JNS 03922

Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue

Daria A. Trojan, Daniel Gendron and Neil R. Cashman

Department of Neurology
McGill University
Montreal Neurological Institute and Hospital
Montreal, Quebec, Canada

(Received 27 May, 1992)
(Revised, received 18 August, 1992)
(Accepted 28 August, 1992)

Journal of the Neurological Sciences, 114 (1993) 170-177

Correspondence to: Neil R. Cashman, M.D., Montreal Neurological Institute, 3801 University Street, Montreal, Quebec, Canada H3A 2B4. Tel.: (514) 398-8532: Fax: (514) 398-8540.

Key words: Postpoliomyelitis syndrome; Neuromuscular junction; Single fiber electromyography; Fatigue; Anticholinesterase; Electromyography

Summary

Disabling generalized fatigue and muscle fatiguability are common features of post-poliomyelitis syndrome (PPS). In 17 fatigued PPS patients, we measured jitter on stimulation single-fiber electromyography (S-SFEMG) for at least 3.5 min before and after i.v. injection of 10 mg edrophonium. We observed reduction in jitter (defined as a significant difference in jitter means before and after edrophonium, unpaired *t*-test $P < 0.05$) in 7 patients, no change in 8, and a significant increase in 2 patients. Blinded to their edrophonium results, the 17 patients were treated with pyridostigmine 180 mg/day for 1 month, with a subjective improvement of fatigue in 9 patients, and with a significant reduction in mean Hare fatigue scores in the entire group of 17 patients (pre = 2.71, and post = 1.71; Wilcoxan signed rank sum test, $P < 0.05$). Edrophonium-induced reduction of jitter on S-SFEMG was significantly associated with pyridostigmine-induced subjective improvement of fatigue (Fisher's exact test, $P < 0.04$). A significant reduction in fatigue with pyridostigmine was observed only in the 7 patients who experienced a significant reduction in jitter with edrophonium (Wilcoxan signed rank sum test, $P = 0.03$). In addition, the 9 pyridostigmine responders experienced a significant reduction in jitter means pre-

and post-edrophonium (100% vs. 88%, Bonferroni corrected, $P < 0.01$). We conclude that neuromuscular transmission as measured by jitter on S-SFEMG can improve with edrophonium in a proportion of PPS patients, and that generalized fatigue and muscle fatiguability in some patients with PPS may be due to anticholinesterase-responsive NMJ transmission defects.

Introduction

Progressive new weakness following decades of motor stability in individuals with antecedent paralytic poliomyelitis has been recognized since the time of Charcot *(Cornil and Lepine 1875; Raymond and Charcot 1875)*. Recent investigators have stressed generalized fatigue and pain as additional features of a "postpoliomyelitis syndrome" *(PPS; Halstead et al. 1985; Codd et al. 1985; Dalakas et al. 1986; Jubelt and Cashman 1987; Speier et al. 1987; Windebank et al. 1987; Munsat 1991)*. PPS is the most prevalent progressive motor neuron disease in developed countries, with an estimated 22-41% *(Codd et al. 1985; Speier et al. 1987; Windebank et al. 1987; Munsat 1991)*, of survivors of paralytic poliomyelitis being at risk for developing the syndrome during their lifetimes. Generalized systemic fatigue is reported by most patients with PPS *(Halstead et al. 1985; Codd et al. 1985; Trojan and Cashman 1989)*, and may be their most disabling symptom.

Fatigue as a symptom of disease is subjective, heterogeneous, and common, which frustrates controlled studies of its cause and treatment. In PPS, patient complaints appear to suggest both "central fatigue" (for example, mental symptoms such as difficulties in concentration and memory), and "peripheral fatigue" (for example, abrupt decline in strength upon sustained exertion). Muscle fatiguability on physical examination and electromyographic evidence of neuromuscular junction (NMJ) transmission defects (such as decrement on repetitive stimulation (Hodes 1948) and increased jitter on single fiber electromyography *(SFEMG; Wiechers and Hubell 1981; Cashman et al. 1987; Wiechers 1988)*, suggest that a proportion of PPS patients may indeed suffer from fatigue referable to the NMJ.

Clinical and electrophysiologic similarities between PPS and other diseases with established NMJ pathology, such as myasthenia gravis (MG) and amyotrophic lateral sclerosis *(ALS; Mulder et al. 1959; Stalberg et al. 1974; Stalberg et al. 1975; Denys and Norris 1979; Bernstein and Antel 1981; Engel 1986; Bradley 1987)*, have prompted the use of anticholinesterase agents such as pyridostigmine for treatment of postpoliomyelitis fatigue and muscle fatiguability *(Raymond 1986; Trojan and Cashman 1989)*. However, it has been difficult to implement a blinded controlled trial of pyridostigmine in PPS fatigue due to associated side effects, predominantly increased gut motility early in treatment.

