Cold Extends Electromyography Distinction between Ion Channel Mutations Causing Myotonia

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Objective: Myotonias are inherited disorders of the skeletal muscle excitability. Nondystrophic forms are caused by mutations in genes coding for the muscle chloride or sodium channel. Myotonia is either relieved or worsened by repeated exercise and can merge into flaccid weakness during exposure to cold, according to causal mutations. We designed an easy electromyography (EMG) protocol combining repeated short exercise and cold as provocative tests to discriminate groups of mutations.

Methods: Surface-recorded compound muscle action potential was used to monitor muscle electrical activity. The protocol was applied on 31 unaffected control subjects and on a large population of 54 patients with chloride or sodium channel mutations known to cause the different forms of myotonia.

Results: In patients, repeated short exercise test at room temperature disclosed three distinct abnormal patterns of compound muscle action potential changes (I-III), which matched the clinical symptoms. Combining repeated exercise with cold exposure clarified the EMG patterns in a way that enabled a clear correlation between the electrophysiological and genetic defects.

Interpretation: We hypothesize that segregation of mutations into the different EMG patterns depended on the underlying pathophysiological mechanisms. Results allow us to suggest EMG guidelines for the molecular diagnosis, which can be used in clinical practice.

Ann Neurol 2006;60:356–365

Nondystrophic myotonic syndromes are disorders of the skeletal muscle excitability that lead to muscle stiffness and delayed relaxation after muscle contraction. Familial forms are due to mutations in genes coding for muscle voltage-gated ion channels.[1–3] Clinical studies have recognized several entities, according to natural history, mode of inheritance, signs, and symptoms. In myotonia congenita (MC), myotonia is increased after periods of rest and declines with repetition of movements (warm-up phenomenon). In paramyotonia congenita (PC), myotonia is conversely increased with exercise repetition (paradoxical myotonia) and cold. Mutations of the chloride channel gene *(CLCN1)* have been found to cause MC, whereas PC has been linked to mutations in the *SCN4A* gene, which encodes the α subunit of the voltage-gated sodium channel.[2,3] However, some mutations of the *SCN4A* gene, distinct of the latter, are linked to myotonic disorders without reinforcement of symptoms after exercise repetition, therefore mimicking chloride channel MC. These phenotypes are usually referred to as potassium-aggravated myotonia[1] or sodium channel myotonia (SCM) when the diagnosis is established without performing potassium-loading test, which is most frequently the case.[3,4]

Assessment of myotonic syndromes relies on the detection of myotonic discharges with needle electromyography (EMG). Several provocative tests using surface-recorded muscle responses have been proposed to distinguish the main clinical phenotypes before the advent of molecular diagnosis: repetitive nerve stimulation,[5,6] short exercise,[7,8] long exercise,[9,10] or cold ex-

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Received Jan 17, 2006, and in revised form Apr 20. Accepted for publication Apr 28, 2006.

This article includes supplementary materials available via the Internet at http://www.interscience.wiley.com/jpages/0364-5134/suppmat

Published online Jun 19, 2006, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20905

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posure.[8,11,12] In a recent study, we showed that changes of the compound muscle action potential (CMAP) after a repeated short exercise and after a long exercise allowed to separate muscle channelopathies into five patterns (I-V), linked to the main clinical phenotypes and to subgroups of ion channel mutations.[13] The first three patterns (I-III) are related to the discrimination of myotonic syndromes with repeated short exercise test (see Supplement 1), whereas patterns IV and V deal with the diagnosis of periodic paralyses by combining short and long exercise tests.

Although sensitivity of the repeated short exercise test was about 85% with respect to discrimination of myotonic syndromes, some mismatches between patterns impaired the predictive value of EMG at room temperature.[13] Because myotonia is enhanced by cold, we designed a straightforward protocol using both cooling and repeated short exercise as provocative tests. By including a large population of 54 patients, we were able to constitute several groups of patients sharing well-characterized ion channel mutations associated with the different forms of myotonia. Results showed that combining repeated exercise and cooling in a single test resulted in changes of muscle electrical response that strongly correlated with the genetic defects.

Subjects and Methods

Patients and Control Subjects

Patients with well-characterized clinical phenotypes and ion channel mutations[1–3] were included in this study. Sodium and chloride channel mutations were identified by bidirectional direct sequencing of polymerase chain reaction–amplified *SCN4A* and *CLCN*1 coding regions and intron–exon boundaries.[14]

Eighteen patients with a MC phenotype and chloride channel mutations were explored (age range, 15–70 years; mean age, 39 years). They were included in the study as two distinct groups according to the mode of inheritance determined by familial history and genetic analysis (see Supplement 2). One homozygous mutation or two different heterozygous mutations were identified in each of the 11 patients with recessive inheritance. Familial history suggested a dominant inheritance in the other seven patients. Five of these patients harbored chloride mutations (A313T, P480L), which have been linked previously in the literature to dominant transmission.[1]

We included 22 patients with a PC phenotype (age range, 6–53 years; mean age, 30 years). Nineteen of these patients, belonging to eight different families, carried one of the most frequent sodium channel mutations responsible for PC (T1313M, R1448C, R1448H). All of these patients reported muscle stiffness that was aggravated by repeated exercise or exposure to cold and could merge into flaccid weakness. In three patients belonging to the same family, molecular analysis showed a new sodium channel mutation, Q270K. These patients reported muscle stiffness and severe paralysis, both induced by cold; the PC phenotype was not clear at room temperature, but striking at cold.

