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Redefining the clinical phenotypes of non-dystrophic myotonic syndromes

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ABSTRACT

Objective: To redefine phenotypical characteristics for both chloride (ClCh) and sodium channelopathies (NaCh) in non-dystrophic myotonic syndromes (NDM).

Methods: In a cross-sectional, nationwide study, standardised interviews and clinical bedside tests were performed in 62 genetically confirmed NDM patients, 32 ClCh and 30 NaCh.

Results: Standardised interviews revealed that ClCh reported a higher frequency of muscle weakness (75 vs 36.7%; $p < 0.01$), the warm-up phenomenon (100 vs 46.7%; $p < 0.001$), and difficulties in standing up quickly (90.6 vs 50.0%; $p < 0.001$), running (90.6 vs 66.7; $p < 0.05$) and climbing stairs (90.6 vs 63.3%; $p = 0.01$). Patients with NaCh reported an earlier onset (4.4 vs 9.6 years; $p < 0.001$), and higher frequencies of paradoxical (50.0 vs 0%; $p < 0.001$) and painful myotonia (56.7 vs 28.1%; $p < 0.05$). Standardised clinical bedside tests showed a higher incidence and longer relaxation times of myotonia in the leg muscles for ClCh (100 vs 60%; mean duration of chair tests 12.5 vs 6.3 s; $p < 0.001$), and in eyelid muscles for NaCh (96.7 vs 46.9%; mean relaxation time of 19.2 vs 4.3 s; $p < 0.001$). Transient paresis was only observed in ClCh (62.5%) and paradoxical myotonia only in NaCh (30.0%). Multivariate logistic regression analyses allowed clinical guidelines to be proposed for genetic testing.

Conclusion: This study redefined the phenotypical characteristics of NDM in both ClCh and NaCh. The clinical guidelines proposed may help clinicians working in outpatient clinics to perform a focused genetic analysis of either *CLCN1* or *SCN4A*.

Non-dystrophic myotonic syndromes (NDM) are a heterogeneous group of skeletal muscle disorders caused by mutations in genes encoding the skeletal muscle chloride (*CLCN1*) or sodium channel (*SCN4A*). Mutations in *CLCN1* are responsible for recessive and dominant myotonia congenita (RMC and DMC), and mutations in *SCN4A* for paramyotonia congenita (PC), potassium-aggravated myotonias (PAM) and hyperkalemic periodic paralyses (HYPP).¹ As suggested by Rüdel *et al*, PAM diagnosed without a potassium-loading test is referred to as a sodium-channel myotonia (SCM).²

Diagnosis of the various types of NDM was originally based on clinical characteristics only. Thomsen was the first to describe DMC, distinguishing the stiffness (myotonia), reduction of stiffness through repetitive muscle contractions (warm-up phenomenon) and the dominant inheritance of the disease.³ In 1957 Becker described a recessive form with a more generalised myotonia in

combination with transient paresis.⁴ Both symptoms also improved with sustained exercise (warm-up phenomenon).⁵ In contrast, myotonia in PC worsens with sustained exercise (paradoxical myotonia). Furthermore, in PC a flaccid paresis may be elicited by cold or long periods of exercise.⁶ PAM is clinically characterised by potassium sensitivity of myotonia and by unusual features as fluctuations in myotonia (myotonia fluctuans), permanent myotonia (myotonia permanens) or acetazolamide-responsive MC.^{7,8} Hyperkalaemic periodic paralysis shows attacks of generalised muscle weakness with or without myotonia.⁹

Since genetic testing became available, several authors have reported a genotype–phenotype mismatch.^{2,10–12} For example, the warm-up phenomenon was assumed to be a specific symptom for chloride channelopathies. However, instead of the expected chloride channel defect, a mutation in the skeletal muscle sodium channel was found in some families with the warm-up phenomenon.^{10–12} The present study aims to redefine clinical phenotypes of NDM segregated by chloride (ClCh) and sodium channelopathies (NaCh). To this end, we conducted standardised interviews and clinical bedside tests in a group of genetically confirmed patients with NDM.

