Inclusion body myositis : a nationwide study

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Muscle weakness in inclusion body myositis is not aggravated due to synaptic dysfunction

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ABSTRACT

Whether or not the neuromuscular junction (NMJ) is affected in inclusion body myositis (IBM) is unclear. To evaluate NMJ function, repetitive nerve stimulation (RNS) with frequencies of 1, 3, 5 and 10 Hz was applied to the ulnar nerve in 42 patients with IBM. None of the patients showed an abnormal decrement. Our study provides no evidence for a NMJ disorder in IBM. Abnormal results on low-rate RNS in patients with muscle weakness most probably exclude IBM.

INTRODUCTION

Inclusion body myositis (IBM) is a slowly progressive myopathy with an insidious onset after the age of 40 years with a male preponderance. Initial symptoms often relate to weakness of the quadriceps muscles, distal arm muscle or pharyngeal muscles.[71] The etiology of IBM is unknown. Endomysial inflammatory infiltrates, invaded muscle fibers, rimmed vacuoles, and abnormal accumulations of a host of proteins such as amyloid β (precursor) protein, nicotinic acetylcholine receptor and its RNA, rapsyn, α_1-antichymotrypsin, apolipoprotein E and cellular prion protein in muscle fibers are prominent histopathological features of the disease.[47] Most of these accumulated proteins are normally only present at the post-synaptic part of the neuromuscular junction. Mild to moderate increases of jitter and blocking have been reported in IBM patients[48,49,72] using single fiber electromyographic (SFEMG) studies. A reduction of acetylcholine receptors at the neuromuscular junctions of patients with myositis has been reported, as in myasthenia gravis.[73] Together this suggests a possible NMJ dysfunction in IBM. Jitter by itself does not cause muscle weakness, but impulse blocking does. In repetitive nerve stimulation abnormality is due to blocking. As far as we know, we for the first time report the use of repetitive nerve stimulation in IBM to study whether NMJ dysfunction adds to the muscle weakness.

PATIENTS & METHODS

Patient selection

IBM patients were recruited from a series of 86 patients known to be living in the Netherlands. The recruitment procedure has been reported in detail.[63] Out of these 86 patients, 5 patients could not be located, 6 had died prior to assessment and 14 refused participation. Logistical reasons further restricted inclusion to 42 patients, 37 of whom had definite and five probable IBM according to clinical and histopathological criteria.[53,63] All patients gave informed consent. To compare the selection of participating patients with the population cohort, the medical records of all 86 patients were reviewed for age (at onset), sex and disease duration. The local ethics board had approved the study.

Methods

All 42 patients were prospectively tested. One investigator (UB) assessed muscle strength according to the Medical Research Council (MRC) six-point scale.[68] Before RNS testing, skin temperature was raised to at least 32 °C with hot water baths. RNS of the ulnar nerve was performed with self-adhesive recording electrodes of 28 x 22 mm (Nicolet Instruments, Madison, Wisconsin) over the hypothenar muscles of the right-sided hand. The ulnar nerve was stimulated just proximal to the wrist at 1.5 times the lowest intensity resulting in a supramaximal response. The hand and stimulator were immobilized with tape.

RNS was performed in trains of 10 stimuli at 1, 3, 5 and 10 Hz. Skin temperature, stimulation intensity and frequency as well as the amplitude and area of all compound muscle

action potentials (CMAPs) was noted. To study the decrement the amplitude of the smallest CMAP during a train of stimuli was expressed as a percentage of the first CMAP amplitude of that train. Test methods and the abnormality criterion of a decrement in amplitude equal to, or more than, 10% have been described previously.[74] The initial CMAP amplitude had to be sufficiently high for reliable analysis, i.e., preferably ≥ 0.5 mV.

RESULTS

The median age of the 42 IBM patients, 31 men, was 69 years (range 50-83). The median disease duration was 11 years (range 1-29). The male sex was over-represented in the investigated group compared with the population group of 86 patients that had a male to female ratio of 2:1.
At the time of investigation 18 patients (43%) had apparent weakness of the hypothenar muscles of MRC grade 4 or less. Mean initial CMAP amplitude was 5.4 ± 1.9 (range 2.5-9.9) mV and the mean initial CMAP area (both negative phase) was 13.7 ± 5.7 (range 4.8-26.6) mVms. No patient had an abnormal CMAP amplitude decrement at any frequency stimulation, nor was there any trend towards a decrease in mean amplitude (table).

Table. *CMAP changes during repetitive nerve stimulation trains.*

Stimulus frequency	Minimum	
	Amplitude	Area
1 Hz	99 ± 3 (91-107)	98 ± 3 (90-103)
3 Hz	99 ± 3 (91-106)	98 ± 2 (91-103)
5 Hz	100 ± 4 (94-112)	98 ± 3 (90-103)
10 Hz	105 ± 5 (95-117)	102 ± 4 (93-114)

CMAP, compound muscle action potential.
Values for minimum amplitude or area indicate the lowest response amplitude or area in a train of responses to 10 stimuli, expressed as percentage of the first response. Data are presented as mean ± standard deviation (range).

DISCUSSION

Previous reports suggested a neuromuscular transmission disorder in IBM using SFEMG. One study reported an increased mean jitter of 83 µsec compared with an abnormality threshold of 60 µsec in 7 of 7 IBM patients.[48] Another study reported less abnormal jitter (mean = 46.5 µsec, normal <40.5 µsec) in 7 of 12 IBM patients[49] and a third study reported increased jitter or blocking in 5 of 17 patients, but only in 1 of 17 at multiple sites.[72] We performed RNS in a large group of IBM patients, but RNS never showed abnormalities, even though the muscles examined were clinically affected. Although the sensitivity of

RNS for neuromuscular transmission disorders is lower compared with SFEMG but its specificity higher, it would seem that neuromuscular transmission in IBM was not essentially affected and synaptic dysfunction did not contribute to weakness in IBM. Therefore, we now believe that the SFEMG abnormalities in IBM are insignificant, as they are in other chronic myopathies.

Interestingly, our results may be of help in discriminating IBM from the Lambert-Eaton myasthenic syndrome (LEMS) and motor neuron disease (MND). Due to similarities in distribution of age, sex and muscle weakness at presentation clinical distinction between these disorders can be difficult. A decremental response with low frequency RNS is invariably present in LEMS. In IBM and MND conventional needle electromyography findings are not distinctive as IBM patients may also show spontaneous muscle fiber activity, polyphasic motor unit action potentials (MUAP) and appear to have an increased number of long duration and high amplitude MUAP's as in MND. However, as up to 53% of patients have a decremental response in MND[75-77] the presence of an abnormal low-frequency RNS is most probably distinctive between MND and IBM.

APPENDIX

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