baseline are summarized in Table 1. HFMSE score at baseline correlated significantly with baseline CMAP amplitudes of all investigated nerves: ulnar (rho = 0.83, $p < 0.001$), median (rho = 0.64, $p < 0.001$), and peroneal (rho = 0.74, $p < 0.001$). Similarly, RULM score at baseline also correlated significantly with baseline CMAP amplitudes of all investigated nerves: ulnar (rho = 0.75, $p < 0.001$), median (rho = 0.64, $p < 0.001$), and peroneal (rho = 0.64, $p < 0.001$). Correlations of baseline CMAP of all examined nerves with other sociodemographic and clinical data of included SMA patients are presented in Table S1 in the Supplementary Appendix.

3.2 | CMAPs at Baseline

Subgroup comparisons of baseline CMAPs for the ulnar, median, and peroneal nerves are presented in Table S2 (Supplemental Appendix). At baseline, CMAPs of all nerves were higher in SMA patients with a baseline HFMSE score of ≥ 35 points compared to those with < 35 points, as well as in SMA patients with a baseline RULM score of ≥ 19 points compared to those with < 19 points. Similarly, CMAPs were higher in SMA type 3 patients compared to SMA type 2, in ambulatory patients compared to non-ambulatory patients, and in patients without scoliosis compared to those with scoliosis. Additionally, the ulnar and median nerve CMAPs were higher in patients with four or more *SMN2* gene copies. Ulnar CMAP was also higher in patients not requiring NIV compared to those with NIV.

A cut-off value of 2.0 mV for ulnar CMAP distinguished SMA type 3 patients from SMA type 2 with a sensitivity of 91.3% and specificity of 88.9% (AUC 0.96, 95% CI [0.92–1.0]). For median nerve CMAP, a cut-off value of 6.5 mV distinguished SMA type 3 patients from SMA type 2 with a sensitivity of 91.7% and specificity of 77.3% (AUC 0.84, 95% CI [0.72–0.96]).

3.3 | CMAPs Trajectories During Nusinersen Treatment

3.3.1 | Median Nerve CMAP Amplitude

We analyzed a total of 589 measurements (over 15 time points) of median nerve CMAP from 78 subjects. Over the 4.5-year observation, there was no effect of time on median nerve CMAP amplitude ($p = 0.059$; Figure 1). We observed an upward trend in median nerve CMAP from baseline (7.8 mV (SE 0.4)) to month 18 (8.4 mV (SE 0.4)), after which median nerve CMAP decreases, reaching its lowest mean value at month 46 (6.7 mV (SE 0.4)) ($p > 0.05$; Figure 1). The trajectories of median nerve CMAP throughout the treatment period showed no difference between SMA type 2 and 3 patients (Figure 1B). Overall, there was a substantially significant, between-patient variability in median nerve CMAP (variance = 5.3, < 0.001).

3.3.2 | Ulnar Nerve CMAP Amplitude

We analyzed a total of 535 measurements (over 15 time points) of ulnar nerve CMAP amplitude from 73 subjects. Over the 4.5-year observation, there was no effect of time on ulnar nerve CMAP amplitude ($p = 0.366$; Figure 2). The trajectories of ulnar nerve CMAP

TABLE 1 | Main sociodemographic and clinical characteristics of all analyzed SMA patients at baseline.

SMA features	
N	78
Male sex (*n*, %)	49 (62.8)
Age at therapy start	
Years, mean ± SD	36.6 ± 12.8
Years, median [min–max]	34.0 [17.0–65.0]
Disease duration	
Years, mean ± SD	31.7 ± 13.0
Years, median [min–max]	30.0 [2.0–59.0]
SMA type (*n*, %)	
SMA type 2	25 (32.1)
SMA type 3	51 (65.4)
SMA type 4	2 (2.6)
Functional status (*n*, %)	
Non-sitter	11 (14.1)
Sitter	40 (51.3)
Walker	27 (34.6)
Walking ability (*n*, %)	
Ambulatory	27 (34.6)
Non-ambulatory	51 (65.4)
SMN2 copy number	
Mean ± SD	3.6 ± 0.7
Median [min–max]	4.0 [2.0–6.0]
SMN2 copy number	
< 4	30 (38.5)
≥ 4	44 (56.4)
Missing data	4 (5.1)
Wheelchair use (*n*, %)	
Never	27 (34.6)
Sometimes	15 (19.2)
Always	36 (46.2)
Scoliosis (*n*, %)	43 (55.1)
NIV (*n*, %)	7 (9.0)
PEG (*n*, %)	1 (1.3)
HFMSE score (*n*)	74
Mean ± SD	23.4 ± 22.9
Median [min–max]	16.0 [0.0–64.0]
RULM score (*n*)	74
Mean ± SD	23.5 ± 12.4
Median [min–max]	24.5 [0.0–37.0]
HFMSE score (*n*, %)	
≥ 35 points	49 (62.8)
< 35 points	25 (32.1)
Missing data	4 (5.1)
RULM score (*n*, %)	
≥ 19 points	47 (60.3)
< 19 points	27 (34.6)
Missing data	4 (5.1)
Ulnar nerve CMAP (*n*)	65
mV, mean ± SD	5.2 ± 4.2
mV, median [min–max]	4.1 [0.5–16.7]
Median nerve CMAP (*n*)	71
mV, mean ± SD	7.9 ± 3.0
mV, median [min–max]	8.0 [1.8–16.2]
Peroneal nerve CMAP (*n*)	26
mV, mean ± SD	6.6 ± 4.2
mV, median [min–max]	5.8 [0.4–15.7]