We designed a trial to assess the effect of anticholinesterase agents on NMJ transmission, and on fatigue in PPS. The primary objective was to determine the effect of the intravenous, short-acting agent edrophonium on NMJ transmission, as assessed by stimulation single-fiber electromyography (S-SFEMG) in fatigued PPS patients. A secondary objective was to determine if a relationship was present between the results of the S-SFEMG/edrophonium test, and the patients' subsequent response to the oral anticholinesterase pyridostigmine. This was performed by administering pyridostigmine to all patients, blinded to the results of the edrophonium test, and rating their fatigue and functional level before and one month after initiation of low dose pyridostigmine.

Materials and methods

Patients and clinical evaluation

Seventeen PPS patients (age range 34-74) and 10 normal control subjects (age range 28-39) provided their informed consent to participate. All PPS patients were evaluated with a standardized history and physical

examination *(Cashman et al. 1987)*, and provided a history consistent with prior paralytic poliomyelitis followed by partial or complete recovery, with at least 25 years of functional stability. For inclusion in the study, all patients complained of at least 2 years of new symptoms, including muscle fatiguability (defined as increased weakness on sustained exertion which improves with rest), general fatigue, and at least 2 of the following 3 symptoms: (a) increased weakness in at least 1 extremity, (b) pain in at least 1 joint or spine, (c) muscle pain in at least 1 extremity. Severity of initial acute poliomyelitis was estimated by use of a 6-point modified index as described by *Klingman et al. (1988)*, with 1 point given for involvement of each of 4 extremities, of speech and/or swallowing, and for respiratory involvement. Other entry criteria included objective muscle fatiguability in at least 1 muscle on physical examination (decline of 1 Medical Research Council *(MRC; Medical Research Council 1982)* strength grade with 20 or less repetitive isotonic contractions), and lack of sufficient response to treatment with more conservative measures (such as rest periods during the day, activity planning, discontinuation of any medications associated with fatigue). No patient has concurrent medical or neurological disorders which could have interfered with the interpretation of electrophysiological testing or could be associated with fatigue.

Electrophysiological evaluation

The 17 patients and 10 controls were studied with S-SFEMG, which allows the evaluation of the NMJ of 1 muscle fiber at a constant stimulation frequency *(Trontelj et al. 1986; Jabre et al. 1989)*, obviating the need for patient voluntary effort required in conventional SFEMG *(reviewed by Stalberg and Trontelj 1979)*. Because of the known variability of jitter with different muscle fiber stimulation rates in other conditions affecting the NMJ *(Stalberg et al. 1974, 1975; Schwartz and Stalberg 1975; Schiller and Stalberg 1978)*, this technique may be the most reproducible electrophysiological method for assessment and comparison of NMJ dysfunction.

Muscles examined in patients had been previously affected by acute paralytic poliomyelitis, and were present in an extremity where the patient reported new decreased muscle endurance and increased fatiguability. NMJ transmission defects in the chosen muscles were confirmed by finding increased jitter by conventional SFEMG in at least 2 muscle fibers out of 20 or fewer fibers sampled, in comparison to the published limits for normal *(Stalberg and Trontelj 1979; Trontelj et al. 1986; Jabre et al. 1989)*. The muscles studied in the 17 patients were the extensor digitorum communis (5 patients), vastus medialis (11 patients), and the rectus femoris (1 patient). The extensor digitorum communis and the vastus medialis were each studied in 5 normal controls.

S-SFEMG was performed according to published techniques *(Trontelj et al. 1986; Jabre et al. 1989)*. The location of the motor point of the muscle being studied was determined with a surface stimulating electrode by finding the area of the muscle over which stimulation produced the greatest muscular contraction with the least voltage. Axonal stimulation was performed with a set of monopolar needles, one inserted near the motor point of the muscle and another subcutaneously, a few centimeters laterally. A rectangular pulse of 0.05 msec duration, with a stimulation frequency of 10 Hz was utilized. The current was adjusted to obtain the greatest twitch at the lowest stimulus intensity. An SFEMG electrode was then introduced in the area of the twitching fascicle (within 2-3 cm of the stimulating electrode), and was advanced slowly to locate a single muscle fiber (or fibers) with a rise time of < 300 μsec and an amplitude of 200 μV. To ensure suprathreshold stimulation (and thus avoid so-called false "stimulus-jitter"), the voltage was increased gradually to ensure steadiness of the amplitude, and shape of the muscle fiber potential from one stimulus to the next. Jitter was computed as the mean consecutive difference of latency from the stimulation artifact to the depolarization of the muscle fiber being studied of at least 50 discharges. To avoid the utilization of fibers activated by direct muscle fiber stimulation (and thus bypassing the nerve and the NMJ), muscle fibers with jitter values of 5 μsec or less were not utilized in

the analysis. We used a DISA electromyograph for the majority of our patients, however, a Tracer Northern and Nicolet Viking electromyographs were also used (1 patient for each). All 3 machines used the same paradigm for calculating jitter.