PATIENTS AND METHODS

Patients

All neurologists across The Netherlands as well as the Dutch Patient Association for Neuromuscular Diseases (VSN) were requested to report all patients with NDM to our research group for a full year. All reported patients aged 18 years and over were invited to the neurology outpatient clinic of the Radboud University Nijmegen Medical Centre and seen once for clinical assessment, needle EMG and collection of blood samples for genetic analysis. Inclusion criteria were a clinical diagnosis of NDM according to established clinical criteria and myotonic discharges upon needle EMG examination.¹³ Exclusion criteria were a clinical or genetic diagnosis of myotonic dystrophy type 1 or type 2, a clinical or genetic diagnosis of primary periodic paralysis without clinical signs of myotonia, serious comorbidity, absence of mutations by direct sequence analysis in *CLCN1* or *SCN4A*, and unwillingness or inability to temporarily stop drug therapy for myotonia. The study was approved by the medical ethics committee of the Radboud University Nijmegen Medical Centre, and all participating patients gave their written informed consent prior to the study.

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Genetic analysis

Genomic DNA was isolated from peripheral blood at the Leiden University Medical Centre and subsequently screened for mutations by direct sequence analysis of *CLCN1* and *SCN4A*.¹⁴ Primer sets designed for amplification of *CLCN1* or *SCN4A* can be found at <http://www.lumc.nl/4080/DNA/CLCN1.html> or [SCN4A.html](http://www.lumc.nl/4080/DNA/SCN4A.html), respectively.

Phenotype characterisation

All clinical evaluations were conducted by the same examiner (JT) who had been amply trained in the standardised examination of patients with non-dystrophic myotonic syndromes.

Standardised interview

A standardised interview was conducted to establish demographic and general clinical aspects (age, sex, age of onset, duration of symptoms, duration prior to diagnosis, use and duration of drug therapy and anaesthesia-related adverse events), specific clinical features such as myotonic features (presence, provoking factors, pattern, frequency and severity (Numerical Rating Scale (NRS), range 1–10), presence of painful myotonia, severity of pain (NRS, range 1–10), course of the disease, other neuromuscular features (presence of muscle weakness), disabilities (disability interfering with household and employment) and, finally, the patient's ability to walk, climbing stairs, stand up quickly, run and play sports.

Standardised neuromuscular examination (clinical bedside tests)

A standardised neuromuscular examination was performed to determine the presence of myotonia in eyelid, hand flexor and leg muscles. Furthermore, the presence or absence of the warm-up phenomenon, paradoxical myotonia and transient paresis was tested. All tests were performed in predefined, standardised positions and environments (20°C) at the same time of the day. Before the study, a trained clinical team pilot tested the draft standardised neuromuscular examination and also repeated this in several patients.

Myotonia assessment

Clinical tests for myotonia were performed after 10 min of rest. Action myotonia in eyelid muscles and right-hand flexor muscles was determined after a maximum voluntary contraction of 3 s, which was initiated and the maximum possible contraction maintained on instruction from the examiner, after which the patients were asked to open their eyes or fist as quickly as possible. Action myotonia in leg muscles was evaluated during a modified "chair test," in which the time required to rise from a standardised chair, to walk around it and to sit down again was measured.¹⁵ Percussion myotonia in the hands and legs was determined with a blow of the percussion hammer on the right thenar and right quadriceps muscle, respectively. Finally, myotonia of each muscle group was scored as positive if action myotonia, percussion myotonia or both were present.

Assessment of the warm-up phenomenon and paradoxical myotonia

The relaxation times of the eyelid muscles and right-hand flexor muscles as well as the performance of the chair tests were timed by stopwatch. The tests were conducted after 10 min of rest and after 10 successive contractions or, for the chair test, 10 consecutive cycles. The warm-up phenomenon was defined as a reduction of the relaxation interval following the contractions or chair test cycles with at least 1 s. Conversely, paradoxical

myotonia was defined as an increase in the relaxation interval with at least 1 s.

Assessment of transient paresis

Presence of transient paresis was evaluated by manually testing the left biceps during isometric muscle force maintained during 5 s. If during this 5 s interval the Medical Research Council (MRC) score fell below 5, the patient was encouraged to do warm-up exercises (ie, 10 strong, successive 10 s contractions with the examiner exerting counterforce).¹⁶ If, following the warm-up exercises, the MRC score had increased by minimally one point, transient paresis was recorded as positive and, if it had not, as negative.