Abbreviations: CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale Expanded; IQR, Interquartile range; max, maximum; min, minimum; mV, millivolt; N, number; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; *SMN2, survival of motor neuron 2* gene.

throughout the treatment period showed no difference between SMA type 2 and 3 patients (Figure 2B). Significant between-subject variability was observed (variance = 9.3, < 0.001).

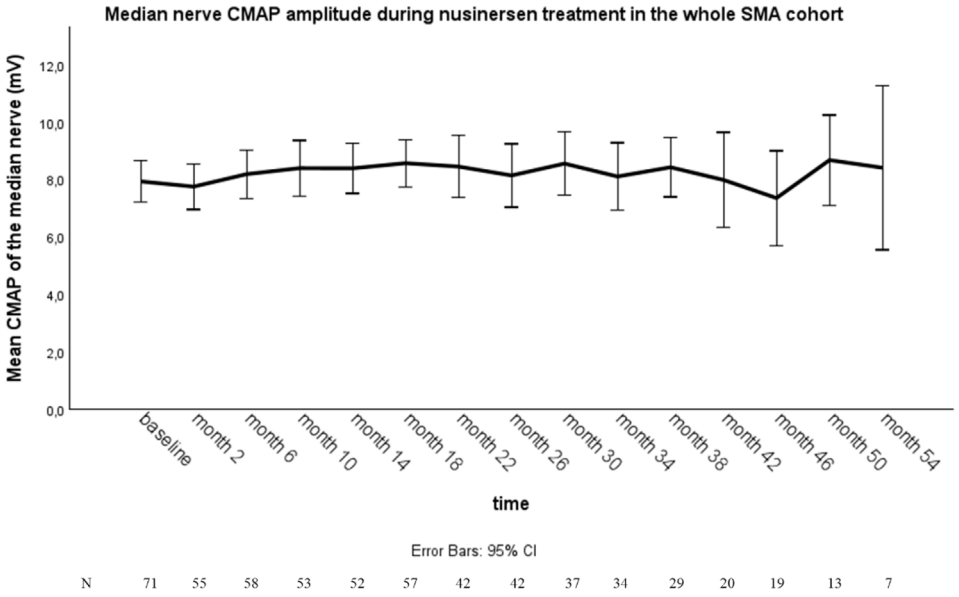
3.3.3 | Peroneal Nerve CMAP Amplitude

We analyzed a total of 206 peroneal nerve CMAP amplitude measurements collected across 15 time points from 26 subjects. Over the 4.5-year observation period, there was no significant effect of time on peroneal nerve CMAP amplitude (=0.056; Figure 3). Due to the small group sizes, subgroup analyses were not conducted. Significant between-subject variability was observed (variance = 12.2, < 0.001).

3.3.4 | Correlations Between Median Nerve CMAP Amplitude and Motor Function

The percentages of SMA patients with worsening, no change, or improvement in HFMSE and RULM scores during nusinersen

