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Neuromuscular transmission abnormalities in myotonic dystrophy type 1: A neurophysiological study

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ABSTRACT

Objectives: Weakness and fatigue are frequent symptoms in myotonic dystrophy type 1 (DM1), mainly as a result of muscle impairment. However, neuromuscular junction (NMJ) abnormalities could play an additional role in determining these manifestations. We aimed to document the possible NMJ involvement in DM1.
Patients and methods: In order to substantiate this hypothesis we performed low rate repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG), in 14 DM1 subjects.
Results: RNS resulted abnormal in four patients while SFEMG revealed a pathological jitter in ten. A significative correlation was found between jitter values and decrementing response ($p < 0.000311$; $r = 0.822$).
Conclusion: These results suggest a possible involvement of NMJ in DM1.

1. Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disease due to the expansion of an unstable trinucleotide (CTG) repeat in the 3′ untranslated region of the myotonic dystrophy protein kinase (*DMPK*) gene, in chromosome 19q.13.3 [1]. It is the most common adult-onset muscular dystrophy [2] with considerable clinical heterogeneity, characterized by muscle weakness, myotonia and systemic manifestations, involving ocular, brain, heart, gastrointestinal, skin, endocrine, and respiratory systems [3].

The weakness remains the main symptom of DM1, whereas some patients may complain of fatigue. These symptoms can derive from muscle fiber damage, evident in biopsies of clinically affected muscles which display internalized myonuclei, sarcoplasmic masses, ring fibers and type 1 fiber atrophy [4]. Another mechanism which could contribute to the weakness of DM1 patients might be a peripheral nerve dysfunction. In this regard, many studies have documented neurophysiological abnormalities consistent with an axonal neuropathy in different frequencies ranging from 17% to 46%, sometimes at subclinical level [5–11], while few others have questioned this finding [12,13]. Concerning fatigue, several factors may contribute in determining it, such as hypersomnolence and sleep disorders, extremely common symptoms in DM1 patients [14,15]; obstructive sleep apnea and impaired central nervous system respiratory drive are the mechanisms implicated [16]. Furthermore, it may be related to the axonal and/or muscle membrane excitability defects [17].

Finally, a neuromuscular junction (NMJ) impairment could be responsible for weakness and fatigue in DM1 patients.

Even though the involvement of this structure in DM1 is supported by histopathological studies showing abnormalities at this level [18,19], an electrophysiological investigation targeted to explore neuromuscular transmission function, by performing low rate repetitive nerve stimulation (RNS) and single fiber eletromyography (SFEMG), has never been performed in DM1.

The aim of this study was to investigate, in a cohort of DM1 patients, NMJ function, and to correlate the neurophysiological data with the clinical and genetic status of the patients.

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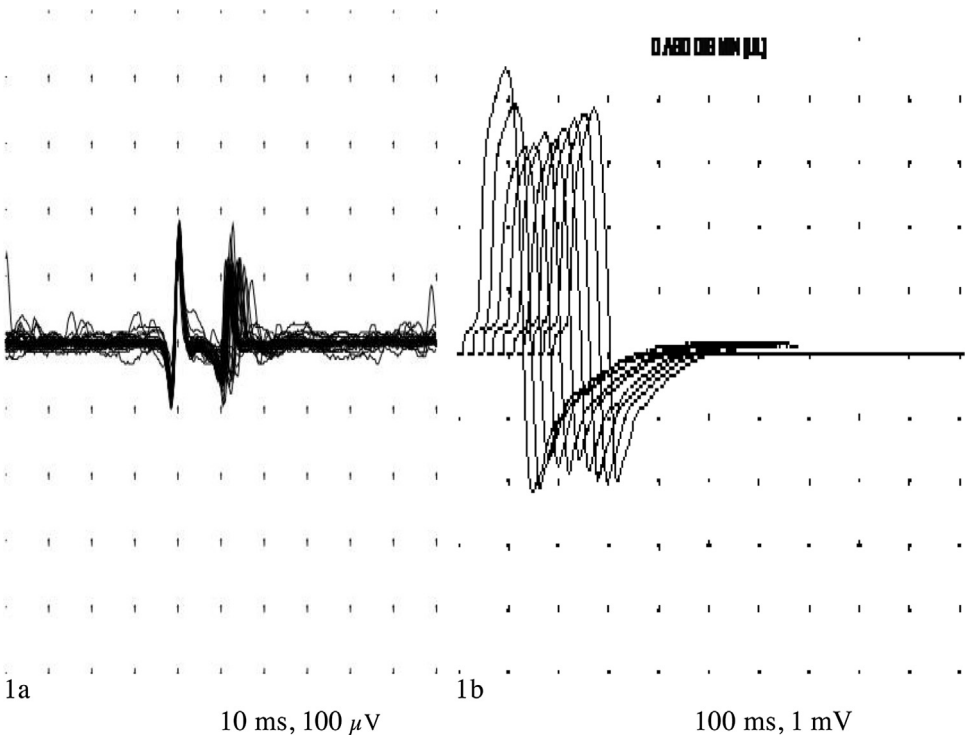

