Prognostic value of decremental responses to repetitive nerve stimulation in ALS patients

Article abstract—Decrement of the thenar compound muscle action potentials (CMAP), after repetitive nerve stimulation (RNS) of the median nerve at 3 Hz, was evaluated in patients with ALS before riluzole therapy. CMAP size as well as motor unit number and size estimates were evaluated twice before and after 1 year of riluzole therapy. The correlation between decrement and CMAP size reduction per year was highly significant ($r = 0.77$), but no relationship could be demonstrated between decrement and other variables. The authors thus propose that decrement after RNS may be used as a predictor of further drop in CMAP size.

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Previous electrophysiologic observations indicate impairment of neuromuscular transmission in patients with ALS.[1-5] Some authors[3,5] correlated decremental responses with the degree of muscle atrophy, whereas others,[1] on the basis of the clinical course, found that decrement was more pronounced in patients with rapidly developing motor neuron disease.

Decremental responses have not been correlated with quantitative parameters that evaluate ALS activity. The current prospective study was designed to analyze the relationship between 1) thenar decrement after slow-rate repetitive nerve stimulation (RNS) and 2) thenar motor unit loss, average surface-recorded motor unit action potential (S-MUAP) size variations and compound muscle action potential (CMAP) size reduction per year by using the adapted multiple point stimulation (AMPS) method in patients with ALS.[7]

Methods. *Participants.* Data were collected from 15 consecutive patients with ALS after having obtained their informed consent; their age ranged from 44 to 71 years (mean, 57 ± 9). These patients fulfilled the clinical and electrophysiologic criteria for definite ALS.[6] However, decrement with slow-rate RNS greater than 20% was not considered an exclusion criterion for the diagnosis of ALS.[6] All patients were screened to exclude any additional pathology affecting peripheral nerves, muscles, or neuromuscular junctions.

None received drug therapy initially, in particular riluzole. All patients received riluzole after the first electrophysiologic and clinical evaluation (T0).

The mean disease duration was 24 ± 17 months (range, 6 to 60). At the start of the study, thenar muscle atrophy, on the side electrophysiologically studied, was absent or mild in four, moderate in seven, and severe in four patients. No quantitative strength measurements of thenar muscles were performed for this study.

Thenar decrement was also studied in a control group of 15 healthy volunteers (age range, 40 to 77 years; mean, 59 ± 15), under identical technical conditions.

Techniques. The stigmatic and reference recording electrodes consisted of 4 cm long by 0.8 cm wide silver foil. The stigmatic electrode was positioned transversely over the thenar eminence, as close as possible to the muscle endplates. The reference electrode was attached over the proximal phalanx of the thumb. The ground electrode (silver foil) was fixed over the dorsum of the wrist (band-pass: 2 Hz to 5 KHz).

All studies were performed on a Nicolet Viking IV EMG machine (Nicolet Instrument Corp.).

In all 15 patients with ALS, RNS was performed over the median nerve at the wrist, 7 cm from the stigmatic electrode. Supramaximal stimuli (150% of the stimulus intensity giving a maximal response) were applied by surface electrodes (Medelec model LBS 53051; inter-electrode distance 2.5 cm) in a train of 10 stimuli, 0.2 msec duration, at a rate of 3 Hz. CMAP decrement was determined as the difference between the fourth and first motor response negative peak area and expressed as a percentage. Postexercise exhaustion was not studied.

CMAP size, thenar motor unit number estimate (MUNE), and average S-MUAP size were measured at the beginning of the study (T0) and after 1 year of riluzole therapy (T1). Five patients did not return for the visit at T1 (two patients died shortly after T0, and three patients were lost for unknown reasons). The number and size of thenar motor units were estimated by the AMPS technique. This method, including its reliability and other advantages, has been presented in detail in previous papers.[7,8] With AMPS, the mean motor unit size is estimated by collecting and averaging a sample of 10 well-identified S-MUAP after stimulation at distinct points along the course of the median nerve between the wrist and elbow. At each stimulation site, only two or three S-MUAP are evoked by incremental stimulation (percutaneous nerve stimulation, 0.05 msec duration, weak intensity gradually increased by increments of 0.1 to 0.5 mA). MUNE is obtained by dividing the maximum CMAP size by the average S-MUAP size.

The hand temperature was maintained above 32 °C for all measurements.

Results are expressed as mean ± 1 SD. A log-transform was applied to decrement to normalize its distribution.