Statistical analysis

The clinical and genetic data were recorded as independent variables in an SPSS database. All data analyses were performed using SPSS version 15.0 for Windows (SPSS, Chicago). To compare CICH with NaCh, DMC with RMC, and PC/HYPP with SCM, we applied the Mann–Whitney U test for independent groups for continuous variables and the χ^2 test for categorical variables. For the distinction between CICH and NaCh, we used multivariate logistic regression analysis. We regarded age, gender and all variables obtained by the standardised neuromuscular examination as possible predictors. To find the best-fitting predictive model, we used backward elimination and log-likelihood χ^2 . Subsequently, we searched for a reduced regression model including only predictors with a log-likelihood χ^2 $p < 0.10$. Next, first-order interactions between all pairs of predictors remaining within the reduced model were tested by forward selection with log-likelihood χ^2 . Finally, we tried to construct a practical instrument for the distinction between CICH and NaCh in daily clinical practice. A p value of less than 0.05 was considered to be statistically significant.

RESULTS**Patient demographics and genetic data**

The 1-year recruitment period yielded a total of 158 patients of whom 110 had been reported by neurologists and 48 by the Dutch Patient Association for Neuromuscular Diseases. Of the former contingent, 38 ultimately refused participation without specifying their reasons, and 23 patients of the latter group were non-responders. Nine patients were unable to participate due to transportation problems, and 26 patients were excluded because of periodic paralysis without clinical myotonia ($n = 7$), unwillingness or inability to temporarily stop drug therapy for myotonia ($n = 5$), misdiagnosis ($n = 2$) or serious comorbidity ($n = 12$). Finally, we included 62 patients with a clinical, electromyographical and genetically confirmed diagnosis of NDM, originating from 48 unrelated families. Thirty-three were men (53.2%) and 29 women (46.8%), and their mean age was 42.3 (SD 11.9) years (range 19 to 68). Direct sequence analysis showed *CLCN1* mutations in 32 and *SCN4A* mutations in 30 patients.¹⁴

Phenotype characterisation**Standardised interview****Differences between CICH and NaCh**

Table 1 shows the prevalence of clinical aspects that were statistically significantly different between CICH and NaCh.

Table 1 Prevalence of clinical aspects derived from the standardised interview that were statistically significantly different between chloride (ClCh) and those with sodium channelopathies (NaCh)

	ClCh	NaCh	p Value
Mean age in years (SD), range	45.7 (10.6), 23 to 60	38.7 (12.3), 19 to 68	0.02
Mean age of onset in years (SD), range	9.6 (7.3), 0 to 31	4.4 (7.0), 0 to 36	<0.001
Mean duration to diagnosis in years (SD), range	12.0 (10.4), 0 to 33	7.7 (11.9), 0 to 51	0.04
Sleep deprivation, provoking factor of myotonia, n (%)	11 (34.4)	19 (63.3)	0.02
Decrease of myotonia after repetitive contractions, n (%)	32 (100)	15 (50.0)	<0.001
Increase of myotonia after repetitive contractions, n (%)	0 (0)	15 (50.0)	<0.001
Presence of muscle weakness, n (%)	24 (75)	11 (36.7)	0.002
Presence of painful myotonia, n (%)	9 (28.1)	17 (56.7)	0.02
Difficulty in climbing stairs, n (%)	29 (90.6)	19 (63.3)	0.01
Difficulty in standing up quickly, n (%)	29 (90.6)	15 (50.0)	<0.001
Difficulty in running, n (%)	29 (90.6)	20 (66.7)	0.02

Differences within ClCh and NaCh

Within the ClCh there were no statistically significant differences between RMC and DMC. Within the NaCh group only muscle weakness showed a significant difference between PC and SCM (PC 85.7% vs SCM 21.7%; $p = 0.002$).

Similarities between ClCh and NaCh

In addition to the discriminating variables, most patients mentioned daily complaints (ClCh: 96.9% and NaCh 83.3%), and myotonia was reported as severe (ClCh: 71.9% ≥ 5 vs NaCh: 67.7% ≥ 5) with symptoms having increased during their lives. Furthermore, patients with painful myotonia rated their pain as severe (ClCh: 77.8% ≥ 5 vs NaCh: 76.5% ≥ 5). Muscle contractions (95.2%), low temperatures (88.7%), and stress and emotions (61.3%) were the main provoking factors for myotonia. In the female patients, both menstruation and pregnancy tended to aggravate the symptoms (menstruation: ClCh: 25% and NaCh: 41%; pregnancy: ClCh: 40% and NaCh: 80%). About 30% of the patients (ClCh: 31.3% and NaCh: 26.7%) had been taking drugs to combat myotonia for a prolonged time (mean duration of drug therapy 10.1 vs 15.3 years). Fifty per cent used mexiletine, the other half carbamazepine, fenytoine, tocainide, procainamide or flecainide. In each group, about one-third of the patients were fully or partially disabled (ClCh: 34.4 and NaCh: 33.3%). Finally,