Fig. 1. Jitter abnormalities (1a) and decrementing response (1b) in a DM1 patient (n.4).

2. Patients and methods

We recruited fourteen genetically confirmed DM1 patients, seven males and seven females, aged 33–74 years (mean 49.7) followed-up at the Neuromuscular Centre of S. Camillo-Forlanini Hospital, Rome, Italy. All subjects gave their informed consent to participate in this study which was approved by the local ethics committee. Twelve healthy subjects (six males and six females, mean age 46 years) served as normal controls and were recruited among hospital staff and outpatients. There was no history of comorbidities which may have caused neuromuscular impairment. In particular, all patients were negative for autoantibodies against acetylcholine receptor or muscle-specific tyrosine kinase. Clinical weakness was assessed applying the Medical Research Council scale (MRC) [20], while the degree of muscle involvement in DM1 patients was evaluated using the Muscle Impairment Rating Scale (MIRS) [21]. The neurophysiological investigation was conducted by means of RNS techniques, using surface electrodes for recording compound muscle action potentials (cMAP) and performing a SFEMG study, with concentric needle electrode [22,23]. In addition, all patients underwent standard nerve conduction studies, evaluating bilaterally the median, ulnar, peroneal and tibial motor nerves, and the sural nerves; values published by Kimura have been considered as normal [22]. SFEMG was performed in extensor digitorum communis (EDC) muscle by voluntary activation and jitter was considered abnormal according to values reported by Kouyoumdjian and Stalberg [24]. RNS at 3 Hz of the ulnar nerve was conducted providing ten stimuli at wrist and recording the responses by surface electrodes at abductor digiti minimi (ADM) muscle; the first and fifth cMAP amplitudes were compared and their difference expressed as a percentage; a decrease greater than 10% was considered abnormal, in accordance to the AAEM Quality Assurance Committee [25]. Pearson's product moment correlation test was adopted to perform correlation analysis between jitter values and CTG repeats, jitter values and MRC score, jitter values and decrementing response at RNS in DM1 patients.

3. Results

Four out of 14 DM1 patients showed only facial weakness, with a MIRS score of 2; the remaining ten patients displayed distal or both distal and proximal muscle weakness (MIRS score 3–5); all patients complained of fatigue. The CTG expansion ranged from 150 to 1430. Standard nerve conduction studies resulted within normal range in all DM1 patients. A 3 Hz, RNS resulted abnormal in four DM1 subjects (28.5%), with a decrementing response ranging from 12% to 20%. Ten out of 14 patients (71.4%) showed abnormal jitter value and impulse blocking; the abnormal findings of a patient are illustrated in Fig. 1.

All the healthy subjects showed normal findings in the neurophysiological tests. A highly significant direct correlation resulted between jitter values and decrementing response ($p < 0.000311$; $r = 0.822$), as reported in Fig. 2. Jitter values did not show significant correlation with CTG repeats number and MRC score. The clinical and electrophysiological data of the patients are reported in Table 1.

4. Discussion

This study documents pathological decrementing response, at short lasting low rate RNS, and jitter abnormalities in DM1 patients, with a solid, direct correlation between them, suggesting a possible motor endplate involvement in DM1.

A decrementing response to RNS has been previously documented in myotonic dystrophy; Brown JC reported two patients in whom a decrement of the cMAP occurred at high frequencies, sustained eight and twenty seconds [26]; subsequently, Aminoff MJ and coll. studied three patients, revealing a declining response to RNS delivered for at least one minute [27]. Both studies reported similar findings in patients with myotonia congenita, more evident with the recessive form. A more recent study reproduced these results, documenting a depression of the cMAP with prolonged low rate RNS in recessive myotonia congenita [28].

The pathophysiological basis of the decrement appears to be at muscle fiber level; regarding myotonia congenita, firstly, Brown JC