Neuromuscular excitability changes produced by sustained voluntary contraction and response to mexiletine in myotonia congenita

Modifications d'excitabilité neuromusculaire produites par une contraction volontaire prolongée et réponse à la mexilétine dans la myotonie congénitale

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KEYWORDS
Chloride conductance;
Myotonia;
Natural activity;
Sodium channel;
Weakness

Summary
Objective. —To investigate the cause of transient weakness in myotonia congenita (MC) and the mechanism of action of mexiletine in reducing weakness.
Methods. —The changes in neuromuscular excitability produced by 1 min of maximal voluntary contractions (MVC) were measured on the amplitude of compound muscle action potentials (CMAP) in two patients with either recessive or dominant MC, compared to control values obtained in 20 healthy subjects. Measurements were performed again in MC patients after mexiletine therapy.

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Results. — Transient reduction in maximal CMAP amplitude lasting several minutes after MVC was evident in MC patients, whereas no change was observed in controls. Mexiletine efficiently reduced this transient CMAP depression in both patients.

Discussion. — Transient CMAP depression following sustained MVC may represent the electrophysiological correlate of the weakness clinically experienced by the patients. In MC, the low chloride conductance could induce self-sustaining action potentials after MVC, determining progressive membrane depolarization and a loss of excitability of muscle fibers, thus resulting in transient paresis. Mexiletine may prevent conduction block due to excessive membrane depolarization, thus reducing the transient CMAP depression following sustained MVC.

Résumé

Objectif. —Étudier la cause de la faiblesse transitoire dans la myotonie congénitale (MC) et le mécanisme d'action de la mexilétine pour la réduire.

Méthodes. — Les modifications d'excitabilité neuromusculaire produites par 1 min de contraction volontaire maximale ont été mesurées sur l'amplitude du potentiel global d'action musculaire (PGAM) chez deux patients présentant une MC récessive ou dominante, comparativement aux valeurs témoins obtenues chez 20 sujets sains. Les mesures ont été effectuées à nouveau chez les patients MC après traitement par la mexilétine.

Résultats. —La réduction transitoire de l'amplitude maximale du PGAM était évidente pendant plusieurs minutes après contraction volontaire maximale chez les patients MC, alors qu'aucun changement n'était observé chez les témoins. La mexilétine a efficacement réduit cette dépression transitoire du PGAM chez les deux patients.

Discussion. —La dépression transitoire du PGAM après contraction volontaire maximale soutenue peut représenter la corrélation électrophysiologique de la faiblesse observée cliniquement chez les patients. Dans la MC, la faible conductance du chlore pourrait induire des potentiels d'action auto-entretenus après contraction volontaire soutenue, déterminant une dépolarisation membranaire progressive et une perte d'excitabilité des fibres musculaires, résultant alors en une parésie transitoire. La mexilétine pourrait empêcher le bloc de conduction d'apparaître en raison d'une dépolarisation membranaire excessive, réduisant ainsi la dépression transitoire du PGAM après contraction soutenue.

Introduction

Myotonia congenita (MC) is an inherited disorder characterized by delayed muscle relaxation and stiffness after voluntary activation. It is caused by mutations of *CLCN1*, which encodes the CLC-1 chloride channel of skeletal muscle fibers. Both autosomal dominant (Thomsen's myotonia) and autosomal recessive (Becker's myotonia) forms are known [17].

The major clinical manifestation of MC is muscle stiffness (myotonia) resulting from abnormal membrane over-excitation. With repeated movements, the intensity of myotonia diminishes over seconds to minutes and may even become asymptomatic, a phenomenon called ''warm-up''. The chloride conductance ensures the electrical stability of the human muscle membrane and is crucial for countering the depolarizing effect of K^+ accumulation in T-tubules during the action potential. In MC subjects, the tubular potassium accumulation resulting from the initially driven activity and the low chloride conductance of myotonic muscle fibres appear to be responsible for the initiation of the myotonic discharge [32].