We also examined 14 patients with sodium channel mutations and a SCM phenotype (age range, 9–62 years; mean age, 40 years). Although all these patients reported muscle stiffness that was neither aggravated by exercise repetition nor associated with weakness, there were some clinical differences between related mutations. The five patients who carried two of the most frequent sodium channel mutations associated with SCM (G1306A, G1306V) reported constant and painful muscle stiffness, which was poorly influenced by exercise. The other patients experienced a warm-up phenomenon, that is, a relief of muscle stiffness by exercise repetition and a worsening by rest, which is reminiscent of chloride channel MC. Although cold aggravated muscle stiffness, these patients did not describe cold-induced paralysis. Five of them carried one of the sodium channel mutations already described as responsible for SCM (V445M, V1293I) or a novel mutation (S804N) located at a codon where another missense mutation was already reported.[1] In the four remaining patients, molecular analysis showed two new SCN4A missense mutations, A715T and I1310N.

Altogether, a total of 54 patients (23 women, 31 men) with ion channel mutations (18 with chloride mutations, 36 with sodium mutations) were compared with a control group of 31 healthy subjects (16 women, 15 men; age range, 19–55 years; mean age, 32 years). MC patients were also compared with a group of seven patients with myotonic dystrophy (DM): four patients with Steinert myotonic dystrophy type 1 (DM1) and three with proximal myotonic dystrophy type 2 (DM2), well characterized both clinically and molecularly. The study was conducted after informed consent of each individual according to the European Union and French bioethics laws, as well as the Convention of Helsinki.

Electromyography Procedure

Patients and healthy control subjects were examined using a standardized EMG protocol derived from those previously described by our team.[13,15] CMAPs were recorded from right and left abductor digiti minimi muscles after electrical stimulation of the ulnar nerves at the wrist. Three provocative tests were performed successively: (1) repeated short exercise test at room temperature *on the right hand* (three abductor digiti minimi contractions of 10 seconds in duration, with 50-second rest interval), (2) cooling test of 7 minutes in duration *on the left hand,* (3) followed by repeated short exercise test at cold. Completion of the whole protocol required 15 to 20 minutes. Examinations were performed in Paris and Lyon, with excellent agreement for the results obtained in the two centers. Procedures of testing and statistical analysis are detailed in Supplement 3.

Results

Cold Alone Induces Similar Changes of Compound Muscle Action Potential in Control Subjects and Patients

In control subjects, the application of an ice bag on the abductor digiti minimi muscle induced a progressive spreading of the CMAP (Fig 1A). In patients with chloride and sodium mutations, changes in CMAP

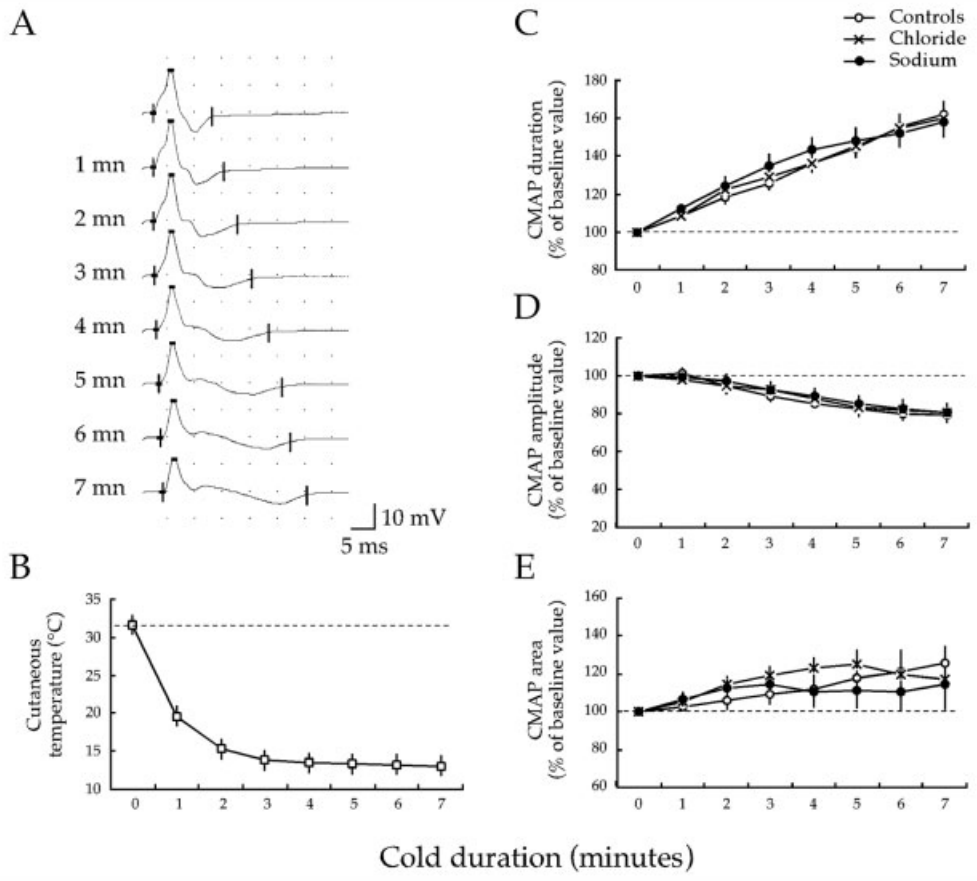

Fig 1. Cold test in control subjects and in patients carrying chloride or sodium channel mutations. (A) Representative increase of compound muscle action potential (CMAP) duration (+140%) and decrease of CMAP amplitude (−25%) in a healthy control subject. Top trace is a recording of the abductor digiti minimi CMAP after ulnar nerve stimulation at wrist at room temperature. Subsequent traces are successive recordings at different times during cold exposure as indicated left to the tracings. Scale between two dots: 5 milliseconds, 10mV. (B) Decrease of the skin temperature, close to the active recording electrode in control subjects. (C–E) Changes in CMAP during cold exposure in 31 healthy control subjects (open circles), *18 patients with chloride channel mutations* (crosses), *and 36 patients with sodium channel mutations* (solid circles). *The duration (C), amplitude (D), and area (E) of the CMAP expressed as a percentage of preexercise values are plotted against the duration of cold exposure.* Symbols *and* vertical bars *represent mean ± standard error of the mean.*