A. Trajectories of median nerve CMAP during nusinersen treatment in the whole SMA cohort



B. Trajectories of median nerve CMAP during nusinersen treatment in SMA type 2 and 3

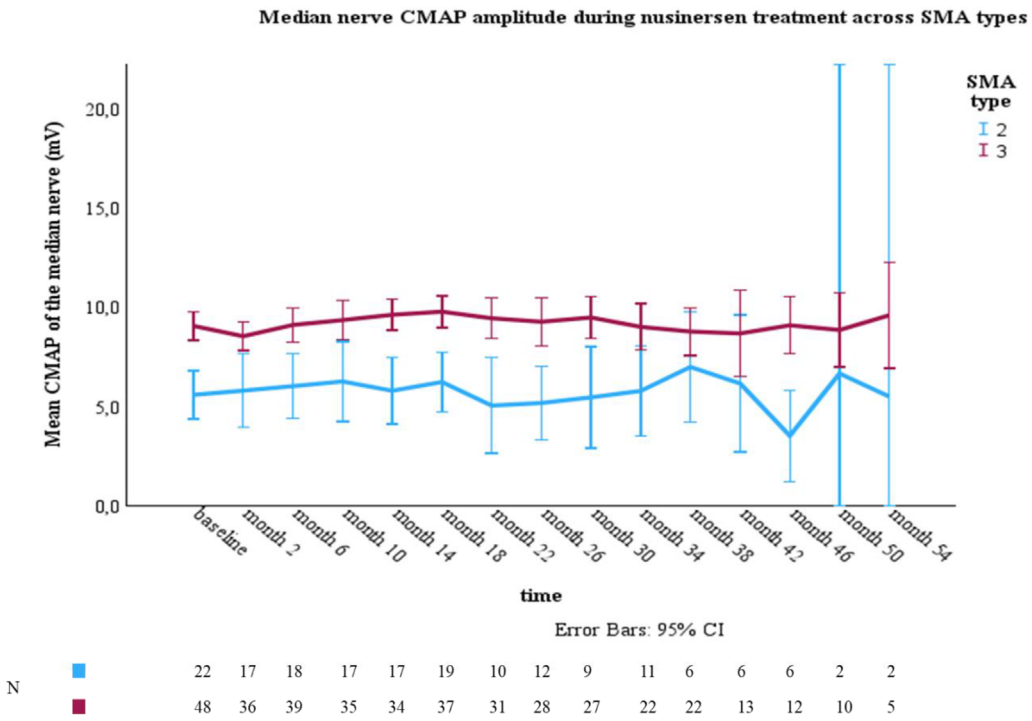
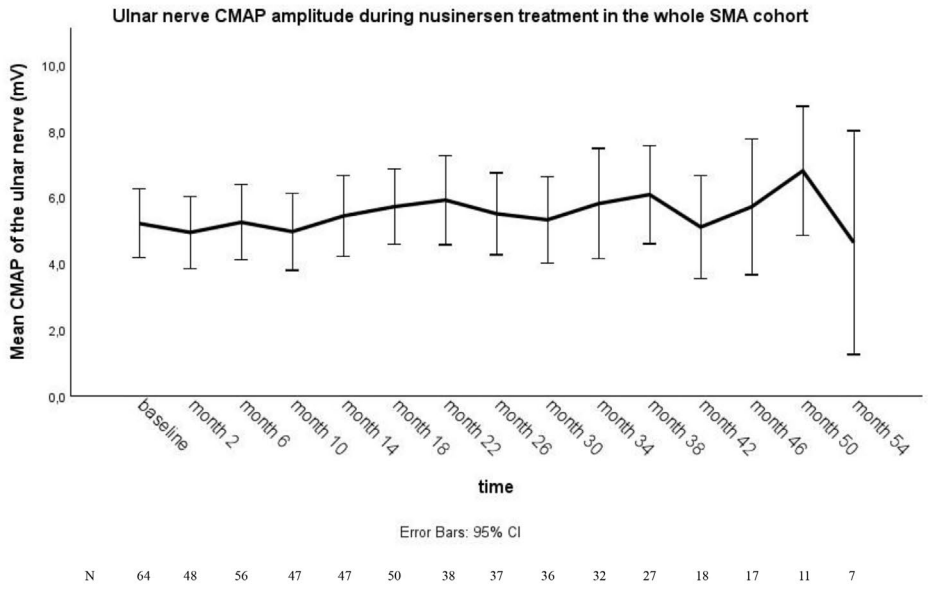


FIGURE 1 | A and B. SMA—spinal muscular atrophy; N—number; mV—millivolt; CMAP—compound muscle action potential; CI—confidence interval; in Figure 1B, data from SMA type 4 patients have not been shown, as this group included only two patients.

therapy are shown in Figures S1 and S2. No statistically significant difference in the change in RULM or HFMSE at any time point was observed between SMA patients with baseline median nerve CMAP less than 5 mV and those with a CMAP of 5 mV or greater ($p > 0.05$). After Bonferroni correction for multiple comparisons, no statistically significant correlations were observed between changes in median nerve CMAP and HFMSE or RULM (Tables S3 and S4).

