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Non-Dystrophic Myotonia: 2-year clinical and patient reported outcomes

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Abstract

Introduction/Aims: Consistency of differences between non-dystrophic myotonias over time measured by standardized clinical/patient-reported outcomes is lacking. Evaluation of longitudinal data could establish clinically relevant endpoints for future research.

Methods: Data from prospective observational study of 95 definite/clinically suspected non-dystrophic myotonia participants (six sites in the United States, United Kingdom, and Canada) between March 2006-March 2009 were analyzed. Outcomes included: standardized symptom interview/exam, Short Form-36, Individualized Neuromuscular Quality of Life (INQoL), electrophysiological short/prolonged exercise tests, manual muscle testing, quantitative grip strength, modified get-up-and-go test. Patterns were assigned as described by Fournier et al. Comparisons were restricted to confirmed sodium channelopathies (*SCN4A*, baseline, year 1, year 2: n=34, 19, 13), chloride channelopathies (*CLCN1*, n=32, 26, 18), and myotonic dystrophy type 2 (DM2, n=9, 6, 2).

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[*]Details for the Consortium for Clinical Investigation of Neurologic Channelopathies can be found in Appendix 1

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that his report is consistent with those guidelines.

Competing interests

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Results: Muscle stiffness was most frequent symptom over time (54.7% – 64.7%). Eyelid myotonia and paradoxical handgrip/eyelid myotonia were more frequent in *SCN4A*. Grip strength and combined manual muscle testing remained stable. Modified get-up-and-go showed less warm up in *SCN4A* but remained stable. Median post short exercise decrement was stable, except for *SCN4A* [baseline to Year 2 decrement difference 16.6% (Q1, Q3: 9.5, 39.2)]. Fournier patterns type 2 (*CLCN1)* and 1 (*SCN4A)* were most specific. 40.4% of participants had a change in pattern over time. INQoL showed higher impact for *SCN4A* and DM2 with scores stable over time.

Discussion: Symptom frequency and clinical outcome assessments were stable with defined variability in myotonia measures supporting trial designs like cross over or combined n-of-1 as important for rare disorders.

Keywords

myotonia congenita; electrodiagnostic testing; quality of life; neuromuscular disorder; genetic testing

Introduction

Non-dystrophic myotonias (NDM) are a rare and diverse group of disorders caused by mutations in skeletal muscle sodium (*SCN4A*) and chloride (*CLCN1*) channels. They include sodium channel myotonias, paramyotonia congenita, hyperkalemic periodic paralysis, and myotonia congenita with characteristic features of myotonia without muscle wasting.[1–5] Many studies have compared features that can distinguish sodium from chloride channel NDM, however, few have evaluated the natural history of NDM as measured by clinical outcome assessments or standard patient-reported outcomes.[4,6–11]

CLCN1 mutations result in myotonia congenita and are inherited in a dominant or recessive fashion with a more severe phenotype associated with recessive mutations. Patients are described as having a muscular appearance, classic myotonia on exam, and decreased severity of myotonia with repeated activity (i.e. 'warm up').[12–15] *SCN4A* associated myotonias are more diverse, ranging from mild myotonia that does not interfere with daily activities to severe muscle weakness and frank episodic paralysis.[16] One unique subgroup, paramyotonia congenita (PMC), demonstrates cold sensitivity and myotonia which 'paradoxically' worsens with repetitive activity.[5,17–19]

NDM can be distinguished from the myotonic dystrophies due to their lack of typical systemic manifestations such as characteristic facial features (i.e. temporal wasting, ptosis), mandibular weakness, cardiac conduction defects, premature cataracts, frontal balding, gonadal insufficiency, and impaired glucose tolerance.[20] Patients with myotonic dystrophy type 2 (DM2) are more likely to resemble those with NDM based on symptoms and physical examination, especially when lacking neurological or systemic features that clearly identify them as having myotonic dystrophy.[21–23]

While cross sectional studies have affirmed the general differences between subtypes of NDM, few longitudinal studies have examined the consistency of these findings over time.[4,7–10,12–19,23–25]Additionally, NDM patients can experience significant lifetime morbidity

due to stiffness and pain related to their muscle symptoms with no clear consensus on the best instrument to measure health impacts.[9,26,27] The NIH-funded Clinical Investigation of Neurological Channelopathies (CINCH) prospectively studied a large cohort of NDM patients utilizing a common infrastructure, shared data elements, and centralized training. Baseline patient-reported and quantitative measures of myotonia in definite or clinically suspected NDM patients have been previously reported.[27] Here we report on longitudinal data collected over 2 years of follow up to better define the phenotypic relationships to underlying mutations associated with NDM and establish clinically relevant endpoints for future research.

Methods

De-identified data from a prospective observational study that occurred from March 2006 to March 2009 as part of the NIH-funded Rare Disease Clinical Research Network's Consortium for CINCH (NCT00244413) was analyzed. Ninety-five subjects were recruited from six academic medical centers in the USA, Canada, and UK. All evaluators were trained to perform outcome measures in a standardized manner at an investigator meeting. The prior protocol was approved by the relevant institutional review boards. Informed consent was obtained from all study participants prior to data collection. The current analysis was deemed non-human subject research after IRB review (data was de-identified and previously collected).