during the cooling test were not significantly different from those observed in control subjects (see Figs 1C–E). Surprisingly, this negative result held for all mutations, including T1313M or R1448C/H sodium channel mutations that caused unambiguous cold-induced paralysis. This led to study of the effects of exercise at cold by combining the two triggering factors.

Cold Precipitates and Aggravates the Pattern I Compound Muscle Action Potential Changes Induced by Exercise in Patients with Paramyotonia Congenita

Repeated short exercise induced marked CMAP changes at room temperature in PC patients carrying the T1313M, R1448C, or R1448H sodium channel mutations (Fig 2D). Immediately after the first exercise, the first component of the CMAP response was slightly reduced in amplitude (mean ± standard error of the mean: −19 ± 7%; $p < 0.05$; range, −64/+26%) and was followed in 17 of 19 patients by 1 to 7 extra discharges of decreasing amplitudes (see Fig 2E). These repetitive discharges that we previously termed *postexercise myotonic potentials* (PEMPs)[13] were present only in the first recordings performed within 10 to 30 milliseconds after exercise completion.

When exercise was repeated, the decline in CMAP amplitude worsened with successive trials (−57 ± 6%; $p < 0.001$, after the third trial), with no recovery during rest intervals (see Fig 2D). This *pattern I* profile correlated with the weakness induced by exercise repetition in these patients. PEMPs recorded after the first trial either decreased in amplitude or did not reappear with the repetition of exercise and the decline in CMAP amplitude.

When repeated short exercise was performed at cold on the contralateral hand in the same patients, there was a drastic decline in CMAP immediately after the