A. Trajectories of ulnar nerve CMAP during nusinersen treatment in the whole SMA cohort



B. Trajectories of ulnar nerve CMAP during nusinersen treatment in SMA type 2 and 3

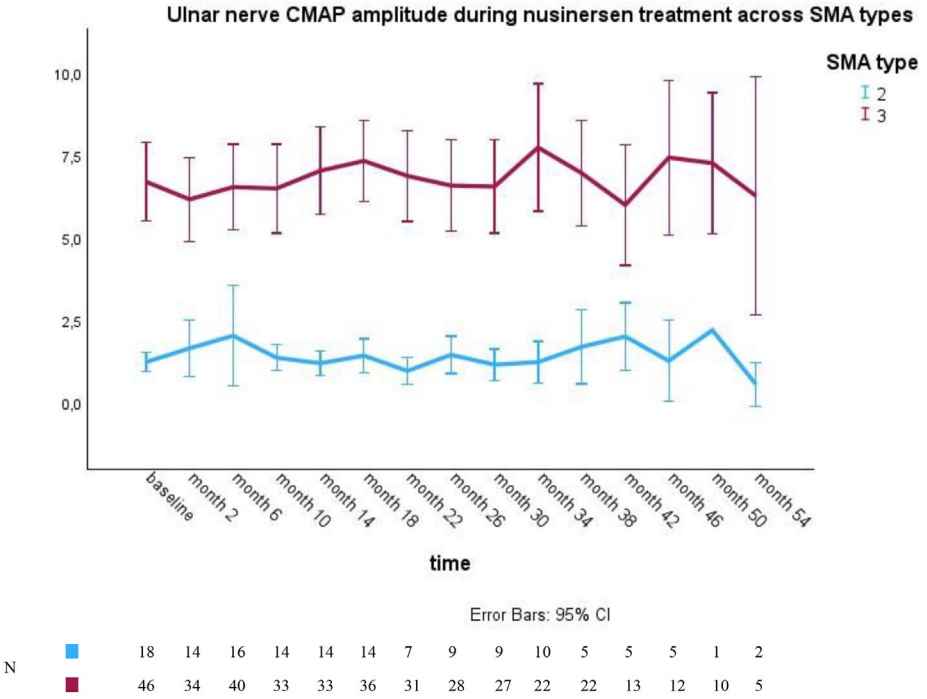


FIGURE 2 | A and B. SMA—spinal muscular atrophy; N—number; mV—millivolt; CMAP—compound muscle action potential; CI—confidence interval; in Figure 2B, data from SMA type 4 patients have not been shown, as this group includes only two patients.

4 | Discussion

This study presents data on CMAP trajectories in, to the best of our knowledge, the largest cohort of adult SMA patients treated with nusinersen, with the longest follow-up period of up to four and a half years. We observed no significant changes in ulnar, median, and peroneal nerve CMAPs throughout the entire treatment period, with no differences in CMAP trajectories between SMA type 2 and 3 patients. These results are consistent with findings from the largest natural history study on neurophysiological parameters in children with SMA, which reported stable CMAP values over time in SMA types 1 and 3, and only a modest decline of −0.007 mV/month in SMA type 2 patients [16]. The natural history of CMAP in adults with SMA, however, remains largely unknown. Interestingly, we observed a non-significant trend towards an increase in median and peroneal nerve CMAP up to month 18, which could possibly reflect the initial treatment effect, as such a trend is not to be expected in the natural