Subjects

Inclusion criteria included: age ≥ 6 years, clinical symptoms/signs of NDM, presence of myotonia on electromyography, and the absence of clinical features suggestive of myotonic dystrophy type I (DM1) such as ptosis, temporal wasting, mandibular weakness, premature cataracts, cardiac conduction abnormalities. Those with genetically confirmed DM2 could be included if they had clinical and electrical myotonia in the absence of typical systemic involvement and/or muscle wasting.[21–23] Participants stopped anti-myotonic medications 5 days prior to each evaluation. For those with a prior history of taking medications associated with electrical myotonia (i.e. fibrate acid derivatives, HMG-CoA reductase inhibitors, chloroquine, colchicine), these medications had to be stopped and myotonia persist upon discontinuation.[28–30] Patients were excluded if they had positive genetic testing for DM1. Participants were studied at an initial 1–2 day outpatient assessment and returned for follow up at one and two years.

Genetic analysis

Genetic testing was performed using a tiered method based on clinical impression following the baseline visit – testing the suspected gene first. Previously published mutations were evaluated first followed by sequencing of the entire chloride channel gene and exons 22 and 24 of the sodium channel.[31,32] If initial testing for *CLCN1* or *SCN4A* mutations was negative, testing was performed for DM1 and/or DM2 if not previously obtained. Participants were grouped as *CLCN1* and *SCN4A* mutations. Those with no identified mutations were not included for analysis/phenotypic comparisons. *SCN4A* participants

were further classified by specific mutation and *CLCN1* were subdivided into recessive or dominant inheritance based on number of mutations and family history.

Outcomes

Baseline demographic data to include age, gender, and self-reported race and ethnicity were reviewed.

Clinical assessment

A standardized symptom questionnaire was administered at baseline; however, no data was available for review from 1 or 2 year follow up visits. For purposes of comparison of the baseline demographic data and standardized symptom questionnaire, three cohorts were defined as those with *SCN4A* mutations, *CLCN1* mutations, or DM2 at baseline (Cohort A), *SCN4A* mutations, *CLCN1* mutations, or DM2 participants with 1 year of follow up data (Cohort B), and *SCN4A* mutations, *CLCN1* mutations, or DM2 with 2 years of follow up data (Cohort C). The purpose of the comparison of the cohorts was to ascertain whether there was attrition bias in baseline characteristics. The instrument collected data on four symptoms: stiffness, weakness, fatigue, and pain. The questionnaire indicated location, frequency, severity, alleviating factors, and precipitating factors in an evaluator-guided interview with severity graded on a 1–9 scale (1=minimal, 9=worst ever experienced). A standardized physical examination/myotonia assessment was performed at baseline and both follow up years. The standard examination tested for presence/absence of myotonia (hand grip, lid lag, eye closure) and percussion myotonia over the thenar eminence and extensor digitorum communis muscle. Warm up and paradoxical myotonia were assessed by having participants perform five sequential 3-second maneuvers (forced handgrip/eye closure followed by rapidly opening the fist or eyes; looking up then quickly returning gaze to neutral) and documenting increase or decrease in myotonia with trials.

Functional evaluation

Gait was assessed by a modified ‘get-up-and-go’ test in which participants rest for 10 minutes then get up from a chair and walk 30 ft as fast as they comfortably can (time captured using a stopwatch). The test was repeated 4 times to evaluate for signs of improved speed (warm up) or decreased speed (paradoxical worsening).[33]

Strength testing

Manual muscle testing was obtained for the shoulder abductors, elbow flexors/extensors, wrist flexors/extensors, hip flexors/extensors/abductors, knee flexors/extensors, and ankle plantarflexion/dorsiflexion. A 13-point modified Medical Research Council scale was used for grading with the total score of all muscles averaged as a composite manual muscle test score.[34] Composite scores were compiled for the upper extremity strength testing, lower extremity strength testing, proximal muscle strength testing (shoulder abductors, elbow flexors/extensors, hip flexors/extensors/abductors, knee flexors/extensors), and distal extremity strength testing (wrist flexion/extension, ankle dorsiflexion/plantarflexion). Quantitative hand grip dynamometry was obtained using a force transducer connected to automatic capturing software (QMA system, Computer Source, Gainesville, GA).[35] Each

hand grip recorded was the best of three maximal voluntary isometric contractions recorded in kg force.