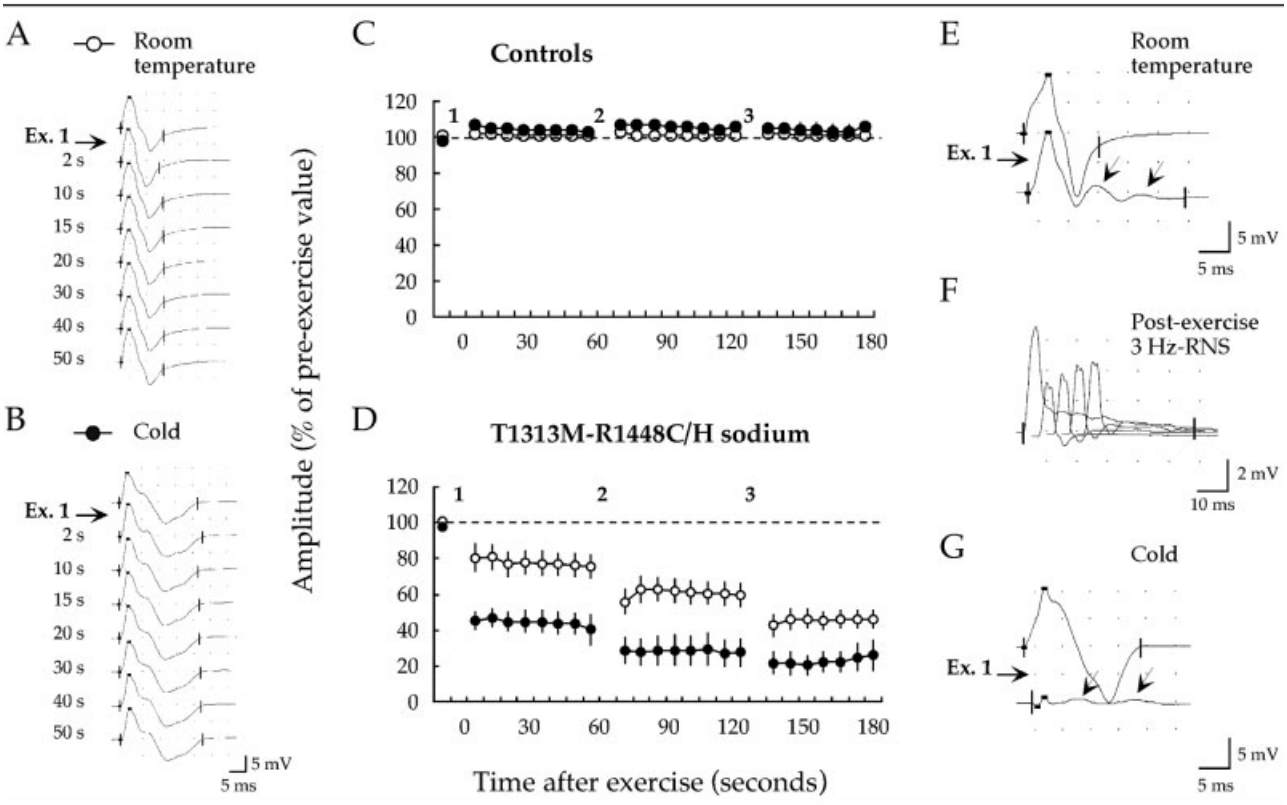

Fig 2. Repeated short exercise test in unaffected control subjects and paramyotonia congenita (PC) patients with T1313M, R1448C, or R1448H sodium channel mutations. (A, B) Recordings of the abductor digiti minimi compound muscle action potential (CMAP) in a control subject during the first of three successive short exercises performed at room temperature on the right hand (A) and after 7 minutes of cold exposure on the left hand (B). Top traces are preexercise recordings. Subsequent traces are postexercise recordings at different times during the 50-second resting period, as indicated left to the tracings. Scale between two dots: 5 milliseconds, 5mV. (C, D) Changes in CMAP amplitude after each of the three exercises (noted as 1, 2, 3*) in 31 unaffected control subjects (C) and in 18 PC patients with T1313M, R1448C, or R1448H sodium channel mutations (D), at room temperature* (open circles) *and at cold* (solid circles). *The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial.* Symbols *and* vertical bars *represent mean ± standard error of the mean. (E, G) CMAP responses in a T1313M patient before and 2 seconds after the first exercise performed at room temperature (E) and at cold (G). Note the appearance of postexercise myotonic potentials (PEMPs) (*arrows *indicate extra potentials). Scale between two dots: 5 milliseconds, 5mV. (F) Repetitive stimulation of the ulnar nerve (RNS; 5 stimuli at 3Hz) 2 seconds after the first exercise performed at room temperature in another T1313M patient. Note the decrease in CMAP amplitude response during the train, with a 61% decrement between the first and the second response. Note also that the PEMPs, elicited by the first stimulation, did not reappear after the stimulations. Scale between two dots: 10 milliseconds, 2 mV.*

first exercise ($-55 \pm 5\%$; $p < 0.001$), equivalent to the effect of three successive exercises at room temperature (see Figs 2D, G). PEMPs were regularly recorded immediately after the first exercise at cold (see Fig 2G). With exercise repetition, the decline in CMAP became more and more pronounced in all patients with T1313M or R1448C/H mutations ($-80 \pm 5\%$; $p < 0.001$, after the third trial, ranging from -47 to -95%), whereas PEMPs did not reappear (see Supplement 4).

Cold Emphasizes or Shows the Pattern II Compound Muscle Action Potential Changes Induced by Exercise in Patients with Chloride Channel Myotonia

In most of the MC patients with well-defined chloride channel mutations, repeated short exercise at room temperature induced CMAP changes that followed a *pattern II* profile: the first exercise caused a significant decrease of CMAP amplitude ($-37 \pm 6\%$; $p < 0.001$); amplitudes returned to normal values within 20 to 40 seconds after exercise cessation (Figs 3A, B); and when exercise was repeated, the postexercise decrease in CMAP amplitude diminished with successive trials ($-11 \pm 4\%$; $p < 0.01$, after the third trial) and was concomitant with the clinical warm-up phenomenon.

Performing the repeated short exercise at cold on the contralateral hand caused postexercise reduction in CMAP amplitude, which matched the pattern II profile (see Fig 3B). However, the declines in CMAP amplitude were significantly emphasized when repeated

short exercise was performed at cold rather than at room temperature, as compared in all MC patients with paired t test ($p < 0.001$).

Further analysis of the effect of exercise according to the mode of inheritance indicated that, in patients with recessive mutations, the first exercise induced a significant drop in CMAP amplitude at room temperature ($-51 \pm 7\%$; $p < 0.001$) that was not modified by cold (see Fig 3C). Conversely, in patients with dominant mutations, CMAP amplitude remained unchanged at room temperature ($-11 \pm 6\%$; p value not significant), but significantly declined when exercise was performed at cold ($-42 \pm 7\%$; $p < 0.001$) (see Fig 3D). Pattern II profile was also observed in myotonic dystrophy patients carrying either the DM1 or DM2 mutations (see Fig 3E), with an average postexercise decrease in CMAP amplitude ($-28 \pm 6\%$; $p < 0.001$) not statistically different from that observed in MC patients with chloride mutations. Cooling did not modify this transient decrement.

Cold Shifts Compound Muscle Action Potential Changes from Pattern II to Pattern I in Some Paramyotonia Congenita Patients

In two of the three PC patients with Q270K sodium channel mutation, repeated short exercise at room temperature caused pattern II CMAP changes similar to those observed in MC patients with recessive chloride mutations, that is, a marked and transient decrease in amplitude immediately after the first exercise ($-60 \pm 12\%$; $p < 0.001$) that disappeared with exercise repetition (Fig 4A). In the three patients, small PEMPs were recorded immediately after the first exercise.