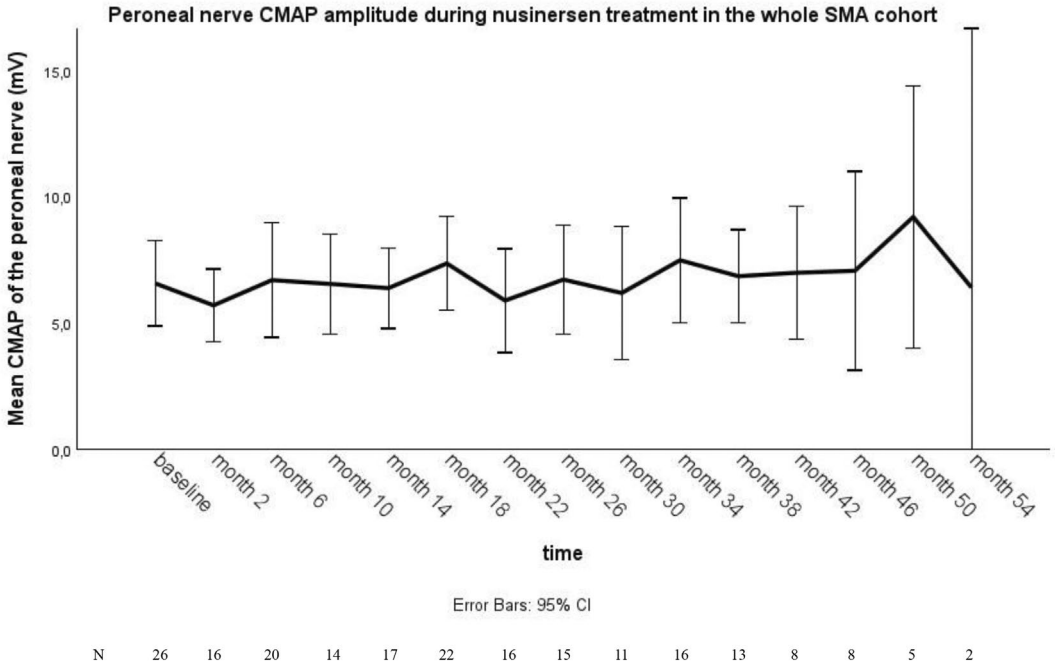


FIGURE 3 | Trajectories of peroneal nerve CMAP during nusinersen treatment in the whole SMA cohort. SMA—spinal muscular atrophy; N—number; mV—millivolt; CMAP—compound muscle action potential; CI—confidence interval.

history of SMA [15]. Furthermore, a substantial proportion of patients in our study also showed a clinically significant improvement (Figures S2 and S3), which may have paralleled the observed electrophysiological improvements.

Electrophysiological improvements following nusinersen initiation in children have been reported in several studies [17, 20, 26, 27]. In contrast, and consistent with our findings, Darras et al. reported long-term results from phase 1/2 studies showing that mean CMAP values remained relatively stable in 28 children (aged 2–15 years) with SMA types 2 and 3 [18]. Only two single-center and one multi-center longitudinal studies, conducted in a limited number of patients, have examined CMAP changes in adults with SMA after nusinersen initiation. Elsheikh et al. reported significant increases in ulnar CMAP at month 10 ($n = 19$; change from baseline: +0.29 mV) and month 14 ($n = 13$; change from baseline: +0.32 mV) in non-ambulatory SMA patients [19]. Similarly, the same group of authors observed significant increases in ulnar CMAP at Month 6 ($n = 13$; change from baseline: +0.35 mV), Month 10 ($n = 13$; change from baseline: +0.41 mV), and Month 14 ($n = 10$; change from baseline: +0.47 mV) in ambulatory SMA patients [28]. Elsheik et al. did not assess the median nerve, which may provide more insightful data, since adult SMA patients show a phenomenon called "reversed split hand", where the abductor pollicis brevis muscle (innervated by median nerve) is relatively well preserved, compared to the abductor digiti minimi (innervated by ulnar nerve) [29]. This is consistent with the study by Kessler et al., which reported significant improvements in median nerve CMAP, but no response in ulnar CMAP, 10 months after the initiation of risdiplam in 18 adult SMA patients [30]. Wang et al. demonstrated improvements in CMAPs of both upper and lower limbs in 25 adult SMA patients over a follow-up period of 2–6 months after nusinersen initiation. Lastly, Kessler et al. reported no changes in ulnar, tibial, and peroneal nerves during risdiplam treatment, while observing an increase in median nerve CMAP [30]. None of these studies employed linear mixed-effects models to analyze longitudinal data and repeated measures. This approach provides a more robust framework, accounting for individual variability over time and reducing the risk of oversimplifications and biases inherent in simpler analyses [31].

The lack of a clear and significant CMAP response following nusinersen initiation in our study raises questions about the suitability of CMAP as a biomarker for treatment response in adults with SMA. In the context of slowly progressive denervation, like in SMA, surviving motor units can expand their territories to reinnervate muscle fibers that have lost synaptic input. This reinnervation may adequately restore the CMAP response to normal levels, making CMAP a less sensitive measure [32]. Therefore, additional measures, such as MUNE and MUNIX, may be needed to complement CMAP in assessing motor neuron input to muscles and monitoring disease progression by evaluating the reduction in motor unit numbers. On the other hand, it is also plausible that, in our adult SMA cohort, nusinersen primarily stabilized the function of surviving but previously non-functional motor neurons and improved neuromuscular junction integrity, rather than inducing substantial reinnervation detectable by CMAP. This interpretation is in line with findings from clinical studies in adult SMA patients, which generally demonstrate stabilization of the motor function or modest functional motor gains [33, 34]. Moreover, contributing factors, such as ambient noise, irregular electrode positioning, and inadequate contact, can lead to substantial errors, especially in small CMAP measurements seen in the later stages of the disease [35]. On the other hand, it is now evident that later stages of the disease exhibit pathological changes that cannot be reversed solely by

SMN restoration [36]. As the disease progresses, the resulting neurodegeneration becomes less reversible, as reflected by the reduced regenerative capacity of motor neurons. This could explain the better CMAP response observed in children with SMA following treatment initiation. In contrast, SMN-independent strategies might be required for adults with SMA [36].