Electrodiagnostic assessment

Electrodiagnostic assessment performed at each visit included a short exercise test before and after cooling, prolonged exercise test using a standardized protocol with minor modifications, and needle electromyography of proximal and distal muscles.[36,37] Compound muscle action potential (CMAP) amplitudes at specific time points before and after periods of exercise were reviewed for both the short and prolonged exercise tests, all recording over the abductor digiti minimi (ADM). The short exercise test consisted of 15 second isometric contraction of the ADM followed by stimulation of the ulnar nerve every 10 seconds for 1 minute. Long exercise testing (LET) consisted of recording CMAPs every minute while the patient was contracting the muscle as strongly as possible with brief periods (3–4 seconds) of rest every 15 seconds for 5 minutes. After exercise, the patient was instructed to relax completely while the CMAP responses were recorded every 2 minutes for 50 minutes afterward.[37] Post-exercise CMAP amplitudes were calculated as percent change from the average pre-exercise baseline measurement measured baseline-to-peak. Abnormal decrement was defined as ≥10% amplitude reduction in the short exercise test and 20% in the prolonged exercise test as previously reported.[36] We assigned patterns as previously described by Fournier et al. using the short exercise test primarily, with use of the prolonged exercise test when the short exercise test was normal (Supplemental Methods). Patterns for all participants were determined by a single evaluator. Electromyographic myotonia was graded on a 1+ to 3+ scale in the right biceps, abductor digiti minimi (ADM), vastus lateralis (VL), tibialis anterior (TA), and a mid-thoracic paraspinal muscles. 1+ myotonia fulfilled the minimal requirements of discharges lasting at least 500 msec and elicited in 3 areas of the muscle outside of the endplate zone, 2+ indicated myotonic discharges in more than half of the needle locations, and 3+ with myotonic discharges elicited with each needle movement in all examined areas (0= no myotonia).[12]

Quality of life instruments

Participants completed the Short Form 36 Item Health Survey (SF-36) and Individualized Neuromuscular Quality of Life (INQoL) instruments at baseline and each follow up. SF-36 is a generic questionnaire designed to assess patients' self-reported health status across physical, mental, and social domains. The items assess eight domains (physical functioning, social functioning, role limitations due to physical, role limitations due to emotional, energy/vitality, mental health, body pain, general health perception) which can be combined to obtain a physical composite score and mental composite score. A higher score indicates better perception of quality of life.[38,39] INQoL has been validated in neuromuscular conditions including dystrophic and non-dystrophic myotonias.[26,40] The instrument contains 45 items covering 10 domains assessing muscle symptoms (weakness, fatigue, pain, muscle locking), impact of the muscle disease on areas of life (activities, independence, social, emotional and body image), and treatment effectiveness. The summary score is a composite of all domains; higher scores indicate a worse perception of quality of life.

Statistical analysis

Standard descriptive statistics, including calculation of the median and first and third quartiles, were used when appropriate for comparison. The test for differences in distribution among the three mutation categories used the Kruskal-Wallis test for continuous data, with longitudinal data assessed as the median differences between baseline and year 1 and baseline and year 2 for each mutation subclass. Pearson's chi-square test without continuity correction was used for testing difference in frequencies among mutation categories at each time point. Only participants with complete data were used in the analysis. Missing data was assumed to be missing at random. All p-values are two tailed with a significance level less than 0.05. All statistical analysis was conducted using JMP Software (Cary, NC).

Results

Baseline Characteristics

Ninety-five participants were recruited Two participants dropped out before study visits. Of the remaining 93, 34.4% had *CLCN1* mutations, 36.6% had *SCN4A* mutations, and 9.7% had DM2(Table 1, Cohort A). None of the DM2 patients had a concomitant mutation in SCN4A or *CLCN1.* One participant had DM1 and 17 others did not have identified mutations and were excluded. Of patients who returned at one year, 50% had *CLCN1* mutations, 38.5% had *SCN4A*, and 11.5% had DM2 (Table 1, Cohort B). For year two, 55.9% *CLCN1* participants, 38.2% *SCN4A*, and 5.9% DM2 were available (Table 1, Cohort C). There did not appear to be significant changes in the baseline characteristics when comparing the 75 with baseline visits, 52 with 1 year, and 34 with 2-year visits. Gender was balanced, except for *CLCN1*, which had a majority of males (73.7%–76.9%). Participants were mainly non-Hispanic Caucasian with no difference in race or ethnicity based on mutation. The frequency of disability and unemployment was stable at each timepoint for *CLCN1*; whereas there was a higher frequency of disability at baseline compared to follow up for *SCN4A*.

Symptom Questionnaire

When comparing most predominant symptoms reported in each Cohort, frequencies of symptoms were similar. One exception was for *SCN4A* participants that reported disability were less likely to return for visits at 1 or 2 years (Table 1).

Examination Findings

Clinical Myotonia Assessment—Eye closure myotonia was more prevalent in *SCN4A*, found in 73.5–79% of participants at each time point, than *CLCN1* (25–38.9%) or DM2 (0–33.3%). Muscle hypertrophy and warm-up were more common in *CLCN1* as compared to *SCN4A* or DM2, however, muscle hypertrophy remained statistically significant throughout all time points. Paradoxical eyelid myotonia and paradoxical hand grip myotonia appeared to be distinguishing features for *SCN4A* at each evaluation, with both demonstrating modest sensitivity (38.5–63.2%) and high specificity of 95–100% at each time point (Table 2).

Manual Muscle Testing and Grip Dynamometry—Weakness at baseline was modest overall with DM2 demonstrating a lower median composite of 4.24 (IQR 4.23–4.51) as

compared to 4.73 (IQR 4.46–4.87) for *SCN4A*and 4.79 (IQR 4.31–4.97) for *CLCN1* (p=0.031). Change in strength at years 1 and 2 of follow up was not significant for any mutation class (Figure 1a). There was no significant difference in median grip strength in either hand at baseline between mutation subclasses and no significant change in grip strength at follow-up for any mutation (Figure 1b).