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Correlation coefficients were computed between variables. Mean values were compared using Student's *t*-test for paired or unpaired data. All results were considered to be significant at the 5% critical level ($p < 0.05$). Calculations were done with SAS (Cary, NC; version 6.12 for Windows) software.

Results. The mean thenar neuromuscular decrement to low-rate RNS of the median nerve was 5.8 ± 1.8% (range, 4 through 9) in the control group (n = 15), permitting us to fix the upper normal limit for decrement at the classic value of 10%. In ALS patients, the mean thenar decrement was 14.9 ± 10.7%. There was a statistical difference between both groups ($p < 0.005$). A decremental response greater than 10% was recorded in 8 (53%) patients with ALS, and the maximum decrement reached 35%.

The five dropout patients had means of CMAP area, MUNE, average S-MUAP size, and thenar decrement at T0 not different from means of the 10 patients who were subsequently studied (CMAP area: $p = 0.95$, MUNE: $p = 0.73$, average S-MUAP size: $p = 0.61$, thenar decrement: $p = 0.64$)

In ALS patients, the mean thenar MUNE measured by AMPS dropped from 39.8 ± 27.1 at T0 to 18.6 ± 19.3 at T1 ($p = 0.002$) (versus 263 ± 117 in normal subjects[8]). The mean motor unit loss per year was 56 ± 24% (range, 27 to 99), and no correlation could be demonstrated with the decrement ($r = 0.57$; $p = 0.08$) (figure 1A).

The mean average S-MUAP size (n = 10) increased from 335 ± 195 μV.ms at baseline T0 to 417 ± 653 μV.ms at T1 ($p = 0.66$) (versus 94.1 ± 30.3 in normal subjects[8]). The mean of individual average S-MUAP size variations per year was 1.3 ± 77% (range: −78 to 170). There was no correlation between the average S-MUAP size variation per year and the decrement ($r = -0.48$; $p = 0.16$) (figure 1B).

The mean thenar CMAP size (n = 10) dropped from 10.8 ± 6.9 mV.ms at T0 to 5.2 ± 5.4 mV/ms at T1 ($p < 0.001$) (versus 21.9 ± 7.7 mV/ms in normal subjects[8]). The mean CMAP size reduction per year was 57 ± 29% (range, 10 to 99). A correlation ($r = 0.77$; $p < 0.01$) was found between the decrement and CMAP size reduction per year (figure 2).

Discussion. Decremental motor responses to slow-rate RNS in patients with ALS were initially described by Mulder, Lambert, and Eaton in 1959.[5] Later, other studies reported similar findings.[1-4] In one of them,[3] the decrement was larger and present more often in muscles showing atrophy. In another one,[1] decrement was found predominantly in patients with rapidly developing symptoms, suggesting that decrement reflects activity or rate of progression of the motor neuron disease. The current study confirms previous electrophysiologic observations indicating that impairment of neuromuscular transmission is not an uncommon feature in ALS. In fact, 53% of patients with ALS had thenar decrement greater than the classic limit of 10% with a maximum value of 35%. These data suggest that more than 20% decrement with slow-rate RNS should not be an exclusion criterion for ALS diagnosis as proposed by Brooks.[6]