Stimulation single-fiber electromyography / edrophonium test

An edrophonium test was performed in the 17 PPS patients while recording jitter in 1 muscle fiber by S-SFEMG. Edrophonium was administered only once for each patient since ethical and technical considerations prevented reinjections. In 12 patients a muscle fiber in the quadriceps muscle was studied, whereas in the remaining 5 patients a muscle fiber in the EDC muscle was studied. The muscle fibers selected for the edrophonium test all had elevated jitter (i.e., jitter above 21.74 μsec for the EDC, and above 23.17 μsec for the quadriceps). Other inclusion criteria included the presence of little or no blocking, and the absence of multiple muscle fibers on the screen (which could have caused mutual interference from any neighboring potentials in the calculation of jitter). Muscle fibers with extremely high jitter and blocking were not utilized for the study because of their instability, and the difficulty in following them for the length of time necessary for this test. Once a suitable fiber was located in each patient, jitter measurements were obtained every 30 sec for at least 3.5 min. Axonal stimulation at a frequency of 10 Hz was performed continuously during the entire period of the edrophonium test (i.e., before and after edrophonium injection). Edrophonium, 2.0 mg, was then injected i.v., followed by 8.0 mg in 2.0 min. Jitter was then measured at the time of injection of edrophonium 8.0 mg and every 30 sec thereafter for at least 3.5 min. All jitter measurements obtained up to 300 sec before edrophonium injection, and between and including 30-300 sec after edrophonium injection were used in subsequent analyses.

Pyridostigmine trial

After edrophonium studies were performed on the 17 patients, oral pyridostigmine was initiated at 30 mg per day, and increased every other day by 30 mg to a maximum dosage of 180 mg/day in 3 divided doses. One patient was maintained on a lower dosage of 120 mg/day since she experienced a significant improvement with a minimum of side effects on this dosage. Patients and treating physician were blinded to the results of the S-SFEMG edrophonium test. Side effects from the medication occurred in 47% of patients, primarily in the initial stages of treatment. These included diarrhea, intestinal cramps, muscle cramps, anxiety, blurred vision, and increased- urinary frequency. In 2 patients, persistent diarrhea and increased urinary frequency necessitated the addition of propantheline and bethanechol, respectively, to pyridostigmine. One patient developed increased weakness on pyridostigmine, which resolved immediately on cessation of the medication.

Fatigue and function scales

To measure clinical response to pyridostigmine, the Hare fatigue index *(Hare et al. 1985)*, the modified Barthel ADL index *(Granger 1982)*, and a modified Klingman mobility index *(Klingman et al. 1988)* were administered for each patient before and 1 month following initiation of treatment. The Hare fatigue symptom scale, originally designed to quantitate exercise-induced fatigue in patients with cardiac disabilities, is an analog scale from 0 to 4 where 0 represents no fatigue, 1 is mild fatigue, 2 is moderate fatigue, 3 is severe, and 4 is unbearable fatigue. The modified Klingman mobility index is a 6 point scale where 0 represents no ambulatory difficulties, 1 is mild ambulatory difficulties without need for braces, 2 is moderate ambulatory difficulties with need for braces, 3 is severe ambulatory difficulties with need for braces and a wheelchair for longer distances, 4 is non-ambulatory, wheelchair bound (manual), 5 is non-ambulatory wheelchair bound (electric), and 6 refers to a bedridden patient. Pyridostigmine responders were defined as those patients who experienced an improvement of at least 20% over their initial scores.

Patients and treating physician were blinded to edrophonium test results.

Statistical analysis

Jitter comparisons between normal controls and post-polio patients were evaluated with the unpaired *t*-test. Change in NMJ transmission due to edrophonium was assessed by comparing pre and post edrophonium jitter means with the unpaired *t*-test. All jitter measurements obtained up to 5 min before and after edrophonium injection (but at least 3.5 min before and after) were used for this and appropriate subsequent analyses. Non-parametric tests were used with non-normal data distributions or ordinal measurement scales (Wilcoxan signed rank sum test for paired data, or Mann-Whitney U test for unpaired data). Fisher's exact test was used to compare proportions. To assess jitter in pyridostigmine responder and non-responder groups, pre- and post-edrophonium jitter means (normalized to 100% of pre-edrophonium values for each patient) were subjected to one-way analysis of variance, followed by post-test analysis using the Bonferroni corrected *P*-value for multiple comparisons. Statistical significance was accepted at $P < 0.05$.