Additional common symptoms of MC include pain, weakness and fatigue [36—38]. In particular, MC patients complain of transient weakness that appears when the muscles are activated after a period of rest; moreover, in some cases the force in relation to muscle volume is constantly reduced [4,8,22,24,35]. However, transient weakness is only rarely reported by patients, who are usually unable to distinguish the stiffness secondary to myotonia from fatigue and weakness following muscle activity.

Brown [4] first observed that a decremental evoked compound muscle action potential (CMAP) was noticeable when myotonic patients attempted sustained activity after rest. The fade of the evoked response was correlated with the timing of a previous conditioning stimulus train or voluntary contraction [4]. At present, the analysis of CMAP size variations in response to short or long exercise tests has become useful in differentiating muscle channelopathies and improving knowledge about their pathogenesis [10,17,27,31].

In the present paper, CMAP changes were recorded before and after 1 min of maximal voluntary contraction (MVC) in two subjects with MC, one with Thomsen's myotonia and another with Becker's myotonia. The results were compared with those of 20 healthy subjects. In both patients, the study was repeated after introduction of mexiletine therapy. Although the effectiveness of mexiletine on both stiffness

and weakness in MC has been demonstrated [29], little is known on the mechanism underlying the effect of mexiletine in reducing weakness.

Methods

Patient 1 (Thomsen's myotonia)

A 40-year-old man presented with a history of stiffness secondary to myotonia from early childhood. The stiffness improved with activity ('warm-up' phenomenon) and got worse with cold temperatures. To assess facial myotonia, the patient was asked to squeeze his eyes and his lips closed for five seconds then rapidly open them. To assess limb function, myotonia was considered present if there was inability to release *hand grip and if there was the* likelihood of tripping and falling when walking. Myotonia was present in all four limbs and facial muscles, hampering the patient in daily life (Video 1). In addition, the patient described weakness after prolonged exercise. Physical examination revealed generalized muscle hypertrophy, most prominent in calves, without apparent loss of muscle strength. However, the patient perceived a drop of power during sustained voluntary activity after rest. This experience was clearly different from the myotonic stiffness and could be detected by clinical examination in both upper and lower extremities. The transient weakness was evaluated with the Medical Research Council (MRC) scale for muscle strength: shortly after the beginning of the muscle contraction there was a decrease of the MRC score (from 5 to 3 or 4) in distal and proximal muscles.

A needle electromyogram (EMG) of both proximal and distal muscles (rectus femoris, tibialis anterior, biceps brachii, extensor carpi radialis, first dorsal interosseus muscles) demonstrated profuse myotonic discharges. Motor unit potentials were of normal morphology. Nerve conduction study of the upper and lower limbs revealed a mild reduction of sensory action potential amplitude of the sural nerves (3 and 4 μ,V), indicating a length-dependent mild sensory axonal polyneuropathy, only affecting the lower limbs. The *CLCN1* gene was screened. Sequence analysis evidenced the heterozygous G/T change at the aminoacidic position 859, leading to the novel p.Gly859Val variant. All the 180 Italian control chromosomes screened were negative for the mutation. The possible pathogenicity was evaluated by the online analysis tools MUTPRED (http://mutpred.mutdb.org) and SIFT (http://sift.jcvi.org), and both indicated p.Gly859Val as damaging. Furthermore, Gly859 is located in CBS2, a domain essential in chloride channel functionality. Unfortunately, DNA samples of the other family members were not available to investigate the hereditary pattern, and to draw a pedigree. Mexiletine was started at a daily dose of 400 mg (200 mg bid) and was then incremented to 600 mg/day (200 mg tid) with a dramatic reduction of myotonia, ''warm-up'' phenomenon, and clinical improvement of muscle strength during sustained activity in the four limbs (Video 2).