In our study, baseline CMAP amplitudes for all examined nerves were significantly correlated with baseline motor scores (HFMSE and RULM), highlighting that CMAP generally reflects the overall motor function in treatment-naïve adult SMA patients. For the first time, a cut-off value for ulnar and median nerve CMAP in treatment-naïve adult SMA patients has been reported to distinguish between SMA type 2 and type 3 patients, demonstrating high sensitivity and specificity (2.0 mV for ulnar CMAP and 6.5 mV for median nerve CMAP). These cut-off values, however, require external validation in an independent cohort of adult SMA patients. We found no correlations of the change in median nerve CMAP amplitude and motor function measured with HFMSE and RULM, after Bonferroni correction for multiple comparisons. The independence of HFMSE/RULM changes from CMAP during nusinersen therapy might suggest that motor function improvements in adults with SMA are not solely determined by motor neuron output. Other factors, such as neuromuscular junction function and muscle integrity, in addition to axonal integrity, likely contribute to overall motor performance. Contrary to that, Kessler et al. observed that CMAP amplitude recovery after risdiplam initiation was followed by improvements in HFMSE and CHOP INTEND scores [30].

Our study offers the strength of a long follow-up period in a large adult SMA patient cohort. However, there are important limitations to consider. The absence of a control group and incomplete follow-up data are notable drawbacks. To address the issue of missing follow-up data and between-subject variability, we utilized a linear mixed-effects model, a method particularly well suited for long longitudinal studies involving heterogeneous cohorts with repeated measures. However, potential non-linearity of CMAP trajectories needs to be acknowledged. To ensure interpretability and minimize the risk of model overfitting given the sample size, we modeled time as a linear term. As a multicenter study, variability in CMAP measurements across centers must also be acknowledged. In particular, the involvement of multiple raters at some centers may have influenced CMAP variability. Additionally, differences in center-specific NCS techniques, suboptimal CMAP amplitude optimization and the absence of a strict study-wide NCS protocol could have contributed to variability. Finally, since electrophysiological measurements require considerable organization in everyday clinical practice and are both time- and personnel-intensive, some centers had missing baseline values. Patients without a baseline CMAP value were excluded from the analyses, as this may have introduced bias. Future multicenter studies should aim to standardize these aspects to enhance data reliability.

In conclusion, CMAP amplitudes of the ulnar, median, and peroneal nerves were a sensitive indicator of disease severity in treatment-naïve patients but remained stable during nusinersen treatment, with no differences in CMAP amplitude trajectories between SMA types 2 and 3. Our findings suggest that CMAP may not serve as a sensitive biomarker for treatment response in adult SMA patients.

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Conflicts of Interest

B.B. received compensation for travel expenses from ITF Pharma GmbH, the German Neuromuscular Society "Deutsche Gesellschaft fuer Muskelkranke" (D.G.M. e.V.), and German Society for Clinical Neurophysiology and Functional Imaging ("Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung"—D.G.K.N. e.V.), and served on advisory boards of Roche, all outside of the submitted work. C.W. received travel compensation from ITF Pharma GmbH outside the submitted work. A.O., O.S.-K., S.K., K.K., S.H., M.F., I.C., B.e.B., C.V., M.T.M., M.T., and M.R. declare no competing interests related to this work. R.G. has received personal honoraria as a speaker/consultant, personal fees from Biogen, Hofmann-La Roche, Zambon, and Sanofi ITF Pharma, and research support from Biogen; all support was received outside the scope of the submitted work. M.D. received honoraria as a speaker/consultant from Biogen, Roche, and Sanofi outside the submitted work. J.C.K. has received consulting fees and compensation for talks from Biogen, Ipsen, Roche, and AbbVie and has served on advisory boards for Biogen and Roche. He was supported by a generous heritage donation from Bettina Fischer, Germany. C.N. received honoraria for services from Biogen, Roche, Sanofi, Argenx, Mitsubishi Tanabe, and Alexion, unrelated to this work. S.P. received honoraria as a speaker/consultant from Biogen GmbH, Roche, Novartis, Cytokinetics Inc., Desitin, Italfarmaco, Amylyx, and Zambon; and grants from DGM e.V., Federal Ministry of Education and Research, German Israeli Foundation for Scientific Research and Development, EU Joint Program for Neurodegenerative Disease Research, and Neurodegenerative Research Inc., outside of the submitted work.

Data Availability Statement

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

References

1. J. R. Nance, "Spinal Muscular Atrophy," *Continuum (Minneap Minn)* 26, no. 5 (2020): 1348–1368.

2. S. Lefebvre, L. Burglen, S. Reboullet, et al., "Identification and Characterization of a Spinal Muscular Atrophy-Determining Gene," *Cell* 80, no. 1 (1995): 155–165.