Results

Previous studies have demonstrated abnormally increased jitter by conventional SFEMG in PPS muscles *(Wiechers and Hubell 1981; Cashman et al. 1987; Wiechers 1988)*. We confirmed NMJ transmission defects in 17 fatigued PPS patients using S-SFEMG, a more controlled technique which eliminates the variation of stimulation rates in voluntarily activated muscles. In 10 normal subjects, mean jitter in the extensor digitorum communis by S-SFEMG (21.7 μsec ± SD 8.7) was similar to that obtained in a previously published report (21.66 μsec ± SD 3.12) *(Jabre et al. 1989)*. There have been no previously published normal values for quadriceps muscles. Mean jitter values obtained in all PPS muscle fibers were significantly higher than those obtained in normal controls (unpaired *t*-test, $P < 0.0005$ for quadriceps, $P < 0.01$ for extensor digitorum communis; see Fig. 1). Even though our normal controls were younger than the PPS patients, and jitter is known to increase slightly with age after approximately 65 years *(Stalberg and Trontelj 1979)*, this effect would have been relatively small compared to the abnormally increased jitter observed in our PPS patients. Only 4 of our patients were over 65 years of age.

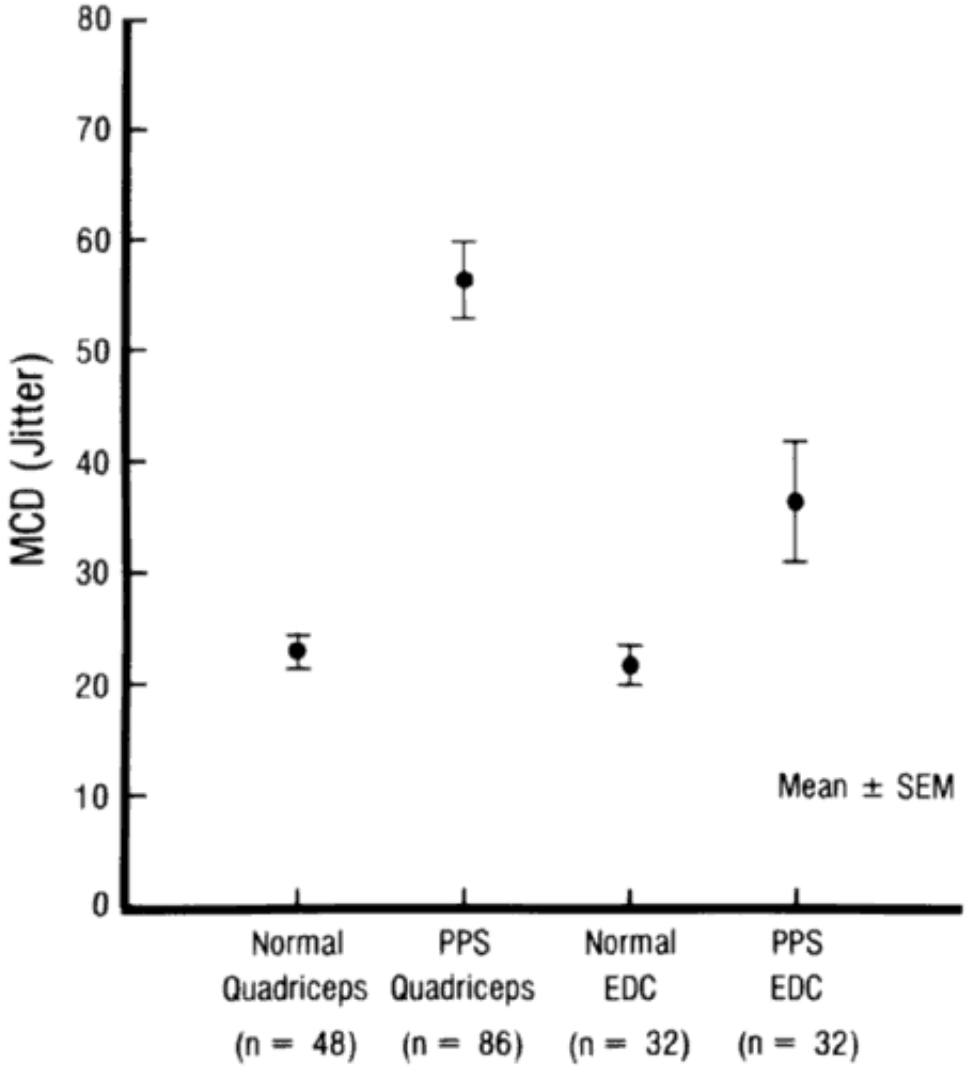

Fig. 1. S-SFEMG jitter is increased in PPS extensor digitarum communis and quadriceps muscles. Mean jitter of PPS extensor digitorum communis muscle fibers (36.61 ±30.9 μsec) ±SD was significantly higher ($P < 0.01$) than that of normals (21.74 ±8.77 μsec). Mean jitter of PPS quadriceps muscle fibers (56.48 ±34.34 μsec) was significantly higher ($P < 0.0005$) than that of normals (23.17 ±8.63 μsec).