Get-up-and-go Testing—*SCN4A* had a faster average performance on the get up and go testing as compared to *CLCN1* and DM2.No group showed changes in their performance during follow up. While *CLCN1* group showed warm up over 4 trials at each visit, as evidenced by their larger reduction in time from Test 1 to Test 4, this phenomenon was not observed in *SCN4A* at any timepoint (Supplementary Table 1).

Electrophysiologic Testing

Short Exercise Testing—Median amplitude decrement for *CLCN1* at room temperature ranged from 18–27%. With cooling it remained similar at all years of follow up. There was no significant percent decrease in amplitude either at room temperature or cooling for DM2. At baseline and year one, *SCN4A* demonstrated a lower initial decrease in amplitude at room temperature, ranging from 3.4–6.5%, with a larger percent amplitude decrement with cooling. There was no increased decrement with cooling at year 2 for *SCN4A* (Fig. 2a). This was a year when there was more substantial drop out of those with PMC phenotypes, with 13 PMC participants at baseline and year 1 and only 8 available for year 2. There was no significant change in the percent decrease in amplitude over time either at room temperature or cooling (Fig. 2b).

Electrical Myotonia—*CLCN1* and *SCN4A* demonstrated median electrical myotonia grades of 3+ in all studied muscle groups at baseline, year 1, and year 2. DM2 demonstrated statistically lower median myotonia grades of 1 in the ADM, biceps, thoracic paraspinals, and TA at baseline (p=0.012, 0.001, 0.001, 0.001). At year 1, DM2 showed statistically lower median myotonia in the biceps (p=0.004) and TA (p=0.0017) with no muscles demonstrating significantly lower median myotonia grades at year 2 (only two DM2 participants were available for evaluation).

Fournier Patterns—Overall proportion of Fournier patterns within mutation subgroups remained relatively stable over time (Figure 3). Within *CLCN1* there were 9 total patients (36%) with a change in their pattern over time while sodium had 8 (42.1%) and DM2 2 (66.7%, n=3). Despite individual variation over time, type II pattern retained a moderate sensitivity (48.1–76.9%) and high specificity (91.3–100%) for *CLCN1* mutations while type I maintained low to moderate sensitivity (sensitivity 32.1–52.6%) but high specificity (91.4–100%) for *SCN4A* mutations.

Quality of Life—The greatest impact on median overall Individualized Neuromuscular Quality of Life score was for *SCN4A* and DM2 compared to *CLCN1* at all time periods (Figure 4a), although, this was only statistically significant at baseline (p=0.017). There was no significant change in the INQoL over time for either of the diseases outside of DM2 (transient improvement of the INQoL score was observed at year one which did not persist

to year 2 follow up). While individual domains of activity limitations, independence, and emotions predominately impacted *SCN4A* and DM2 as compared to *CLCN1* at baseline, this did not remain statistically significant at any follow up period (Supplementary Table 2). The most impacted domains for *SCN4A* and *CLCN1* at all follow up periods were muscle weakness and muscle locking. The SF-36 physical composite score and mental composite score were not significantly different for the three cohorts ($p \geq 0.10$) and remained stable over time, although the physical composite was at the lower end of normal for all mutations as opposed to the mental health composite (Figure 4b).

Discussion

While clinical presentation may help distinguish between *CLCN1* and *SCN4A* mutations, there is overlap between these two NDMs. As previously reported, hand grip myotonia was the most common symptom shared between these conditions.[8,10] While muscle hypertrophy and warm-up were more typical of *CLCN1*, there was overlap with *SCN4A* and only muscle hypertrophy remained statistically significant throughout all follow up periods. Paradoxical eyelid and handgrip myotonia remained distinguishing examination features throughout all time points for *SCN4A* mutations. This expands upon prior data regarding paradoxical myotonia being a distinguishing feature of *SCN4A* mutations and further supports its utility as an adjunct for distinguishing *SCN4A* from *CLCN1* when the patient has a negative result or variant of unknown significance on genetic testing and non-distinguishing electrophysiologic examination.[9,41]

Functional measures including manual muscle testing, get-up-and-go testing, and grip dynamometry were stable over time. As future treatment trials are likely to target myotonia, evidence for warm-up in the timed get-up-and-go test in *CLCN1* that was stable over time may make this a useful functional motor outcome measure for future trials targeting myotonia, which has a negative impact on perceived quality of life in non-dystrophic myotonia patients.[6,26] One important caveat, as outlined by the outliers in our *CLCN1* handgrip assessment (Supplementary Fig. 1), is that in recessive *CLCN1* subjects, evaluators must be careful to standardize measurements of handgrip strength or other outcome measures to eliminate the potential effects of warm-up. Recessive *CLCN1* mutations have been previously shown to result in a decrease in the initial peak force of the handgrip, compared to dominant mutations, which improves with subsequent handgrips.[11]