Cold induced two striking changes in Q270K patients. The first was a pattern inversion. Repeated short exercise at cold induced a pronounced decline in

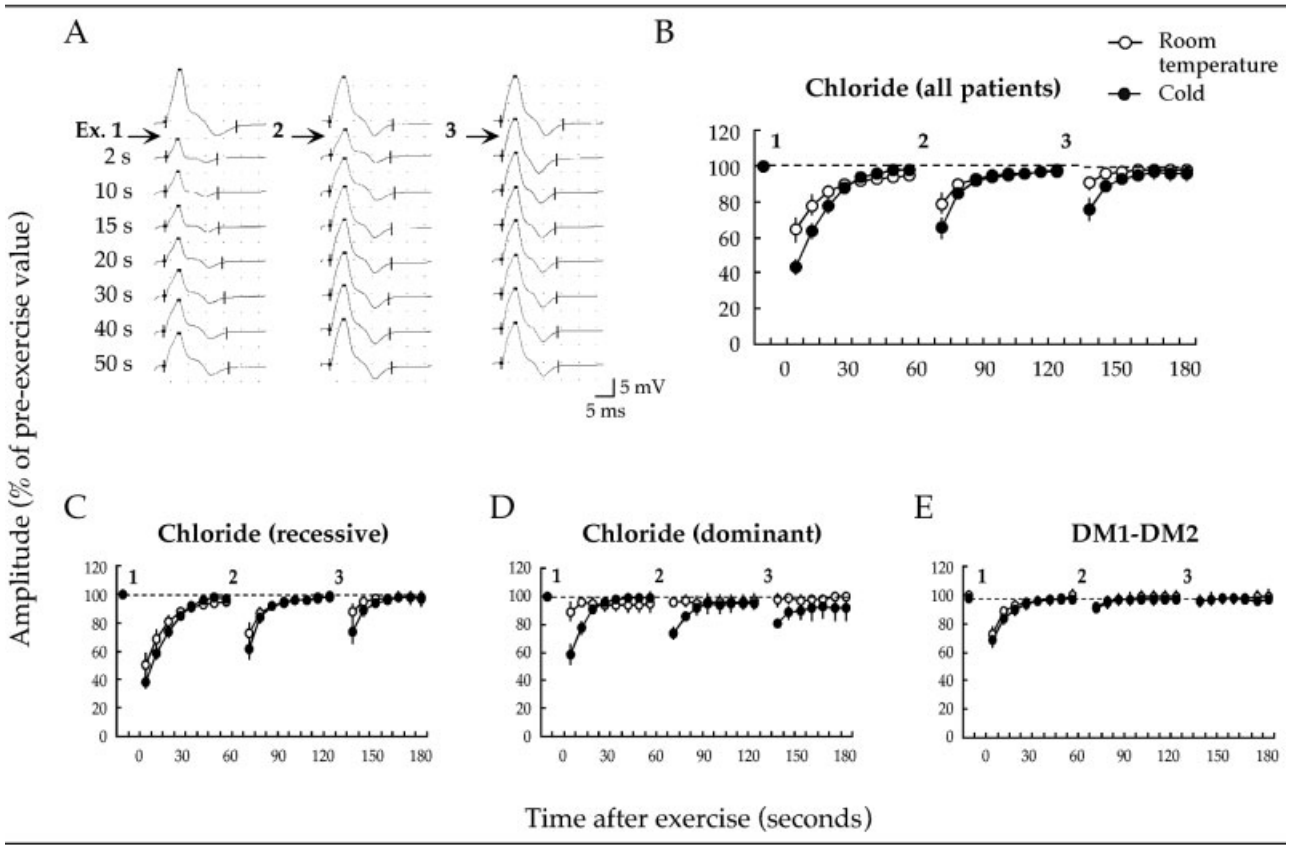

Fig 3. Repeated short exercise test in myotonia congenita (MC) patients with chloride channel mutations and in myotonic dystrophy (DM) patients. (A) Three successive short exercises (Ex. 1, 2, 3) performed at room temperature in a MC patient carrying the Q807X homozygous chloride channel mutation. Top traces are preexercise recordings. Subsequent traces are postexercise recordings at different times during the 50-second resting periods, as indicated left to the tracings. Note that the decrease in compound muscle action potential (CMAP) amplitude is gradually relieved with exercise repetition (−81%, −37%, −19%). Scale between two dots: 5 milliseconds, 5mV. (B–E) Changes in CMAP amplitude after the three exercise trials (noted as 1, 2, 3*) in all 18 MC patients with CLCN1 mutations (B), in the 11 MC patients with recessive CLCN1 mutations (C), in the 7 MC patients with dominant CLCN1 mutations (D), and in the 7 patients with DM1 or DM2 mutations (E), at room temperature* (open circles) *and at cold* (solid circles). *The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial.* Symbols *and* vertical bars *represent mean ± standard error of the mean.*

CMAP amplitude, worsening with exercise repetition ($-84 \pm 3\%$; $p < 0.001$), without recovery between the trials (see Fig 4A), that is, a pattern I profile, reminiscent of the effects of exercise at cold in PC patients with T1313M/R1448C/H mutations. Second, in all Q270K patients, the CMAP elicited after the first exercise at cold were followed by postexercise waves (PEWs see Fig 4B) somewhat different from PEMPs (see Supplement 5).

Cold Shows Compound Muscle Action Potential Changes Reminiscent of Pattern I in Sodium Channel Myotonia Patients with Particular Mutations

In agreement with the clinical absence of exercise-induced weakness, 12 of 14 SCM patients displayed a *pattern III* at room temperature, that is, no CMAP decline after repeated short exercise (see Figs 4D–F), even though myotonic discharges were detected by needle EMG.

Exercise repetition at cold induced no significant CMAP change in the patients carrying one of the most frequent SCN4A mutations responsible for SCM (see Figs 4E, F). In contrast, performing repeated short exercise at cold unveiled a pattern shift in all patients with A715T or I1310N mutations (see Fig 4D). A transient decrease of CMAP amplitude was evidenced, which worsened from the first ($-16 \pm 5\%$; $p < 0.01$) to the third exercise ($-51 \pm 12\%$; $p < 0.001$). Although this progressive decrement with exercise repetition was reminiscent of pattern I, the reduction in CMAP amplitude was less marked than that observed in PC patients, with a partial recovery within 30 seconds after the end of exercise. We propose to classify this *forme fruste* as a *partial form of pattern I* (see Supplement 6).