Jitter values in the muscle fiber used for the SSFEMG / edrophonium test were recorded continuously every 30 sec for at least 3.5 min before and 3.5 min after injection of edrophonium 10 mg. After edrophonium, mean jitter declined (for example, Fig. 2) in 7 patients (defined as a significant reduction in mean jitter between pre- and post-edrophonium injection, unpaired *t*-test, $P<0.05$), was unchanged in 8 patients, and was significantly increased in 2 patients. (The phenomenon of edrophonium-induced increased jitter in a subset of NMJ is described in myasthenia gravis, and is of uncertain significance *(Stalberg et al. 1974.)* Reduction of jitter with edrophonium was not associated with the severity of pre-edrophonium jitter. In other words, severity of NMJ transmission defect did not predict improvement with edrophonium. In addition, there was no significant difference between edrophonium responders and non-responders with respect to age, sex, age at acute poliomyelitis, acute poliomyelitis severity score, duration of new symptoms, presence of weakness and pain, or pre-treatment fatigue and function scores (Fisher's exact test and Mann-Whitney U test, $P> 0.05$).

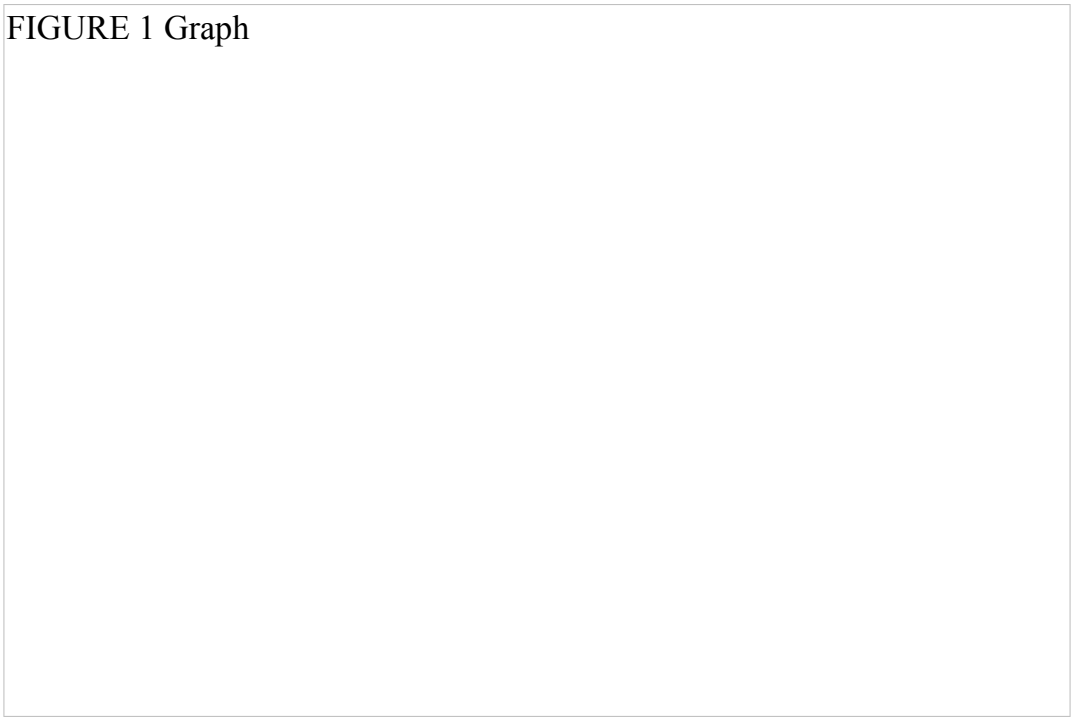

Fig. 2. Pre- and post-edrophonium jitter as determined by S-SFEMG in the vastus medialis muscle of a pyridostigmine responder. Upper panels show examples of raw data; the numerical jitter value is determined by the mean consecutive difference between the stimulation artifact (single arrows) and the unstable potential (double arrows) in 50 superimposed stimulations. Jitter means (lower panels) were recorded every 30 sec for 5 min before and 5 min after injection of edrophonium 10 mg (2 mg test dose followed by 8 mg 2 min after). Mean jitter for the 5 min before edrophonium (95.3 ±5.09 μsec SEM) significantly differed from mean jitter for the 5 min after edrophonium (47.6 ± 8.41 μsec, $T = 4.65$, $P < 0.0001$). Thus, this subject was judged to have a significant reduction in jitter with edrophonium in the studied unstable potential.

Nine of the 17 fatigued patients reported improvement on the Hare fatigue symptom scale 1 month after initiation of pyridostigmine. These patients experienced a reduction in systemic fatigue of 20-88% (mean 56%). Patients described dose-related fluctuations in fatigue which were consistent with the pharmacokinetics of pyridostigmine. All 9 patients also reported decreased muscle fatiguability, such as increased distance of ambulation, and the ability to perform activites which they has previously been unable to do. Of these 9 responders, 1 patient also improved in activities of daily living (modified Barthel index), and 1 improved in mobility (modified Klingman mobility index). Even though only 2 of 9 pyridostigmine responders showed improvement on the functional scales utilized, all 9 patients reported improved daily function and requested continuation of the medication (despite the presence of mild side effects in some). Duration of treatment in the responders ranged from 0.3 to 2.3 years, mean 1.22 years. A comparison of mean fatigue scores before and after treatment with pyridostigmine in the entire group of 17 patients revealed a statistically significant difference between these scores (Wilcoxan signed rank sum test, $P = 0.0039$, mean before treatment 2.71, mean after treatment 1.71). Comparison of pyridostigmine responders with non-responders revealed no significant differences with respect to age, sex, age at acute poliomyelitis, acute poliomyelitis severity score, duration of new symptoms, and presence of weakness and pain. However, patients who responded to pyridostigmine were significantly more fatigued on the pre-treatment Hare fatigue scale than patients who did not respond (Mann-Whitney U test, $P = 0.01$).

