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Effect of mexiletine on transitory depression of compound motor action potential in recessive myotonia congenita

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HIGHLIGHTS

- Transient muscle weakness, a frequent symptom of nondystrophic myotonias, can be measured by the transient compound muscle action potential depression.
- Mexiletine, the currently preferred antimyotonic drug, efficiently reduces the transient compound muscle action potential depression.
- The 3 Hz prolonged low-rate repetitive nerve stimulation might be considered a helpful tool to objectively assess the anti-myotonic effect of drugs in myotonic patients.

ABSTRACT

Objective: We aim to demonstrate the effect of mexiletine on the compound muscle action potential (CMAP) amplitude transitory depression (TD) in a cohort of patients with recessive myotonia congenita.
Methods: We evaluated 21 patients with recessive myotonia congenita referred to our institute from 1990 to 2013 and treated with mexiletine chlorhydrate. All patients underwent prolonged 3 Hz repetitive nerve stimulation (3 Hz-PLRS) before and after the beginning of treatment.
Results: We observed in all subjects a reduction of CMAP amplitude TD after the beginning of treatment. The mean value of the TD nadir before starting mexiletine treatment was −62.0% and reduced to −28.8% after the therapy was started (51.6% reduction, $p < 0.001$).
Conclusions: The 3 Hz-PLRS is configured as a neurophysiological test able to indirectly detect and quantify, through the measurement of TD, the clinical phenomenon of the transitory weakness that occurs in myotonic syndromes due to CLCN1 mutations.
Significance: This neurophysiological test might be considered a helpful tool to assess the effect of anti-myotonic drugs, as mexiletine, in recessive myotonia congenita.

1. Introduction

Non-dystrophic myotonias (NDM) are a group of genetic disorders due to dysfunction of ion channels that regulate muscle membrane resting potential and excitability (Matthews et al., 2010; Mankodi and Thornton, 2002; Trivedi et al., 2014). NDM can be caused by loss-of-function mutations of the skeletal muscle ClC-1 chloride channel (dominant or recessive myotonia congenita) or gain-of-function mutations of the skeletal muscle voltage-gated Nav1.4 sodium channel (dominantly inherited paramyotonia congenita and potassium-aggravated myotonia).

NDM are characterized by two contrasting phenomena: abnormal membrane over-excitation resulting in muscle stiffness (myotonia) and muscle inexcitability clinically manifesting as flaccid paralysis (periodic paralysis) or transient weakness (Matthews et al., 2010; Mankodi and Thornton, 2002; Raja Rayan and Hanna, 2010). Periodic palsy, when associated with myotonia, is usually indicative of a sodium channel dysfunction, while myotonia plus transient weakness (TW) strongly suggests a chloride channel dysfunction (Trip et al., 2009; Raja Rayan and Hanna, 2010).

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TW occurs at the beginning of a voluntary muscle contraction and quickly vanishes. It is easily masked by the overlapping myotonia, and is thus rarely reported as a symptom, which renders its clinical appreciation quite difficult even for qualified clinicians. An objective and reproducible detection of TW would thus represent a useful tool for clinicians, guiding the genetic testing toward CLCN1 mutations, thereby saving time and costs.

A transient depression (TD) of the compound muscle action potentials (CMAP) is the physiological counterpart of TW (Aminoff et al., 1977). TD is detected by a short exercise test (Streib, 1987; Deymeer et al., 1998; Fournier et al., 2004, 2006), as well as by repetitive nerve stimulations (RNS) (Lambert et al., 1952; Ricker and Meinck, 1972; Colding-Jorgensen et al., 2003) and can be quantified by comparing the amplitude of the CMAP recorded at rest with that recorded immediately after a maximal effort or at the end of the RNS.

Both tests show a good sensitivity in detecting TD but often fail in obtaining the maximum value of TD, because of the limited patients' compliance in performing the maximum effort or tolerating 8–10 Hz RNS for an adequate period.

Recently, using a prolonged 3 Hz repetitive nerve stimulation (3 Hz-PRNS), we monitored the CMAP amplitude variations that occur throughout the whole stimulation (Modoni et al., 2011). We demonstrated that the 3 Hz-PRNS protocol, when sustained for at least 45 s, is always able, in patients affected by recessive myotonia congenita, to detect the maximum CMAP depression (thereafter called Transient Depression Nadir or TDN) before the recovery due to the warm-up phenomenon. Reproducible results were obtained when the test was performed after an adequate period of rest lasting 20 min. Such properties make the 3 Hz-PRNS a valuable tool useful for a quantitative evaluation of TD and possibly for measuring drug effects.