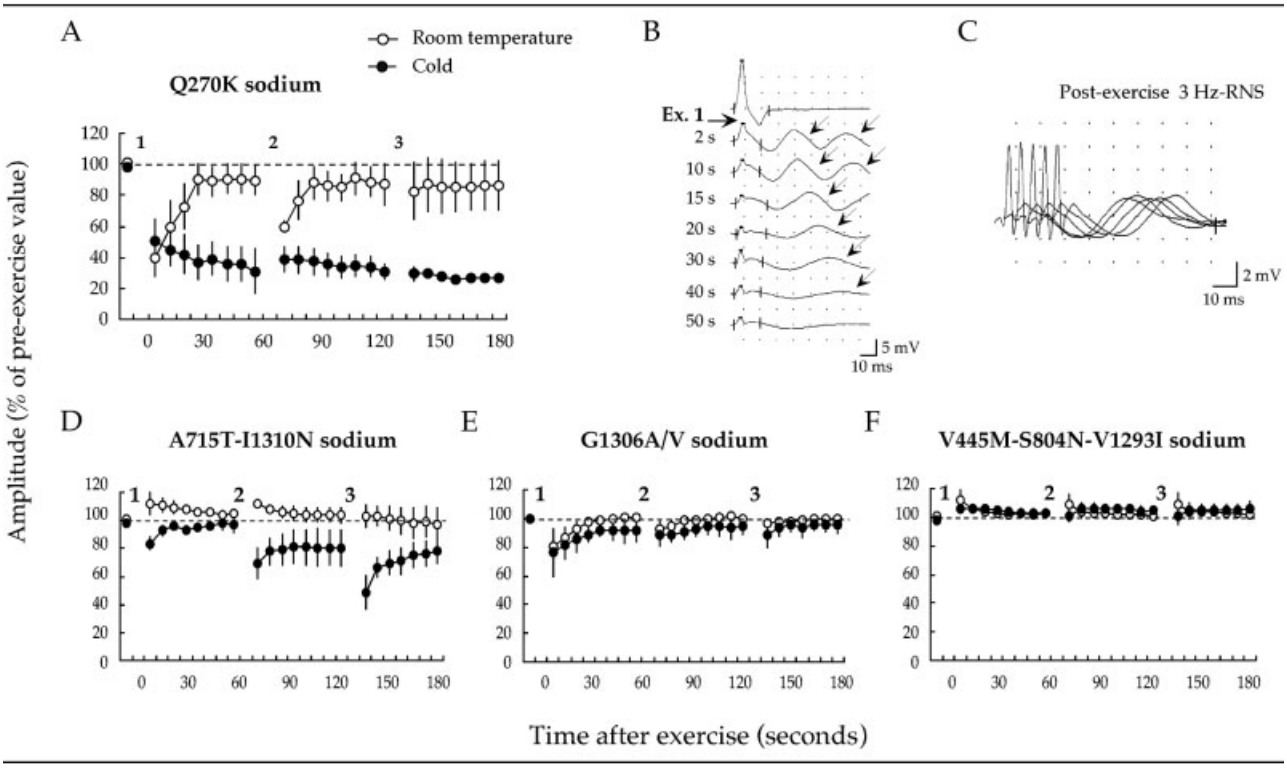

Fig 4. Repeated short exercise test in paramyotonia congenita (PC) patients with Q270K sodium channel mutations and sodium channel myotonia (SCM) patients. (A, D–F) Changes in compound muscle action potential (CMAP) amplitude after three short exercises (noted as 1, 2, 3*) in three PC patients with Q270K sodium channel mutations (A), in four SCM patients with A715T or I1310N sodium channel mutations (C), five SCM patients with G1306A or G1306V sodium channel mutations (D), and five SCM patients with V445M, S804N, or V1293I sodium channel mutations (E), at room temperature* (open circles) *and at cold* (filled circles). *The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial.* Symbols *and* vertical bars *represent mean ± standard error of the mean. (B) CMAP recordings before (top trace) and at different times after the first short exercise performed at cold in a patient carrying the Q270K sodium channel mutation. Note the decrease in CMAP amplitude and the appearance of postexercise waves (PEWs;* arrows*). Scale between two dots: 10 milliseconds, 5mV. (C) Repetitive stimulation of the ulnar nerve (RNS; 5 stimuli at 3Hz) 2 seconds after the first exercise performed at cold in another Q270K patient. Note that PEWs persisted after each CMAP during the 3Hz stimulation. Scale between two dots: 10 milliseconds, 2mV.*

Cold Helps Discriminate between Phenotypes When Combined with Repeated Short Exercise

The distribution of electrophysiological phenotypes at room temperature and at cold was analyzed for the different groups of mutations (Table). Pattern I was observed in the 22 PC patients carrying either one of the most recurrent mutations responsible for PC (T1313M or R1448C/H) or the Q270K mutation. At room temperature, pattern I was displayed by all these patients except three, who displayed pattern II. It was unmistakable at cold in all the 22 PC patients. Pattern I was also observed in a partial form in the four SCM patients with A715T or I1310N mutations, but not in the other SCM patients or in the MC patients.