complications during anaesthesia were reported in 21.7% in ClCh and in 23.3% in NaCh: two patients with a NaCh showed myotonia in tongue and throat muscles, which hampered their intubation. One patient with a NaCh showed abundant myotonia in his abdominal muscles, which made it necessary to cancel surgery. Two patients with a ClCh were excessively fatigued for a prolonged time, and eight patients, four ClCh and four NaCh, experienced an excessive increase of their myotonia.

Standardised neuromuscular examination

Differences between ClCh and NaCh

Table 2 shows the results of the standardised neuromuscular examinations. Eleven of the 16 variables differed statistically significantly between the two NDM groups. Most noticeable were the higher occurrence and longer relaxation times of myotonia in the leg muscles for ClCh and in the eyelid muscles for NaCh.

Furthermore, paradoxical myotonia was exclusively present in the NaCh and transient paresis in ClCh.

Differences within ClCh and NaCh

In ClCh, transient paresis showed no differentiation between RMC (66.7%) and DMC (0%) ($p = 0.13$). Furthermore, there were no other differentiating variables between the two MC types. In NaCh, the presence of myotonia in the leg muscles ($p = 0.05$), action myotonia ($p = 0.10$) and percussion myotonia of the right quadriceps muscle ($p = 0.09$) showed a trend for differentiation between SCM and PC (table 3). However, only the warm-up phenomenon contributed statistically significantly to the differentiation between SCM and PC (table 3).

Similarities between ClCh and NaCh

Both groups exhibited a high incidence and similar severity of myotonia in the hand-flexor muscles, and both displayed the warm-up phenomenon.

Practical instrument of parameters for the distinction between ClCh and NaCh

Tables 4, 5 show the results of the final logistic regression model.

The resultant model only comprises myotonia in eyelid muscles and transient paresis. The log-likelihood χ^2 values of this model are 59.47 by 2 df ($p < 0.001$), and the ROC area-under-the-curve parameter is 0.947 (asymptotic 95% CI 0.884 to 1.000). Based on these results simple rules for an effective and practical instrument to distinguish ClCh from NaCh can be described: if both eyelid myotonia and transient paresis are

Figure 1 Clinical guideline for genetic testing based on the standardised clinical bedside tests.

Research paper

Table 2 Clinical features as obtained from the standardised neuromuscular examinations in the patients with chloride (ClCh; n = 32) and sodium channelopathies (NaCh; n = 30)

	ClCh	NaCh	p Value
Action myotonia right-hand flexor muscles, n (%)	29 (90.6)	27 (90.0)	0.93
Action myotonia leg muscles, n (%)	29 (90.6)	7 (23.3)	<0.001*
Percussion myotonia right abductor pollicis brevis, n (%)	28 (87.5)	26 (86.7)	0.92
Percussion myotonia right quadriceps, n (%)	27 (84.4)	17 (56.7)	0.02*
Myotonia in eyelid muscles, n (%)	15 (46.9)	29 (96.7)	<0.001*
Myotonia in right and flexor muscles, n (%)	29 (90.6)	29 (96.7)	0.32
Myotonia in leg muscles, n (%)	32 (100)	18 (60.0)	<0.001*
Mean relaxation time (s) of patients with myotonia in eyelid muscles after one contraction (SD), range	4.3 (3.7), 0.7 to 13.1	19.2 (14.1), 1.0 to 54.5	<0.001*
Mean relaxation time (s) of patients with myotonia in eyelid muscles after 10 contractions (SD), range	0.7 (0.8), 0 to 2.9	14.1 (18.0), 0 to 79.9	<0.001*
Mean relaxation time (s) of patients with myotonia in hand muscles after one contraction (SD), range	4.7 (3.9), 1.1 to 17.5	5.6 (6.5), 0.7 to 30.7	0.90
Mean relaxation time (s) of patients with myotonia in hand muscles after 10 contractions (SD), range	1.1 (1.2), 0 to 5.9	7.9 (19.3), 0 to 99.0	0.01*
Mean duration (s) of the chair test after rest (SD), range	12.5 (5.7), 5.2 to 29.9	6.3 (2.2), 4.0 to 15.5	<0.001*
Mean duration (s) of the chair test after 10 cycles (SD), range	7.0 (2.1), 4.3 to 15.3	5.7 (1.0), 4.0 to 8.9	<0.01*
Warm-up phenomenon, n (%)	30 (93.8)	23 (76.7)	0.05
Paradoxical myotonia, n (%)	0 (0)	9 (30.0)	<0.001*
Transient paresis, n (%)	20 (62.5)	0 (0)	<0.001*