While there was variability within individual participants with regards to Fournier patterns over time, the type II pattern retained high specificity for *CLCN1* mutations while type I maintained high specificity for *SCN4A* mutations over time. The sensitivity for *CLCN1* and *SCN4A* mutations over time was lower than prior descriptions of these patterns, however, the specificity remained comparable.[36,41,42] Variability over time supports prior conclusions that electrophysiologic testing is not sensitive or specific enough to be relied upon solely for diagnosis and that Fournier patterns may not be useful outcome measures for future clinical trials targeting myotonia.[27] With increased access to genetic panels, short exercise testing and Fournier patterns are no longer relied upon for initial diagnosis but retain utility in resolving variants of undetermined significance (VUS) or in the setting of negative genetic testing.[6]

There was no change in the percent amplitude decrement pre/post cooling for individual mutations over time and cooling increased the sensitivity of detecting significant amplitude decrements greater than 10% both at baseline and year one of follow up. The finding of relatively stable amplitude decrements over time in these subgroups supports possibly using change in amplitude decrement as an additional surrogate for treatments in the future, as has been suggested previously.[43]

Contrary to prior findings, patients with *CLCN1* mutations in our cohort had better quality of life overall (INQoL) at baseline as compared to *SCN4A* or DM2, with the trend continuing throughout the study.[26] Given ability to detect subtle differences between mutation subgroups, as well as targeted inclusion of the most significant factors associated with detrimental impact on quality of life (muscle weakness, muscle locking/myotonia, fatigue), the INQoL appears ideally suited for inclusion in future clinical trials outcome measures. Within NDMs, weakness and muscle locking were consistently rated as the most detrimental features impacting quality of life (INQoL). These findings are in concordance with the most significant factors associated with quality-of-life impacts on prior studies and may serve as preferred outcomes for clinical trials.[9,26]

Drop out between baseline (75 participants), year one (52 participants) and year two (34 participants), does significantly lower the power. Those who remained for all follow up visits likely introduce bias toward participants who were more likely to enroll in an observational study or maintain close medical follow up. The higher frequency of disability at baseline compared to follow up for *SCN4A* may suggest those patients who returned for follow up may be more functionally independent and less severely affected. Our cut off of 20% for the LET may have been too conservative and may have resulted in a few patients being diagnosed as a Type IV or V pattern as opposed to Type III. Based on a recent analysis, the appropriate cut-off for the prolonged exercise test in future studies of NDM, excluding those with periodic paralysis, should likely be greater than 40%.[44]

Despite the limitations, prospective data from this NDM cohort provides information that is applicable to future clinical trial design. Standardized assessments can be performed at multiple centers which may allow for larger studies with more rapid recruitment. The stability of functional measures over time supports these as potential targets for future interventions and provides a baseline to detect change with interventions. The stability over 1–2 years highlights the importance of trial design for rare disorders and need for cross-over clinical and n-of-1 trials in the development of interventions, as highlighted in a prior study of mexiletine for NDM.[45]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADM	abductor digiti minimi
CINCH	Clinical Investigation of Neurological Channelopathies
CLCN1	chloride voltage-gated channel 1 gene
CMAP	compound muscle action potential
DM1	myotonic dystrophy type 1
DM2	myotonic dystrophy type 2
INQoL	Individualized Neuromuscular Quality of Life
LET	long exercise test
NDM	Non-dystrophic myotonias
PMC	paramyotonia congenita
SCN4A	sodium voltage-gated channel alpha subunit 4 gene
SF-36	Short form 36 Item Health Survey
TA	tibialis anterior
VL	vastus lateralis

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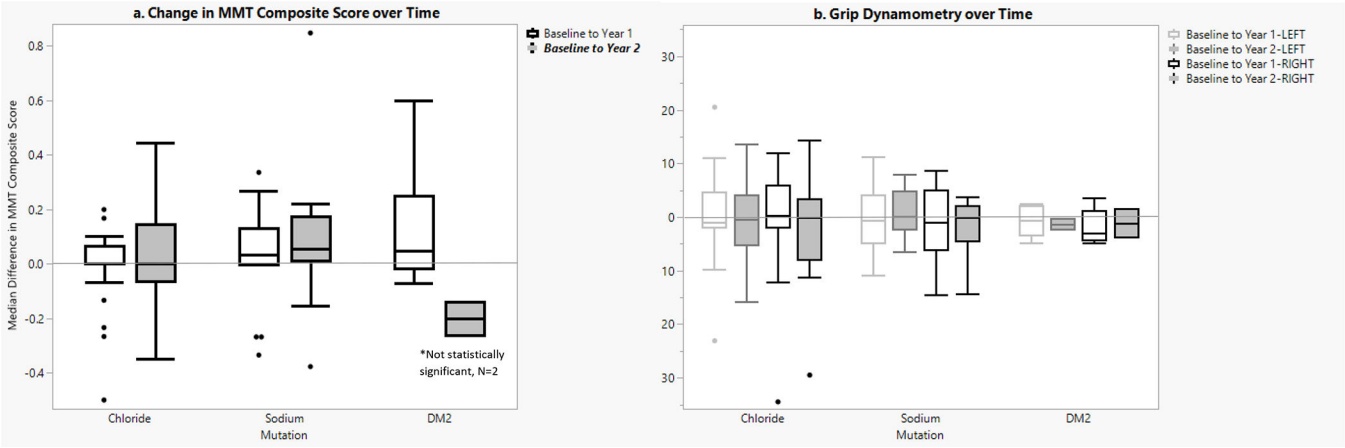

Figure 1. Changes in overall manual muscle testing composite scores (a) and in grip dynamometry (b) over time.