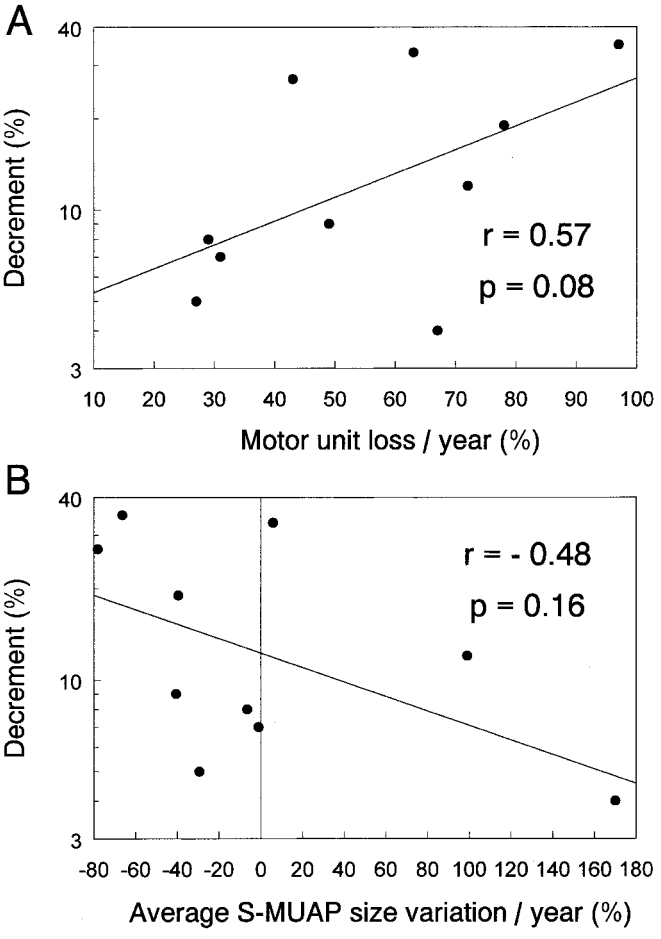

Figure 1. Relationship between thenar decrement and (A) motor unit loss per year and (B) average surface-recorded motor unit action potential (S-MUAP) size variation per year in 10 patients with ALS.

Thenar decrement (before riluzole therapy), thenar motor unit loss, CMAP, and average S-MUAP size variations per year (on the basis of two measurements before and after 1 year riluzole therapy) were evaluated in 10 ALS patients. RNS was only per-

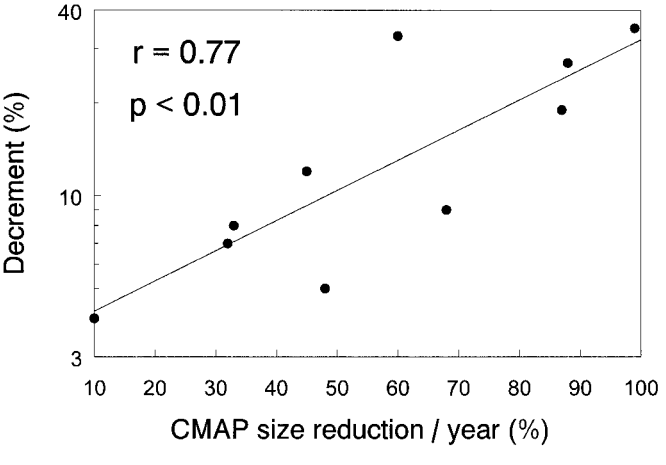

Figure 2. Relationship between thenar decrement and compound muscle action potential (CMAP) reduction per year in 10 patients with ALS.

formed before therapy to avoid a possible influence of riluzole on decrement. Myasthenia is reported as an adverse effect of riluzole by the manufacturer and in one recent observation.[9] The correlation between decrement and CMAP size reduction per year was highly significant (figure 2), but the decrement was neither significantly correlated with the motor unit loss nor with the average S-MUAP size variation per year (figure 1). We thus suggest that the percentage of decrement after slow-rate RNS might be interpreted as a predictor of further drop in CMAP size. The greater the decrement, the greater the subsequent drop in CMAP size.

This result might be considered paradoxical. In fact, because a drop in CMAP size is the product of motor unit loss and average S-MUAP size variation, why were these parameters not correlated with decrement? Motor unit loss is the primary pathologic process in ALS and cannot by itself explain decremental motor responses of the remaining motor units. The average S-MUAP size results from the interaction of at least three distinct processes: motor unit loss, collateral reinnervation, and motor unit degeneration. One or more of these processes could explain pathologic decrements in ALS, but their role might be concealed within the average S-MUAP size parameter because these three processes influence the motor unit size in different ways: 1) Preferential loss of large or small units induces either an average S-MUAP size decrease or increase. This size effect derived from the motor unit loss is unlikely to explain the decremental responses. 2) In ALS, the motor unit size increases by collateral reinnervation.[10] If reinnervation is the required substrate for decrement, the greatest chance to see it should be in larger reinnervated motor units. However, this seems not to be the case. In fact, a study of neuromuscular transmission in isolated motor unit potentials (MUP) indicates that decrements were more frequent and severe in small MUP.[2] Another explanation should be emphasized, however. In acute forms of ALS, short survival times of reinnervated motor units might prevent full reinnervation maturation and enlargement of motor unit size. Thus, a high degree of reinnervation immaturity, with reduced safety factor at immature reinnervated endplates and intermittent axonal conduction blocks at newly formed nerve endings, might be an explanation for decremental motor responses. 3) At advanced stages of the disease, motor units may undergo degeneration with a decrease in their size. Based on the observation that decrement was found more frequently and with more severity in small MUP, it may be suggested that synaptic transmission failure at neuromuscular junctions undergoing degeneration is probably an important factor accounting for the decrements.[2]

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