*p<0.05.

absent OR if transient paresis is present (regardless of the absence or presence of eyelid myotonia) a ClCh is most likely (see table 6). Conversely, if eyelid myotonia is present, and transient paresis is absent, a NaCh is the most likely conclusion (table 6).

The sensitivity and specificity of this test for ClCh are 90.6% and 96.7%, respectively. Thus, the combination of the individual results and their multivariate regression analyses showed that the presence or absence of paramyotonia, transient paresis and eyelid myotonia discriminate between chloride and sodium channelopathies (fig 1).

DISCUSSION

In this systematic cross-sectional study with a thorough standardised clinical protocol and a robust methodology, we were able to redefine the clinical phenotypes of non-dystrophic myotonic syndromes. Using one of the largest genetically confirmed NDM cohorts of both ClCh and NaCh, we showed novel genotype–phenotype correlations and confirmed earlier ones. Previously, Becker and colleagues^{17 18} had thoroughly studied the clinical picture of NDM in the pregenetic era. Fialho *et al* recently reported a large cohort of ClCh,¹⁹ while Matthews *et al* described a large cohort of NaCh.²⁰ This study included both ClCh and NaCh, allowing a direct comparison of the two phenotypes.

The main result of our study is the high frequency and severity of myotonia in the eyelid muscles in NaCh and in the leg muscles in ClCh. Furthermore, we confirmed that transient paresis is a unique clinical feature for ClCh and paradoxical

myotonia for NaCh. Interestingly, the warm-up phenomenon was demonstrated in both NDM groups. Another remarkable finding is that 28.1% of the ClCh patients and 56.7% of those with NaCh experienced painful myotonia, whereas myotonia is usually considered painless.¹

The distribution pattern of myotonia in our study differs between ClCh and NaCh. Original reports described the distribution patterns of MC as generalised with leg muscles often severely affected.¹⁷ Rüdél *et al*,² Eulenburg⁶ and Streib²¹ reported a predilection of myotonia in PC for facial, tongue, throat and hand muscles. In Matthews' genetically confirmed PC population, 26 of the 32 patients reported myotonia in the face and the upper limbs.²⁰ Although we, as yet, have to do without an established explanation for the different distribution patterns of myotonia in ClCh and NaCh, we hypothesise that they may partly be explained by the fact that in most ClCh patients, the eyelid muscles are already “warmed up” as a result of blinking, while a subgroup of NaCh patients still show myotonia. Alternatively or concurrently, the distribution patterns of voltage-gated chloride and sodium channels may differ for the various muscles. For example, human facial muscles probably contain more sodium channels than human skeletal muscles.^{22 23}

The high incidence of the warm-up phenomenon (76.7%) in our NaCh group is remarkable. Initially, the warm-up phenomenon was predominantly reported for ClCh and was only rarely observed in NaCh.¹⁰ However, in about 20% of our patients with the initial suspicion of a “DMC” phenotype, we detected a mutation in *SCN4A* (NaCh).¹⁴ All these patients

Table 3 Clinical features as obtained from the standardised neuromuscular examinations in the patients with paramyotonia congenita (PC; n = 7) and sodium channel myotonias (SCM; n = 23)

	PC	SCM	p Value
Myotonia in leg muscles, n (%)	2 (28.6)	16 (69.6)	0.05
Action myotonia leg muscles, n (%)	0 (0%)	7 (30.4)	0.10
Percussion myotonia right quadriceps, n (%)	2 (28.6)	15 (65.2)	0.09
Warm-up phenomenon, n (%)	2 (28.6)	21 (91.3)	0.001*

*p<0.05.