Patient 2 (Becker's myotonia)

A 38-year-old woman complained from childhood of stiffness that improved with activity (''warm-up'' phenomenon)

and worsened with cold. In addition, she described weakness after prolonged exercise. The clinical examination was performed in the same manner as described above for patient 1. Mild myotonic phenomenon was evident only in the hands. Physical examination revealed muscle hypertrophy, most prominent in pelvic girdle and quadriceps muscles without *hypostenia.* The transient weakness was perceived by the patient as an unexpected lapse of power during sustained activity, mostly in the distal muscles. An EMG showed the presence of myotonic discharges mainly involving the distal muscles of the upper and lower limbs. Motor unit potentials were of normal morphology. The nerve conduction study was normal. Analysis of *CLCN1* revealed the known mutation p.Phe167Leu (exon 4) and the novel p.Ser289Arg (exon 8) substitution in compound heterozygous state. Mexiletine 400 mg/day (200 mg bid) was started leading to marked improvement of the symptomatology. In particular, the myotonic phenomenon almost disappeared with improvement of muscle strength during sustained activity in the four limbs.

Electrophysiology

Both the electrophysiological and clinical tests were performed before patients were put on mexiletine, and three months after initiation of this treatment. In both patients, examinations were carried out at the same time of the morning. The post mexiletine tests were performed about three hours after mexiletine intake.

To carry out repetitive nerve stimulation studies (RNS), ulnar nerve was stimulated at the wrist. The peak-to-baseline amplitude and the negative peak area of the motor response potentials from abductor digiti minimi (ADM) muscle were measured, and the percentage decrement was calculated between the 1st and 10th responses. Any decremental response of 10% or more was considered abnormal. RNS was performed at 3 Hz, 5 Hz, and 10 Hz.

The CMAPs were evoked in ADM by electrical stimuli applied to the ulnar nerve at the wrist. We examined the changes in size of the maximum CMAP before and after MVC of ADM for 1 minute. During the electrophysiological test, the subjects were lying supine on a bed, with their right arm placed parallel to the body, in a neutral position. Special care was taken to prevent any change of position of the wrist and finger joint during ADM contraction and in subsequent minutes. The stimuli were delivered before MVC, immediately after MVC, and at 1-3-5-7 and 10 minutes post-MVC.

The intensity of stimulation was fixed at the level required to obtain a maximum CMAP before contraction, and then kept constant over the entire study period. Data were compared with those obtained in 20 control subjects (ten females and ten males; age range, 25—55 years). The controls were healthy volunteers selected from the medical, paramedical and administrative staff of our department. All CMAPs values were normalized to their maximum (expressed in percentage).

The ethics committee of University of Siena, Italy, approved the study and all patients gave written informed consent.
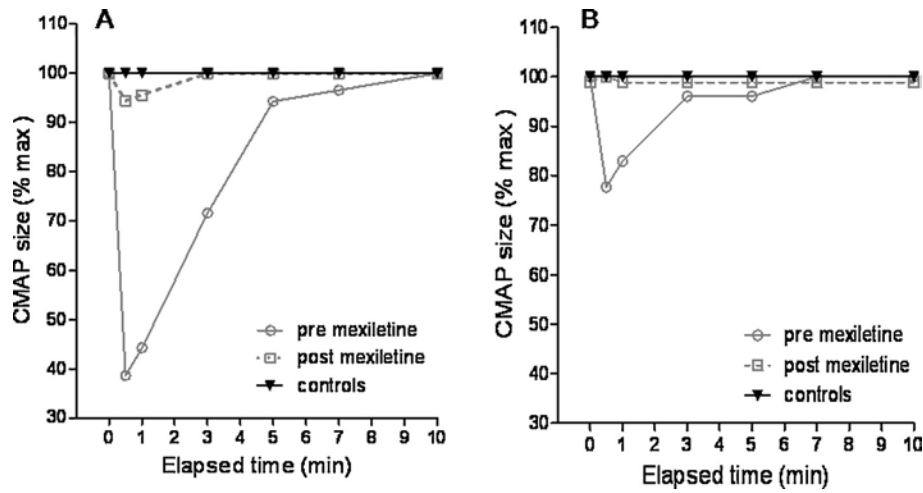
Figure 1 Amplitude of the compound muscle action potential (CMAP) recorded from the abductor digiti minimi muscle in response to supramaximal ulnar nerve stimulation at the wrist, before and up to 10 minutes after a 1 min exercise of maximum voluntary contraction (time ''0'' being the value measured before contraction; each data being the average of 4—5 CMAPs). Label A refers to patient 1 (Thomsen's myotonia); label B refers to patient 2 (Becker's myotonia).