A significant association was seen between SSFEMG / edrophonium test results and clinical response to

pyridostigmine. Six of 7 patients with decreased jitter on edrophonium were less fatigued with pyridostigmine, and 7 of 10 patients with no change or increased jitter on edrophonium did not respond to pyridostigmine (Fisher's exact test, $P < 0.04$). We then separately analyzed this relationship from the perspectives of edrophonium response and pyridostigmine response. The 7 patients who has significantly decreased jitter on edrophonium injection experienced significant reduction of fatigue with pyridostigmine (fatigue pre = 3.0, post = 1.5; Wilcoxan signed rank sum test, $P = 0.03$; Fig. 3). The minor reduction of fatigue with pyridostigmine in the 10 patients who did not experience jitter reduction on edrophonium injection did not reach statistical significance (pre = 2.5, post = 1.85; $P = 0.25$).

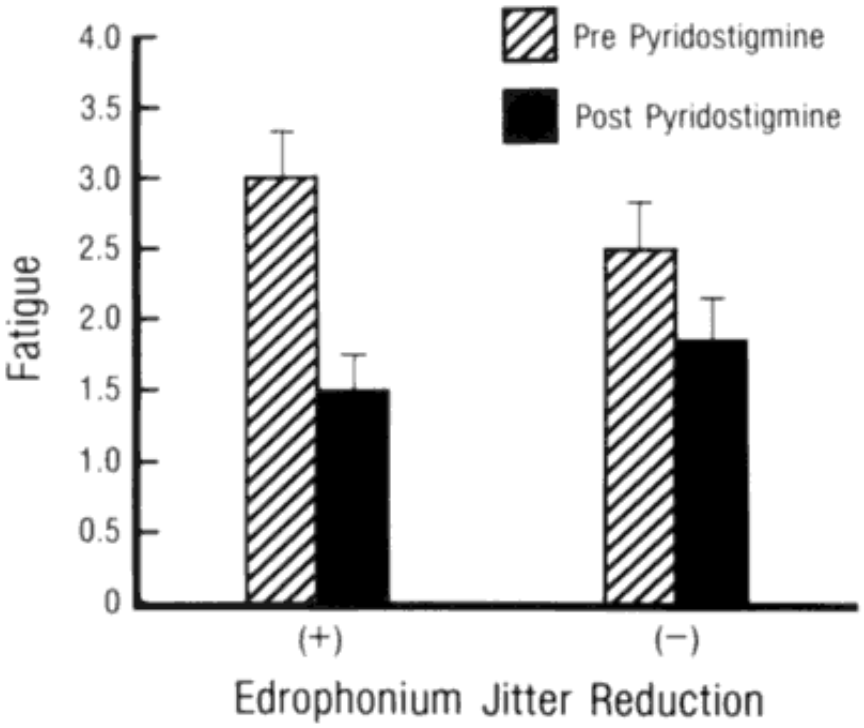

Fig. 3. Reduction in jitter with edrophonium predicts response of fatigue to pyridostigmine. In 7 patients with significant jitter reduction on edrophonium (+), but not in 10 patients without jitter reduction (-), a significant reduction in fatigue is reported (Hare fatigue index) with oral pyridostigmine therapy (mean fatigue score 3.0 pre-pyridostigmine, 1.5 post-pyridostigmine, Wilcoxan signed rank sum test, $P = 0.0313$). Error bars = SEM.

Conversely, when jitter means (normalized to 100% of pre-edrophonium mean) of the 9 pyridostigmine responders were compared to the 8 pyridostigmine nonresponders (Fig. 4), ANOVA analysis revealed significant variability between patient groups ($F = 14.04$, $P < 0.0001$). A significant reduction in jitter means pre- and post-edrophonium was observed in the 9 pyridostigmine responders (100 vs. 88%, Bonferroni corrected, $P<0.001$). The decline and subsequent increase in jitter on edrophonium injection is consistent with the known pharmacokinetics of edrophonium (Fig. 4). A significant difference was also observed between the post-edrophonium jitter means of the 9 pyridostigmine responders in comparison with the 8 non-responders (101 vs. 88%, $P<0.001$). No difference was noted between pyridostigmine non-responder jitter means pre- and post-edrophonium. Thus, response to pyridostigmine was associated with reduction of jitter on edrophonium injection.