Table 4 Results of the final logistic regression model with type of channelopathy as the dependent outcome measure (n = 62)

Predictors	B	SE	Wald	df	Significance	Odds ratio	95% CI for OR lower to upper
Myotonia in eyelid muscles	4.47	1.22	13.49	1	<0.001	87.00	8.023 to 943.355
Transient paresis	-22.69	7812.13	0.00	1	0.998	0.00	0.00 to ∞
Constant	-2.20	1.05	4.35	1	0.037	0.011	

were sodium-channel myotonias (SCM).¹⁴ Hence, the warm-up phenomenon is a clinical feature in RMC, DMC as well as SCM. Although the warm-up phenomenon has now been established as a clinical feature in both types of NDM, its pathophysiological mechanism is still unclear.²⁴

Transient paresis is a unique clinical feature in ClCh. The prevalence (62.5%) of this phenomenon in our patients with *CLCN1* mutations is comparable with earlier reports of RMC.^{25–26} This is congruent with the fact that only two of our patients were diagnosed as having DMC. Due to the patient distribution in The Netherlands, this phenomenon cannot distinguish RMC from DMC. However, Fialho *et al* showed that generalised muscle hypertrophy, transient paresis, and depressed tendon reflexes occurred more frequently in RMC than in DMC.¹⁹

In parallel with the transient paresis in ClCh, our study confirmed that paradoxical myotonia is unique for NaCh. However, the symptom was only observed in 30.0% of our NaCh patients, but it should be noted that we saw no patients with hyperkalaemic periodic paralysis with myotonia, only seven patients with PC and a relatively large number of patients with SCM. Furthermore, we only tested at room temperature. Future studies should also test patients at lower temperatures, although in these conditions some patients with PC will show paradoxical myotonia, while others will exhibit a flaccid (periodic) paralysis.²¹

A crucial point in the literature of NDM is the quantification of myotonia.²⁷ For this reason, dedicated equipment and computerised protocols to quantify myotonia in hand muscles have been employed.^{28–29} However, the purpose of our study was not to quantify myotonia in the hand muscles but to investigate, using a daily practice neurological examination, the clinical pattern of myotonia in three different body regions (face, hands, legs) for ClCh as well as for NaCh. Moreover, the employed devices are not useful for facial or for leg muscles. Therefore, we developed standardised clinical bedside tests, which are easily applicable in every outpatient clinic.¹⁰ We were the first to develop such a standardised, robust and detailed methodology for clinical bedside tests of myotonia in three different body regions. In fact, all patients showed clear myotonia in at least one body region. It is the ultimate goal to quantify these phenomena with special devices, as the resultant parameters will be important to set clinical endpoints in future randomised controlled trials. As we were aware of the crucial points about the quantification of myotonia, we only

used the presence or absence of the different clinical phenomena for our multivariate logistic regression analysis.

A formal test–retest assessment is the ultimate guarantee for the quality of our study. However, myotonia especially fluctuates under different conditions. We standardised these conditions. Furthermore, a trained clinical team pilot tested the draft standardised neuromuscular examination and also repeated this in several patients. We detected robust and reliable data. Subsequently, the clinical team amply trained one examiner who performed all clinical bedside tests. Finally, we have unpublished data of the same patient population for high-density surface EMG. Hereby, we also observed force profiles. Actually, all patients with a transient paresis in our study (n = 20) showed a decline in their force of the left biceps shortly after contraction (data not shown). Subsequently, all 20 patients showed an increase in their force after repetitive contractions. Since none of the other patients showed such force profiles, the presence of transient paresis was confirmed by a retest. Of course we are aware that such a good test–retest result is probably not the case for the warm-up phenomenon and paradoxical myotonia. However, the standardised interviews support these data.