Results

Repetitive nerve stimulation at 3 and 5 Hz was unremarkable in both subjects, whereas at 10 Hz a **significant** CMAP amplitude drop was evident in Patient 1 (11%) and Patient 2 (16%). In both patients, the decrement became non-**significant** after the introduction of mexiletine therapy.

Fig. 1 shows the decrease in CMAP amplitude and the recovery time after MVC with respect to the test CMAP amplitude before MVC in MC patients, whereas no change was observed in controls. In Patient 1, CMAP amplitude reduction peaked in the first 10 s after the end of the MVC (61% reduction, from 8.8 mV to 3.4 mV); it took 10 minutes for CMAP amplitude to return to control value. In patient 2, CMAP amplitude reduction was less (23%, from 9.1 mV to 7 mV) and it took 3 minutes to return to control value.

When the measurements were performed under mexiletine therapy, the maximal CMAP depression after MVC was reduced from 61 to 6%, with only 3 minutes to return to control value in patient 1, whereas CMAP depression after MVC was no longer observable in patient 2.

Discussion

Some MC patients show CMAP amplitude decrement to repetitive nerve stimulation, which correlates with the presence of transient weakness rather than with the severity of myotonia, according to concomitant recordings of CMAP and muscle strength under isometric conditions performed in autosomal recessive MC [2,4,14,15,23]. In the present study, we found a transient reduction in maximal CMAP amplitude after 1 min of MVC in two MC patients, whereas no change was observed in normal controls. This suggests that virtually all ADM motor axons could be still activated after sustained contraction in healthy subjects, in line with previous studies [3,25,26].

Our findings in Patient 2 are similar to those reported by McKay et al. [18] in one case of Becker's myotonia. Since a marked decrement is generally believed to be a hallmark of recessive MC, it was somewhat surprising that the patient with dominant MC had more decrement than the patient with recessive MC. However, both dominant and recessive MC mutations share similar pathophysiology, affecting the muscle-specific chloride channel. In addition, previous studies have shown that large decrements in CMAP amplitude occasionally occurred after contraction in dominant MC, with the magnitude of decrement possibly related to mutation type [7,8] and differences in allelic expression of the *CLCN1* gene [9]. On the other hand, no data have previously been reported regarding CMAP recordings after 1 minute of MVC in dominant MC. In this respect, we emphasize the novelty of the results obtained in Patient 1 with dominant MC.

The putative factors responsible for activity-induced CMAP depression could be located anywhere from the motor neuron to the muscle fiber. However, we have to consider that the Cl^- conductance contributes to 85% of the resting membrane potential in muscle fibers [5], but to only 10% of the resting membrane potential in motor axons [30]. Indeed, the role played by Cl^- channels in the human motor axons remains debated and moreover the parameters of motor axonal excitability were found to be normal in MC in a previous study [18]. The most probable explanation is that the sustained MVC provokes extreme muscle depolarization due to Na^+ influx, thus determining an increased Na^+ channel inactivation leading to muscle hypoexcitability. Indeed, it is documented that natural muscle contraction activity may be associated with elevation of extracellular K^+ concentrations, which in turn could depress muscle responses. The influence of elevated extracellular K^+ concentrations and slow-inactivation of Na^+ channels induced by excessive depolarization may result in a decrease of sarcolemmal excitability and the reduction in the number of excitable muscle fibers explains CMAP amplitude decrease [19,20,28]. On the other hand, the reduced amount of CLC-1 chloride channels in muscle fiber membrane of MC patients diminishes the hyperpolarizing Cl^- currents so that