Up to date, the preferred anti-myotonic drug is mexiletine, an easily available oral class Ib anti-arrhythmic (Conte Camerino et al., 2007). Mexiletine recently received orphan drug designation in NDM by EMA and FDA. The drug produces a use-dependent block of voltage-gated sodium channels (the higher is the frequency of action potential discharges, the greater is the block) that is the basis for its specific effect on pathologic overexcited tissues, such as the myotonic muscle. In patients with chloride channel myotonia, mexiletine thus probably decreases repetitive motor unit discharges by blocking wild-type sodium channels, since it is not known to affect ClC-1 channels (Lehmann-Horn and Jurkat-Rott, 1999; Jurkat-Rott and Lehmann-Horn, 2001; Trip et al., 2006). Although the efficiency of mexiletine in relieving myotonia has been proved in clinical trials (Logigian et al., 2010; Statland et al., 2012), there is no available information regarding mexiletine effects on transient weakness.

The aim of this study was to verify whether mexiletine may inhibit the CMAP TD in patients affected by recessive myotonia congenita, using the 3 Hz-PRNS.

2. Patients and methods

From January 1990 to October 2013, 54 patients with genetic diagnosis of recessive myotonia congenita (Becker myotonia) were admitted to our institute. Fifty patients came from Italy, one from Romania and three from Albania.

According to the clinical severity, a subgroup of 21 patients has been treated with mexiletine chlorhydrate ("Mexiletina Cloroidrato," Stabilimento Chimico Farmaceutico Militare Italiano, Florence, Italy) for a period ranging from 2 months to 8 years.

Demographic and genetic data are summarized in Table 1. In one patient (case #15) one mutation only could be detected. In another patient (case #11) one mutation (p.G190S) was inherited as a dominant tract and a second mutation (p.C861P) as a recessive tract.

Table 1
Demographic, genetic, and neurophysiological findings of our cohort of patients with recessive myotonia.

Case, gender	Mutations		Age of onset (years)	Age at test (years)	TD test (− %)	TD re-test (− %)	Test re-test TD change (%)	Interval test Re-test (months)	Mexiletine dosage (mg)	Treatment duration (months)	Last drug intake (h)	TD without Mexiletine (− %)	TD with mexiletine (− %)	TD change after therapy (%)
#1, M	F167L	R105C	14	31	19	23	−4	72	200 × 1	73	4	23	19	4
#2, M	G190S	E500X	5	54	90	87	3	72	200 × 3	98	1.30	87	71	16
#3, M	R894X	2364+2T>A	7	28	53	49	4	45	200 × 3	2	1	49	42	7
#4, M	R976X	E422K	4	27	57	56	1	45	200 × 4	87	3	56	47	9
#5, M	1471+1G>A	IVS10-14dcg	8	19	78	75	3	77	200 × 3	96	1	75	21	54
#6, F	180+3A>T	180+3A>T	9	46	57	61	−4	2	200 × 2	2	3	61	23	38
#7, M	180+3A>T	180+3A>T	7	65	43	73	−30	23	200 × 3	12	3.30	73	23	50
#8, F	1471+1G>A	E422K	12	33	63	26	37	33	200 × 2	12	4.30	26	26	0
#9, F	G190S	E547k	2	30	50	54	−4	108	200 × 1	2	3.30	54	37	17
#10, M	180+3A>T	R421H	5	29	–	–	–	–	200 × 2	5	1	69	43	26
#11, M	G190S	C861P	7	36	–	–	–	–	200 × 3	85	2.30	93	45	48
#12, M	del. ex. 9	del. ex. 9	8	68	–	–	–	–	200 × 2	24	2	85	27	58
#13, M	C481X	C481X	9	39	–	–	–	–	200 × 2	2	2	78	43	35
#14, F	del. 11:1183	A437E	6	40	–	–	–	–	200 × 3	3	2.30	66	20	46
#15, M	G482R	?	5	16	–	–	–	–	200 × 3	12	1	47	5	42
#16, M	G482R	T550R	3	17	–	–	–	–	200 × 2	24	1.30	53	14	39
#17, M	2404+1G>A	2404+1G>A	10	37	–	–	–	–	200 × 2	8	6	53	20	33
#18, M	1471+1G>A	A535D	5	8	–	–	–	–	100 × 2	2	6	53	9	44
#19, F	180+3A>T	378–379 ins. C	1	6	–	–	–	–	75 × 3	7	2.30	72	14	58
#20, F	1110–1111DC	IVS10–5T>G	8	42	–	–	–	–	200 × 2	2	4.30	47	10	37
#21, M	180+3A>T	R421H	5	24	–	–	–	–	200 × 2	5	4	81	46	35

M: male; F: female; TD: transitory depression; del.: deletion; ex.: exon; ins.: insertion.