3. J. W. Day, R. S. Finkel, C. A. Chiriboga, et al., "Onasemnogene Abeparvovec Gene Therapy for Symptomatic Infantile-Onset Spinal Muscular Atrophy in Patients With Two Copies of SMN2 (STR1VE): An Open-Label, Single-Arm, Multicentre, Phase 3 Trial," *Lancet Neurology* 20, no. 4 (2021): 284–293.

4. J. R. Mendell, S. A. Al-Zaidy, K. J. Lehman, et al., "Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy," *JAMA Neurology* 78, no. 7 (2021): 834–841.

5. D. C. De Vivo, E. Bertini, K. J. Swoboda, et al., "Nusinersen Initiated in Infants During the Presymptomatic Stage of Spinal Muscular Atrophy: Interim Efficacy and Safety Results from the Phase 2 NURTURE Study," *Neuromuscular Disorders* 29, no. 11 (2019): 842–856.

6. E. Mercuri, B. T. Darras, C. A. Chiriboga, et al., "Nusinersen Versus Sham Control in Later-Onset Spinal Muscular Atrophy," *New England Journal of Medicine* 378, no. 7 (2018): 625–635.

7. R. S. Finkel, E. Mercuri, B. T. Darras, et al., "Nusinersen Versus Sham Control in Infantile-Onset Spinal Muscular Atrophy," *New England Journal of Medicine* 377, no. 18 (2017): 1723–1732.

8. T. Hagenacker, C. D. Wurster, R. Gunther, et al., "Nusinersen in Adults With 5q Spinal Muscular Atrophy: A Non-Interventional, Multicentre, Observational Cohort Study," *Lancet Neurology* 19, no. 4 (2020): 317–325.

9. G. Baranello, B. T. Darras, J. W. Day, et al., "Risdiplam in Type 1 Spinal Muscular Atrophy," *New England Journal of Medicine* 384, no. 10 (2021): 915–923.

10. B. T. Darras, R. Masson, M. Mazurkiewicz-Beldzinska, et al., "Risdiplam-Treated Infants With Type 1 Spinal Muscular Atrophy Versus Historical Controls," *New England Journal of Medicine* 385, no. 5 (2021): 427–435.

11. E. Mercuri, G. Baranello, O. Boespflug-Tanguy, et al., "Risdiplam in Types 2 and 3 Spinal Muscular Atrophy: A Randomized, Placebo-Controlled, Dose-Finding Trial Followed by 24 Months of Treatment," *European Journal of Neurology* 30, no. 7 (2023): 1945–1956.

12. C. Wurster and S. Petri, "Progress in Spinal Muscular Atrophy Research," *Current Opinion in Neurology* 35, no. 5 (2022): 693–698.

13. H. S. Lapp, M. Freigang, T. Hagenacker, M. Weiler, C. D. Wurster, and R. Gunther, "Biomarkers in 5q-Associated Spinal Muscular Atrophy-A Narrative Review," *Journal of Neurology* 270, no. 9 (2023): 4157–4178.

14. M. G. Pino, K. A. Rich, and S. J. Kolb, "Update on Biomarkers in Spinal Muscular Atrophy," *Biomarker Insights* 16 (2021): 11772719211035643.

15. M. Gavriilaki, M. Moschou, V. Papaliagkas, et al., "Biomarkers of Disease Progression in Adolescents and Adults With 5q Spinal Muscular Atrophy: A Systematic Review And Meta-Analysis," *Neuromuscular Disorders* 32, no. 3 (2022): 185–194.

16. K. J. Swoboda, T. W. Prior, C. B. Scott, et al., "Natural History Of Denervation in SMA: Relation to Age, SMN2 Copy Number, and Function," *Annals of Neurology* 57, no. 5 (2005): 704–712.

17. M. Richard, R. Barrois, I. Desguerre, et al., "Correlations Between Clinical Motor Scores and CMAP in Patients With Type 2 Spinal Muscular Amyotrophy Treated With Nusinersen," *Archives de Pédiatrie* 31, no. 1 (2024): 26–31.

18. B. T. Darras, C. A. Chiriboga, S. T. Iannaccone, et al., "Nusinersen in Later-Onset Spinal Muscular Atrophy: Long-Term Results From the Phase 1/2 Studies," *Neurology* 92, no. 21 (2019): e2492–e2506.

19. B. Elsheikh, S. Severyn, S. Zhao, et al., "Safety, Tolerability, and Effect Of Nusinersen in Non-Ambulatory Adults With Spinal Muscular Atrophy," *Frontiers in Neurology* 12 (2021): 650532.