The aim of our study was to redefine the clinical phenotypes of ClCh and NaCh. The results allowed us to propose clinical guidelines for genetic testing (fig 1). In 2006, Fournier *et al* proposed electrophysiological guidelines to focus genetic testing.³⁰ They distinguished between three different repetitive nerve stimulation patterns.³⁰ Since a repetitive nerve stimulation test detects hypoexcitability of the skeletal muscle membrane, clinically observed as muscle weakness, the clinical features observed in the different subgroups of non-dystrophic myotonias may explain the different patterns detected by Fournier. For instance, most patients with ClCh experience transient paresis followed by the warm-up phenomenon. This short period of muscle weakness corresponds with the initial hypo-excitability, followed by a progressive increase in CMAP amplitude after the short exercise test by Fournier (EMG pattern Pattern II). This effect is not shown in SCM. These patients do not show any kind of muscle weakness and also show a very stable repetitive nerve stimulation pattern (pattern III). The frequent warm-up phenomenon detected in these patients could be puzzling. However, the warm-up phenomenon in chloride channelopathies reduces transient paresis (muscle weakness) as well as myotonia. Since there is no muscle weakness in SCM, the warm-up phenomenon in SCM

Table 5 Test results of myotonia in eyelid muscles and transient paresis in the final model

Predictor	Model log	Change in -2log		Significance of change
	Likelihood	Likelihood	df	
Myotonia in eyelid muscles	-25.13	23.84	1	<0.001
Transient paresis	-32.09	37.77	1	<0.001

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Table 6 Cross-table showing the relationship between the clinical bedside tests (transient paresis and myotonia in eyelid muscles) and type of channelopathy (chloride channelopathies (ClCh) and sodium channelopathies (NaCh); n = 62)

Tests	ClCh	NaCh
Myotonia in eyelid muscles absent AND Transient paresis absent OR Transient paresis present	29	1
Myotonia in eyelid muscles present AND Transient paresis absent	3	29

probably only reduces myotonia. It would be interesting to correlate clinical and neurophysiological tests in the SCM in more detail. PC patients may show either paradoxical myotonia and/or weakness after successive short exercises or cold exposure. We only tested paradoxical myotonia and have no clinical correlate with the progressive hypo-excitability detected by Fournier (pattern I). Most probably successive short exercises of the same muscle group may clinically induce such a weakness in this group of patients. Finally, Fournier detected a hypo- or inexcitability of the muscle membrane after cold exposure in PC patients. We detected a paralysis of the hand muscles in two of the seven PC patients after cold exposure (data not shown). However, since it was too difficult to define a standardised clinical outcome measurement after cold exposure for PC patients (PC patients after cold exposure may show muscle weakness, paradoxical myotonia or paralysis), we removed this item from our protocol. Moreover, the clinical features in PC highly depend on the type of mutation.³⁰ Nevertheless, standardised clinical tests after cold exposure should also be developed.

CONCLUSIONS

We systematically investigated 62 patients with a genetically confirmed diagnosis of non-dystrophic myotonic syndromes and redefined the clinical phenotypes of chloride and sodium channelopathies. The results allowed us to propose clinical guidelines for genetic testing. These may at least help clinicians working in outpatient clinics to perform focused genetic analysis of either *CLCN1* or *SCN4A*. However, if this test is negative, the other gene should subsequently be analysed, too.