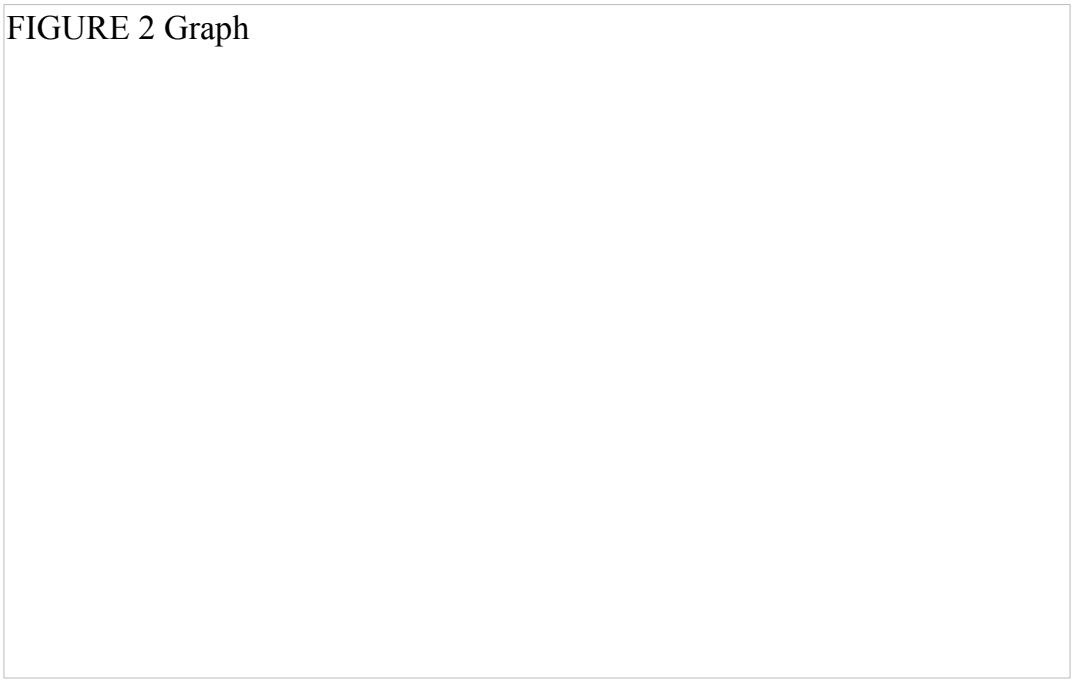

Fig. 4. Reduction of fatigue with pyridostigmine is associated with reduction of jitter on edrophonium injection. Patients who report > 20% improvement in Hare fatigue score with oral pyridostigmine (o) are significantly more likely than non-responders (·) to have experienced reduction of jitter on injection of intravenous edrophonium. Jitter plots normalized to 100% of pre-edrophonium mean jitter. Significant differences in jitter means are observed comparing pyridostigmine-responding patients ($n = 9$) pre and post edrophonium (Bonferroni corrected $P < 0.001$), and between pyridostigmine-responding and non-responding patients ($n = 8$), post edrophonium ($P < 0.001$). There is no significant difference of jitter means of pyridostigmine non-responding patients pre and postedrophonium ($P > 0.8$). Error bars = SEM

Discussion

Using S-SFEMG, we have confirmed that NMJ transmission defects are present in patients with antecedent poliomyelitis. Increased jitter on single-fiber electromyography has been noted in other diseases with NMJ pathology *(Stalberg et al. 1974, 1975; Schwartz and Stalberg 1975; Engel 1986; Bradley 1987; Schiller and Stalberg 1987)*. In MG, increased jitter is predominantly due to post-synaptic defects, from autoimmune destruction and blocking of endplate acetylcholine receptors *(Engel 1986)*. In botulism and myasthenic syndrome, the defect is thought to be presynaptic, due to defective release of acetylcholine *(Schwartz and Stalberg 1975; Schiller and Stalberg 1978)*. In ALS, the defect is probably presynaptic, secondary to intermittent conduction failure along immature, poorly myelinated terminal axonal sprouts, or to suboptimal release of acetylcholine *(Stalberg et al. 1975; Denys and Norris 1979; Bernstein and Antel 1981; Bradley 1987)*.

Increased jitter in PPS may reflect several distinct pathological processes. Following widespread denervation consequent to motor neuron cell death in paralytic poliomyelitis, surviving motor neurons undergo extensive distal sprouting to innervate denervated muscle fibers, enlarging the motor unit 7-fold or more *(Coers and Woolf 1959; Lange et al. 1989)*. Recent studies suggest that increased jitter in poliomyelitis, classically thought to occur transiently in reinnervation due to immaturity of axonal sprouts, may never normalize *(Wiechers 1988)*. In addition, constant "remodeling" of motor units apparently occurs in poliomyelitis patients without new symptoms *(Cashman et al. 1987; Lange et al. 1989; Ravits et*

al. 1990), which is presumably accompanied by increased jitter from turnover of immature reinnervating axonal sprouts. Thus, the finding of increased jitter decades after poliomyelitis can be due to an asymptomatic instability of neuromuscular transmission in enlarged, actively remodeling motor units. However, increased jitter could also be caused by irreversible degeneration of axonal sprouts, which is the most likely pathoetiology of new weakness in PPS *(Wiechers and Hubell 1981; Wiechers 1988)*. It is possible that an early phase of axonal degeneration is manifested by NMJ transmission defects due to defective synthesis, storage, or release of acetylcholine.