At room temperature, the group of patients with pattern II was mainly composed of 91% of MC patients with recessive chloride channel mutations, whereas the group of patients with pattern III gathered 86% of the MC patients with dominant chloride channel mutations and 79% of the SCM patients. Cold clarified the correlations between EMG and genetic defects: 100% of the recessive and 71% of the dominant MC patients displayed pattern II after exercise at cold, whereas pattern III was composed with 80% of the SCM patients carrying the G1306A/V, V445M, S804N, or V1293I mutations. Finally, each of patterns II and III included two mismatched patients, with mutations of sodium and chloride channel genes, respectively.

Discussion

A new EMG protocol, painless and easy to apply, was designed to compare the effects of cold and repeated short exercise in a large population of patients with various mutations of chloride and sodium channels causing myotonia. As reported previously,[13] repeated short exercise at room temperature disclosed three distinct patterns of changes in muscle electrical activity (patterns I-III), which nicely correlated with the clinical symptoms. Although cold alone induced no significant effect, its combination with repeated exercise clarified the EMG patterns, which enabled clear correlations between the EMG outcome and the genetic defect. We hypothesize that mutations were segregated into the different EMG patterns according to the underlying pathophysiological mechanisms.

Distinctive Electromyography Signs of Sodium Channel Mutations Responsible for Paramyotonia

All patients but one who carried one of the most frequent sodium channel mutations responsible for PC (T1313M, R1448C, R1448H) displayed pattern I at room temperature. This pattern is characterized by a postexercise decrease of the muscle electrical response, aggravated by exercise repetition, with occurrence of PEMPs. T1313M and R1448C/H mutations induced both a marked slowing of sodium channel inactivation and an increase in the sustained current.[16–18] These effects can account for membrane hyperexcitability with myotonia or membrane inexcitability with paralysis, according to the degree of depolarization.[17,19] Accumulation of external K^+ by repeated exercise will further enhance membrane depolarization, ultimately leading to sarcolemma inexcitability and muscle weakness.

Exposure to cold accelerated and reinforced the exercise-induced decline in muscle excitability. Notably, by itself, cold did not impair the responsiveness of muscle fibers. In vitro electrophysiological studies have shown that cooling induces a membrane depolarization by slowing both channel kinetics[20] and the activity of the sodium/potassium pump.[21] One may suggest that in PC, cold adds its depolarizing effects to those of repeated exercise, thereby precipitating muscle excitability failure.[22,23]

On exposure to cold, pattern I was shared by all patients with T1313M, R1448C, or R1448H mutations and by patients carrying the new SCN4A mutations, Q270K, A715T, or I1310N. Most of the latter dis-

Table. Distribution of the Electromyography Patterns after Repeated Short Exercise Test at Room Temperature and at Cold

Clinical Phenotype	Mutations	Patients, n	Pattern of Response to Repeated Short Exercise at Room Temperature			Pattern of Response to Repeated Short Exercise at Cold		
			I	II	III	I	II	III
PC	*SCN4A*: T1313M, R1448C, or R1448H	19	**95%**	5%	0%	**100%**	0%	0%
PC	*SCN4A*: Q270K	3	33%	**66%**	0%	**100%**	0%	0%
MC	*CLCN*1 (recessive)	11	0%	**91%**	9%	0%	**100%**	0%
MC	*CLCN*1 (dominant)	7	0%	14%	**86%**	0%	**71%**	29%
SCM	*SCN4A*: A715T or I1310N	4	25%	0%	**75%**	**100%***	0%	0%
SCM	*SCN4A*: G1306A or G1306V	5	0%	40%	**60%**	0%	40%	**60%**
SCM	*SCN4A*: V445M, S804N, or V1293I	5	0%	0%	**100%**	0%	0%	**100%**

PC = paramyotonia congenita; MC = myotonia congenita; SCM = sodium channel myotonia. * = partial I; boldface denotes main pattern.