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REFERENCES

1. **Lehmann-Horn F**, Rüdel R, Jurkat-Rott K. Nondystrophic myotonias and periodic paralyses. In: Engel AG, Franzini-Armstrong C, eds. *Myology*. 3rd edn. New York: McGraw-Hill, 2004:1257–300.
2. **Rüdel R**, Ricker K, Lehmann-Horn F. Genotype–phenotype correlations in human skeletal muscle sodium channel diseases. *Arch Neurol* 1993;**50**:1241–8.
3. **Thomsen J**. Tonische Krämpfe in willkürlich beweglichen Muskeln in Folge von erebter psychischer Disposition (Ataxia muscularis?). *Arch Psychiatr Nervenkrankheiten* 1876;**6**:702–18.
4. **Becker PE**. Zur Frage der Heterogenie der erblichen Mytonien. *Nervenarzt* 1957;**28**:455–60.
5. **Drost G**, Blok JH, Stegeman DF, et al. Propagation disturbance of motor unit action potentials during transient paresis in generalized myotonia: a high-density surface EMG study. *Brain* 2001;**124**:352–60.
6. **Eulenburg A**. Über einer familiäre durch 6 Generationen verfolgbare Form kongenitaler Paramyotonie. *Neurol Zbl* 1886;**5**:265–72.
7. **Trudell RG**, Kaiser KK, Griggs RC. Acetazolamide-responsive myotonia congenita. *Neurology* 1987;**37**:488–91.
8. **Ricker K**, Moxley RT 3rd, Heine R, et al. Myotonia fluctuans. A third type of muscle sodium channel disease. *Arch Neurol* 1994;**51**:1095–102.
9. **Gamstorp I**. Adynamia episodica hereditaria. *Acta Paediatr* 1956;**45**:1–126.
10. **Trip J**, Faber CG, Ginjaar HB, et al. Warm-up phenomenon in myotonia associated with the V445M sodium channel mutation. *J Neurol* 2007;**254**:257–8.
11. **Barchi RL**. Phenotype and genotype in the myotonic disorders. *Muscle Nerve* 1998;**21**:1119–21.
12. **Jurkat-Rott K**, Lehmann-Horn F. Muscle channelopathies and critical points in functional and genetic studies. *J Clin Invest* 2005;**115**:2000–9.
13. **Lehmann-Horn F**, Rüdel R. Non-dystrophic myotonias and periodic paralyses. In: Emery AEH, ed. *Diagnostic criteria for neuromuscular disorders*. 2nd edn. London: Royal Society of Medicine Press, 1997:31–6.
14. **Trip J**, Drost G, Verbove DJ, et al. In tandem analysis of *CLCN1* and *SCN4A* greatly enhances mutation detection in families with non-dystrophic myotonia. *Eur J Hum Genet* 2008;**16**:921–9.
15. **Webster DD**. Critical analysis of the disability in Parkinson's disease. *Mod Treat* 1968;**5**:257–82.
16. **Medical Research Council**. *Aids to the investigation of the peripheral nervous system*. London: Her Majesty's Stationery Office, 1975.
17. **Becker PE**, Knusmann R, Kuhn E, eds. *Myotonia congenital and syndromes associated with myotonia: clinical-genetic studies of the nondystrophic myotonias*. Stuttgart: Thieme, 1977.
18. **Becker PE**, ed. *Paramyotonia congenita (Eulenburg)*. Stuttgart: Thieme, 1970.
19. **Fialho D**, Schorge S, Pucovska U, et al. Chloride channel myotonia: exon 8 hot-spot for dominant-negative interactions. *Brain* 2007;**130**:3265–74.
20. **Matthews E**, Tan SV, Fialho D, et al. What causes paramyotonia in the United Kingdom? Common and new *SCN4A* mutations revealed. *Neurology* 2008;**70**:50–3.
21. **Streib EW**. Paramyotonia congenita. *Semin Neurol* 1991;**11**:249–57.
22. **Caldwell JH**. Clustering of sodium channels at the neuromuscular junction. *Microsc Res Tech* 2000;**49**:84–9.
23. **Happak W**, Liu J, Burggasser G, et al. Human facial muscles: dimensions, motor endplate distributions, and presence of muscle fibers with multiple motor endplates. *Anat Rec* 1997;**249**:276–84.
24. **Van Beekvelt MC**, Drost G, Rongen G, et al. Na⁺–K⁺-ATPase is involved in the warming-up phenomenon in generalized myotonia. *Muscle Nerve* 2006;**33**:514–23.
25. **Koch MC**, Ricker K, Otto M, et al. Evidence for genetic homogeneity in autosomal recessive generalised myotonia (Becker). *J Med Genet* 1993;**30**:914–17.
26. **Deymeier F**, Cakirkaya S, Serdaroglu P, et al. Transient weakness and compound muscle action potential decrement in myotonia congenita. *Muscle Nerve* 1998;**21**:1334–7.
27. **Trip J**, Drost G, van Engelen BG, et al. Drug treatment for myotonia. *Cochrane Database Syst Rev* 2006;(1):CD004762.
28. **Logigian EL**, Blood CL, Dilek N, et al. Quantitative analysis of the "warm-up" phenomenon in myotonic dystrophy type 1. *Muscle Nerve* 2005;**32**:35–42.
29. **Moxley RT 3rd**, Logigian EL, Martens WB, et al. Computerized hand grip myometry reliably measures myotonia and muscle strength in myotonic dystrophy (DM1). *Muscle Nerve* 2007;**36**:320–8.
30. **Fournier E**, Viala K, Gervais H, et al. Cold extends electromyography distinction between ion channel mutations causing myotonia. *Ann Neurol* 2006;**60**:356–65.