Box and whisker plots show the distribution of median difference in composite scores from baseline to year 1 (empty) and baseline to year 2 (gray filled). The box represents 50% of the population, center line the median, whiskers adjacent upper/lower values, and dots outliers. The gray line indicates zero, or no change between interval follow ups. MMT = manual muscle testing.

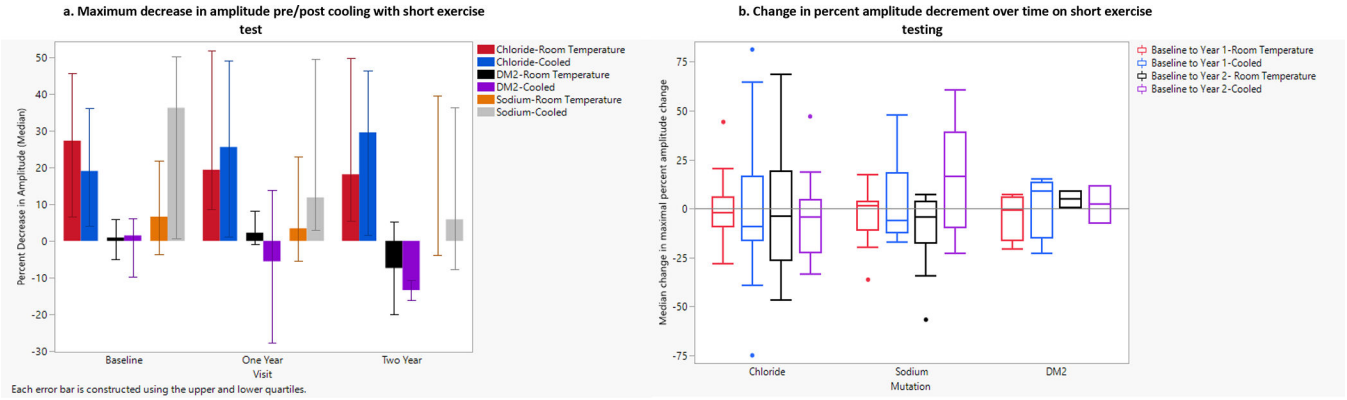

Figure 2. Maximum decrease in amplitude pre and post cooling (a) and change in percent maximal amplitude decrement (b) with the short exercise test over time.

(a) Bars represent the median overall amplitude change with error bar constructed with the upper and lower quartiles for chloride at room temperature (red) and cooled (blue), DM2 at room temperature (black) and cooled (purple), and sodium at room temperature (orange) and cooled (gray). (b) Box and whiskers plots show the distribution of median differences from baseline to year one at room temperature (red), baseline to year one after cooling (blue), baseline to year two at room temperature (black) and baseline to year two cooled (purple). The box represents 50% of the population, center line the median, whiskers adjacent upper/lower values, and dots outliers. The gray line indicates zero, or no change between interval follow ups.