Edrophonium has been found to ameliorate NMJ transmission defects in MG and ALS (two disorders with muscle fatiguability and inconstant generalized fatigue) as measured by repetitive stimulation and SFEMG studies *(Mulder et al. 1959; Stalberg et al. 1974; Stalberg and Trontelj 1979)*. An early study by Hodes has also shown that neostigmine (an intravenous anticholinesterase) can improve NMJ transmission in patients with prior paralytic poliomyelitis, as assessed by repair of decrement on repetitive stimulation *(Hodes 1948)*. We have confirmed these findings in fatigued patients with prior paralytic polio utilizing the intravenous anticholinesterase edrophonium and a more sensitive measure of NMJ transmission adequacy. In our study, 7 of 17 fatigued PPS patients demonstrated a statistically significant amelioration of abnormal neuromuscular junction transmission (as measured by jitter on S-SFEMG) with edrophonium in a continuously activated muscle fiber. The fact that only about half of the studied abnormal NMJ's displayed improved transmission with edrophonium suggests some heterogeneity of transmission defect etiology in PPS, as discussed above.

Generalized fatigue, reported in up to 89% of PPS patients *(Jubelt and Cashman 1987)*, is a complex and common symptom attributed to a wide variety of etiologies, both "central" and "peripheral" *(Gow et al. 1987)*. Among the central problems cited to underly fatigue in PPS patients are chronic pain, depression, "type A" behavior, dysfunction of the reticular activating system, sleep disorders, and respiratory dysfunction *(Bruno and Frick 1987; Kohl 1987; Fischer 1987; Halstead 1991)*. Suggested peripheral defects, involving the motor unit itself, include metabolic exhaustion of massively sprouted motor neurons, NMJ transmission defects, and muscle abnormalities such as overuse myopathy and fiber type disproportion *(McComas et al. 1973; Jubelt and Cashman 1987; Grimby and Einarssen 1987; Munsat et al. 1987; Perry et al. 1988)*. In our study, we found a significant association between the results of the S-SFEMG / edrophonium test and subjective fatigue response to low-dose pyridostigmine. These findings suggest that peripheral mechanisms (i.e., NMJ transmission defects) may underlie fatigue in a propertion of PPS patients.

Anticholinesterase agents, which inhibit the hydrolysis of acetylcholine in the neuromuscular junction and prolong its effect, can clearly be associated with acute and chronic toxicity (both pre- and post-synaptic) in normal experimental animals, and probably in human patients *(reviewed by Munsat 1984)*. However, the potentially "excitotoxic" doses used in the past for MG (sometimes exceeding 2 g pyridostigmine per day) are far in excess of those we have used in PPS fatigue (180 mg/day). Despite the common benign side effect of increased gut motility, and reversible increased weakness in 1 patient, we have not observed chronic toxicity in PPS patients maintained for years on this low dose.

In conclusion, our trial indicates that NMJ transmission defects can ameliorate with anticholinesterases in fatigued post-polio patients, and that these defects may be a cause of fatigue in a proportion of this patient population. We believe that our study provides a physiologic rationale for the use of anticholinesterases in fatigued PPS patients unresponsive to other therapeutic measures, however, it does not assess the long-term risks and benefits of this therapy. Therefore, we recommend further controlled clinical trials prior to the widespread use of pyridostigmine in PPS.

Acknowledgements This work was supported in part by the Fonds de la Recherche en Santé du Québec, The Quebec March of

Dimes, and the Quebec Post-Polio Syndrome Association. We are indebted to the patients who participated in this study, and to EMG technicians Lora Tombari and Susan Murray for their expert assistance, and to L. Cetola and R. Cashman, who assisted in the preparation of the manuscript.

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The Secretary, Lincolnshire Post-Polio Network
PO Box 954, Lincoln, Lincolnshire, LN5 5ER United Kingdom
Telephone: +44 (0)1522 888601
Facsimile: +44 (0)870 1600840
Email: info@lincolnshirepostpolio.org.uk
Web Site: www.lincolnshirepostpolio.org.uk

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Document preparation: Chris Salter, Original Think-tank, Cornwall, United Kingdom.
Document Reference: <URL:http://www.zynet.co.uk/ott/polio/lincolnshire/library/trojan/anticholinesterase_rnjtd.html>
Created: 9th October 1998
Last modification: 30th January 2010.