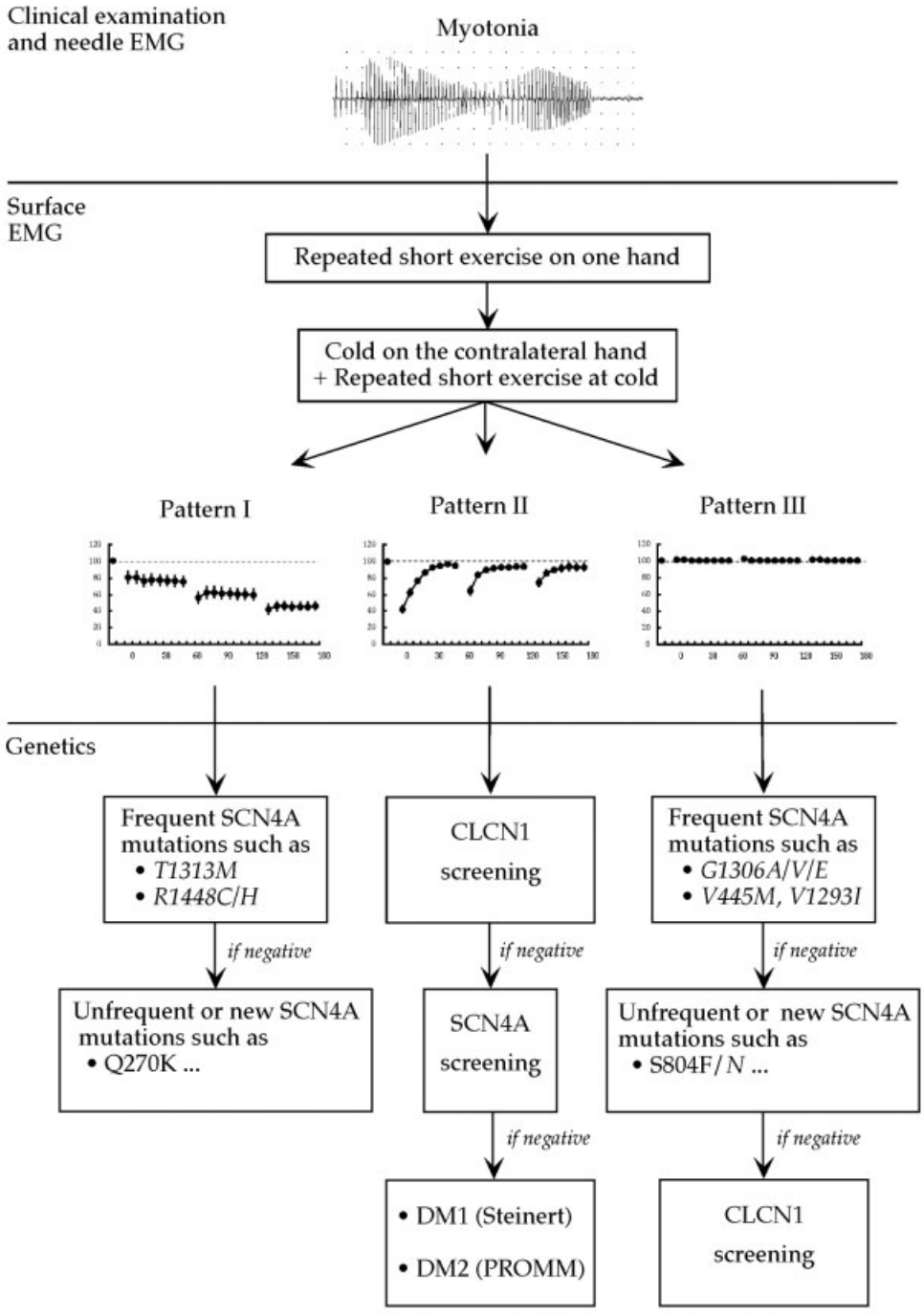

Fig 5. Genetic guidelines based on the electromyography (EMG) patterns obtained by repeated short exercise test and cold.

played patterns II or III at room temperature, mimicking MC or SCM phenotypes, so that cold unveiled EMG defects that were not noticeable at room temperature (see Supplements 5 and 6).

On the whole (Fig 5), we propose that in clinical practice, the observation of pattern I guides toward the most recurrent SCN4A mutations responsible for PC (T1313M, R1448C, and R1448H). If such analysis turns out to be negative, we suggest searching for new SCN4A mutations, such as Q270K or, in case of partial pattern I, A715T or I1310N.

Discrimination between Chloride and Sodium Channel Mutations

At room temperature, almost all MC patients with recessive chloride channel mutations displayed a transient decrease of CMAP amplitude when a short exercise was performed after rest. Pattern II is characterized by a

CMAP recovery with exercise repetition and is in line with the well-established clinical feature that in MC patients, myotonia is relieved by exercise. This may be related to some physiological processes that normally participate in membrane repolarization after exercise, such as an increased activity of the sodium/potassium pump. Conversely, most MC patients with dominant chloride channel mutations did not show any change in CMAP after exercise (pattern III). This difference was in agreement with previous reports that showed lower decrements of CMAP with a 10Hz repetitive stimulation in dominant versus recessive MC.[6,24,25]

Interestingly, our results showed that cold unveiled a significant decrease in CMAP after exercise in many patients with dominant chloride mutations; this result was a reversal from pattern III to II with an increased sensitivity of the tests with respect to discrimination of chloride mutations. When EMG at cold shows pattern II, we suggest screening first the CLCN1 chloride channel gene and second the SCN4A gene, because pattern II was also found in two patients carrying G1306A/V sodium channel mutations (see Fig 5). At last, if the CLCN1 and SCN4A analysis remains negative, we recommend looking for myotonic dystrophy mutations. Indeed, although clinical and familial features are usually different, most patients with DM1 or DM2 mutations displayed pattern II in the same way as patients with chloride channel defects. This result is in accordance with the demonstration of chloride channel dysfunction in myotonic dystrophy.[26]

Distinctive Electromyography Signs of Sodium Channel Mutations Responsible for Sodium Channel Myotonia

At room temperature, most SCM patients did not show any change in CMAP after exercise and belonged to pattern III together with dominant chloride channel mutants. Although exposure to cold induced a shift from pattern III to II in chloride channelopathies, it split SCM patients into partial pattern I and pattern III. As discussed earlier, exercise repetition at cold induced a progressive CMAP decline (partial pattern I) in patients with A715T or I1310N mutations. This was not observed in most patients carrying frequently encountered SCM mutations (G1306A/V, V445M, or V1293I), for whom excitability was not altered by combining exercise and cold trials. This EMG outcome fits nicely with the symptoms, because patients with pattern III displayed neither exercise- nor cold-induced episodes of muscle weakness (see Supplement 7).

We propose that the observation of pattern III after cold exposure guides toward the most recurrent mutations responsible for SCM (G1306A/V, V445M, S804N, and V1293I; see Fig 5). If SCN4A screening remains negative, the CLCN1 gene must be analyzed.

Overall, combining exercise repetition with cold exposure makes the EMG examination powerful enough to guide the molecular diagnosis in clinical practice with a good predictive efficiency.

We thank the members of Résocanaux for fruitful discussions and acknowledge the support of groupement d'Intérêt Scientifique-Institut des Maladies Rares.

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