20. W. C. Weng, Y. K. Hsu, F. M. Chang, et al., "CMAP Changes Upon Symptom Onset and During Treatment in Spinal Muscular Atrophy Patients: Lessons Learned From Newborn Screening," *Genetics in Medicine* 23, no. 2 (2021): 415–420.

21. P. F. Hsieh, H. J. Lai, Y. C. Kuo, et al., "Mechanisms of Functional Improvement Behind Nusinersen Treatment in Adult Spinal Muscular Atrophy," *Experimental Neurology* 389 (2025): 115230.

22. A. Pechmann, K. Konig, G. Bernert, et al., "SMArtCARE—A Platform to Collect Real-Life Outcome Data of Patients With Spinal Muscular Atrophy," *Orphanet Journal of Rare Diseases* 14, no. 1 (2019): 18.

23. J. Montes, M. P. McDermott, E. Mirek, et al., "Ambulatory Function in Spinal Muscular Atrophy: Age-Related Patterns of Progression," *PLoS One* 13, no. 6 (2018): e0199657.

24. E. S. Mazzone, A. Mayhew, J. Montes, et al., "Revised Upper Limb Module for Spinal Muscular Atrophy: Development of a New Module," *Muscle & Nerve* 55, no. 6 (2017): 869–874.

25. M. Main, H. Kairon, E. Mercuri, and F. Muntoni, "The Hammersmith Functional Motor Scale for Children With Spinal Muscular Atrophy: A Scale to Test Ability and Monitor Progress in Children With Limited Ambulation," *European Journal of Paediatric Neurology* 7, no. 4 (2003): 155–159.

26. D. Kariyawasam, A. D'Silva, J. Howells, et al., "Motor Unit Changes in Children With Symptomatic Spinal Muscular Atrophy Treated With Nusinersen," *Orphanet Journal of Rare Diseases* 92, no. 1 (2020): 78–85.

27. D. Li, N. Sun, L. Xiang, et al., "Neurophysiological Characteristics in Type II and Type III 5q Spinal Muscular Atrophy Patients: Impact of Nusinersen Treatment," *Drug Design, Development and Therapy* 18 (2024): 953–965.

28. B. Elsheikh, S. Severyn, S. Zhao, et al., "Safety, Tolerability, and Effect of Nusinersen Treatment in Ambulatory Adults With 5q-SMA," *Frontiers in Neurology* 12 (2021): 650535.

29. R. Gunther, C. Neuwirth, J. C. Koch, et al., "Motor Unit Number Index (MUNIX) of Hand Muscles is a Disease Biomarker for Adult Spinal Muscular Atrophy," *Clinical Neurophysiology* 130, no. 2 (2019): 315–319.

30. T. Kessler, G. Sam, W. Wick, and M. Weiler, "Evaluation of Risdiplam Efficacy in 5q Spinal Muscular Atrophy: A Systematic Comparison of Electrophysiologic With Clinical Outcome Measures," *European Journal of Neurology* 31, no. 1 (2024): e16099.

31. J. I. Murphy, N. E. Weaver, and A. E. Hendricks, "Accessible Analysis of Longitudinal Data With Linear Mixed Effects Models," *Disease Models & Mechanisms* 15, no. 5 (2022): 048025.

32. W. D. Arnold, P. N. Porensky, V. L. McGovern, et al., "Electrophysiological Biomarkers in Spinal Muscular Atrophy: Preclinical Proof of Concept," *Annals of Clinical Translational Neurology* 1, no. 1 (2014): 34–44.

33. R. Gunther, C. D. Wurster, S. Brakemeier, et al., "Long-Term Efficacy and Safety of Nusinersen in Adults With 5q Spinal Muscular Atrophy: A Prospective European Multinational Observational Study," *Lancet Reg Health Eur* 39 (2024): 100862.

34. T. Hagenacker, L. Maggi, G. Coratti, et al., "Effectiveness of Nusinersen in Adolescents and Adults With Spinal Muscular Atrophy: Systematic Review and Meta-Analysis," *Neurology and Therapy* 13, no. 5 (2024): 1483–1504.

35. D. S. T. Kariyawasam, A. D'Silva, C. Lin, M. M. Ryan, and M. A. Farrar, "Biomarkers and the Development of a Personalized Medicine Approach in Spinal Muscular Atrophy," *Frontiers in Neurology* 10 (2019): 898.

36. N. Hensel, S. Kubinski, and P. Claus, "The Need for SMN-Independent Treatments of Spinal Muscular Atrophy (SMA) to Complement SMN-Enhancing Drugs," *Frontiers in Neurology* 11 (2020): 45.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Supporting Information