K$^+$ accumulation in the T-tubular lumen depolarizes the surface membrane **sufficiently** to initiate self-sustaining action potentials, causing a prolonged (myotonic) contraction [1]. Further cumulative and excessive muscle membrane depolarization, such as could occur after prolonged MVC, may trigger transient hypoexcitability related to a depolarization block, as discussed above. Our findings of transient CMAP depression and delayed recovery of excitability following sustained MVC may represent the electrophysiological correlate of the weakness clinically experienced by MC patients.

After the introduction of mexiletine therapy, the CMAP depression following MVC was markedly reduced in the patient with Thomsen's myotonia and disappeared in the patient with Becker's myotonia. Both patients also showed no further CMAP amplitude decrement following high-frequency RNS under mexiletine. In MC patients, mexiletine is thought to decrease repetitive motor unit discharges by blocking Na$^+$ channels, since it does not seem to interact with Cl$^-$ channels [11,33]. How such a mechanism may explain the positive effect of mexiletine on transient CMAP depression following sustained contraction remains to be **clarified.** In fact, given the negative effects of mexiletine on motor axon excitability properties in humans [13], one would expect an opposite effect compared to that observed in the present study and also to that previously shown by McKay et al. [18].

It is well known that Na$^+$ channel blockers improve myotonic stiffness, but also weakness and tiredness [21,24], which could explain the overall clinical amelioration of myotonic patients reported in a recent clinical trial with mexiletine [29]. Mexiletine produces an activity-dependent block of voltage-gated Na$^+$ channels (the higher is the frequency of action potential discharges, the greater is the block) at the origin of its specific effect on disease-related hyperexcitability, such as in the myotonic muscle. The correlation between myotonic stiffness and weakness in MC is not surprising from a pathophysiological perspective [8]. In fact, the block of the myotonic discharge may prevent further activity-dependent block due to excessive membrane depolarization, thus reducing CMAP depression following sustained voluntary contraction. Thus, the most noticeable change in post-MVC CMAP depression after therapy was observed in Patient 1 who had the most severe myotonic phenomenon and showed the greatest clinical response.

In Video 2, the reduction of the ''warm-up'' phenomenon was evident after mexiletine therapy. The ''warm-up'' phenomenon is an established clinical feature in chloride channelopathies, though it has also been shown to occur in other myotonic syndromes [6,16,34]. The mechanism remains unknown. Proposed mechanisms for warm-up include Na/K-ATPase up-regulation, decreasing intracellular pH, Na$_v$1.4 slow-inactivation or K+ shift into the T-tubules [6,16]. On the basis of the mechanism of action of the mexiletine (see above) and its proven effectiveness in reducing the ''warm-up'' phenomenon in different channelopaties [29,34], it is plausible that this drug produces lower neuronal firing rate that in turn will lead to lesser activity-dependent axonal hyperpolarization [12]. These changes could conceivably decrease fiber excitability, thus decreasing the likelihood of myotonic discharges and consequently the ''warm-up'' phenomenon.

Conclusion

Our study further confirms that in both recessive and dominant MC, a proportion of muscle fibers cannot maintain their response to nerve stimulation after sustained MVC. This phenomenon likely represents the physiological counterpart of the weakness clinically experienced by the patients. The remarkable recovery of neuromuscular excitability following the introduction of mexiletine suggests a common mechanism underlying myotonic stiffness and weakness in MC. Our results are based on only two cases hence need to be confirmed in a larger sample of patients.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version

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