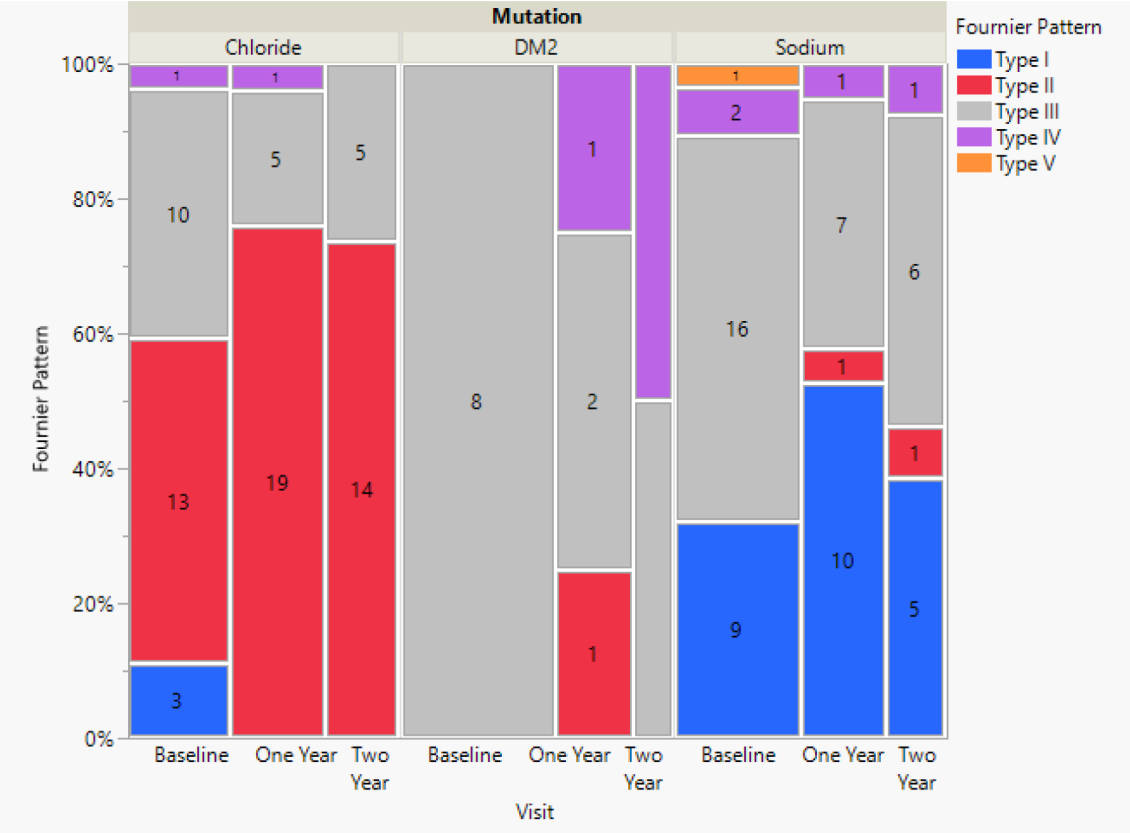

Figure 3. Change in distribution of Fournier patterns over time.

Bars represent the percent of the total population available for follow up at each time period (baseline, year one, year two) with type I (blue), type II (red), type III (gray), type IV (purple), and type V (orange) patterns. Number within each bar represents the total number of participants with the pattern at each time point for each mutation. At baseline, 5 *CLCN1* participants, 6 *SCN4A* participants, and 1 DM2 participants were missing data for analysis.

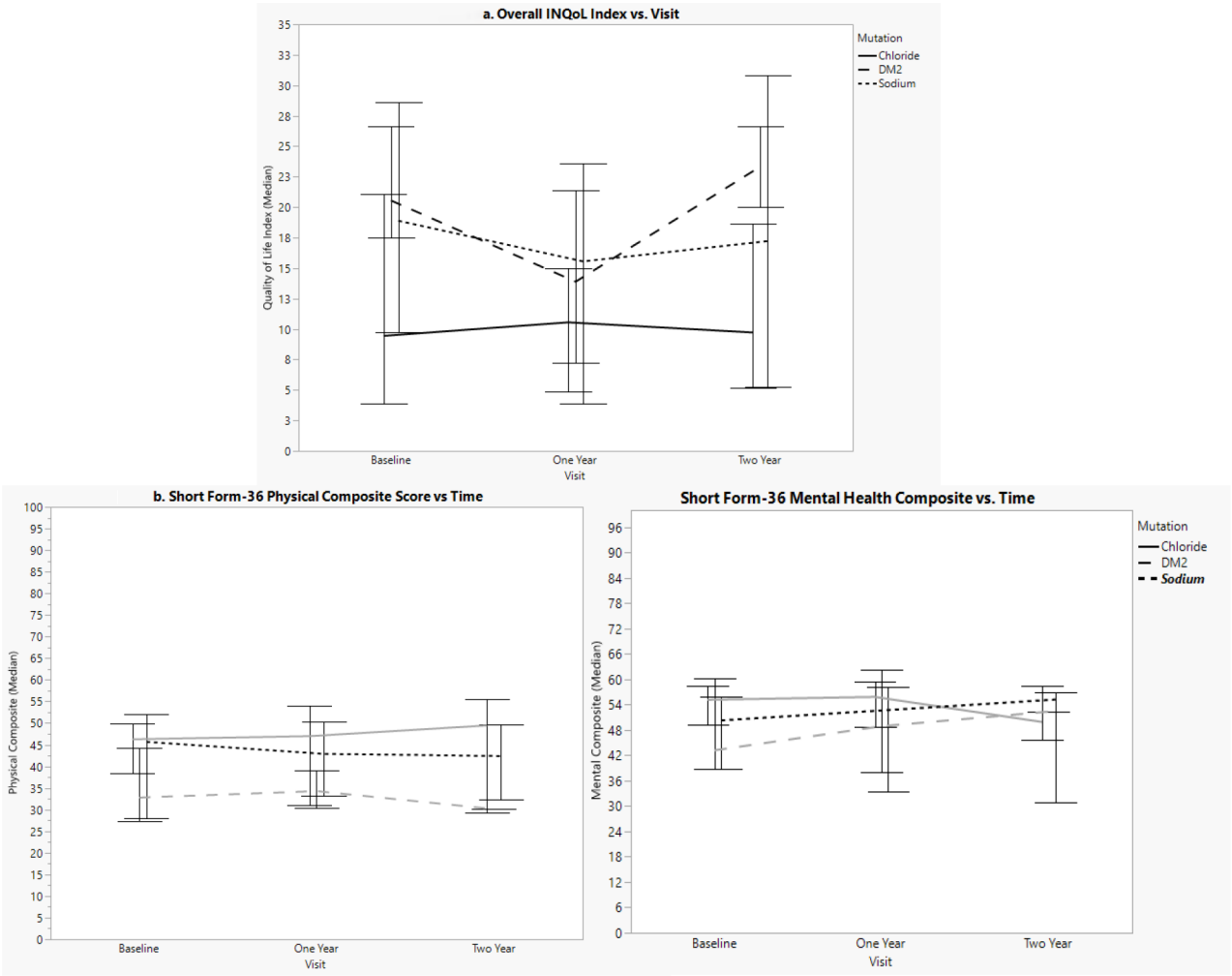

Figure 4. Median overall quality of life index as measured by the Individualized Neuromuscular Quality of Life assessment (INQoL) (a) and Short Form-36 (SF-36) physical composite (b, left) and mental health composite (b, right) over time.

Overall median score for chloride mutations (solid line), DM2 mutations (dashed line), and sodium mutations (dotted line) is plotted over time with error bars representing the upper and lower quartiles.

Table 1

Baseline Characteristics

Mutation	*CLCNI*			*SCN4A*			DM2		
	Cohort A	**Cohort B**	**Cohort C**	**Cohort A**	**Cohort B**	**Cohort C**	**Cohort A**	**Cohort B**	**Cohort C**
n	32	26	19	34	20	13	9	6	2
Age (yrs), median (IQR)	41 (28.3–51.5)	44.5 (27–53.5)	47 (35.5–54.5)	49 (37–57)	47 (35–55)	45 (38–53)	49 (44–62)	50 (47.8–68)	47.5 (46.8–48.3)
Gender, female, n (%)	8 (25)	6 (23.1)	5 (26.3)	18 (52.9)	11 (55)	8 (61.5)	6 (66.7)	3 (50)	2 (100)
Ethnicity, Non-Hispanic, n (%)	32 (100)	26 (100)	19 (100)	30 (100)	20 (100)	13 (100)	9 (100)	5 (100)	2 (100)
Race, White, n (%)	27 (84.4)	22 (87.5)	16 (84.2)	29 (85.3)	20 (100)	13 (100)	8 (88.9)	4 (66.7)	2 (100)
Disability due to disease, n (%)	1 (3.1)	1 (4.2)	1 (5.9)	8 (23.5)	2 (10)	1 (7.7)	1 (11.1)	1 (16.7)	0 (0)
Unemployed due to disease, n (%)	1 (3.1)	1 (4.2)	1 (5.9)	5 (14.7)	2 (10)	2 (15.4)	2 (22.2)	2 (33.3)	1 (50)
Most Predominant Symptom									
Stiffness, n (%)	24 (75)	19 (73.1)	14 (73.7)	16 (47.1)	11 (55)	8 (61.5)	1 (11.1)	1 (16.7)	0 (0)
Pain, n (%)	5 (15.6)	5 (19.2)	4 (21.1)	5 (14.7)	3 (15)	2 (15.4)	3 (33.3)	1 (16.7)	1 (50)
Weakness, n (%)	0 (0)	0 (0)	0 (0)	10 (29.4)	6 (30)	3 (23.1)	4 (44.4)	3 (50)	0 (0)
Fatigue, n (%)	3 (9.4)	2 (7.7)	1 (5.3)	3 (8.8)	0 (0)	0 (0)	1 (11.1)	1 (16.7)	1 (50)

[a]All information in table collected at baseline visit only, therefore, Cohort A=group completing initial visit, Cohort B=group completing 12 month visit, Cohort C=group completing 24 month visit

Table 2

Clinical Exam Findings

Mutation	*CLCNI*			*SCN4A*			DM2			P values (baseline, year 1, year 2)[a]
	Baseline	Year 1	Year 2	Baseline	Year 1	Year 2	Baseline	Year 1	Year 2	
n	32	26	18	34	19	13	9	6	2	
Eye Closure Myotonia, n (%)	8 (25)	9 (34.6)	7 (38.9)	25 (73.5)	15 (79)	10 (76.9)	3 (33.3)	2 (33.3)	0	<0.001, 0.009, 0.06
Hand Grip Myotonia, n (%)	24 (75)	21 (80.8)	12 (66.7)	26 (76.5)	10 (52.6)	7 (53.9)	3 (33.3)	2 (33.3)	0	0.032, 0.035, 0.364
Muscle Hypertrophy, n (%)	24 (75)	22 (84.6)	13 (72.2)	14 (41.2)	8 (42.1)	5 (38.5)	0	0	0	<0.001, 0.001, 0.049
Paradoxical Eyelid Myotonia, n (%)	0	0	1 (5.6)	17 (50)	12 (63.2)	8 (61.5)	0	1 (16.7)	0	<0.001, <0.001, 0.002
Paradoxical Handgrip Myotonia, n(%)	1 (3.1)	0	0	17 (50)	10 (52.6)	5 (38.5)	1 (11.1)	1 (16.7)	0	<0.001, <0.001, 0.013
Warm-Up Phenomenon, n (%)	24 (75)	19 (73.1)	13 (72.2)	12 (35.3)	5 (26.3)	5 (38.5)	2 (22.2)	1 (16.7)	0	0.001, 0.002, 0.090

[a]Pearson's chi-square test without continuity correction comparing frequency of examination finding across genetic subtypes at each time point