JNS 04083

Stimulation frequency-dependent neuromuscular junction transmission defects in patients with prior poliomyelitis *

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

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

(Received 12 November, 1992)
(Revised, received 2 March, 1993)
(Accepted 30 March, 1993)

Journal of the Neurological Sciences, 118 (1993) 150-157

* This work was reported in part at the 1991 meetings of the American Academy of Physical Medicine and Rehabilitation (Washington D.C., October 29, 1991).
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: Poliomyelitis; Neuromuscular junction; Electromyography; Neuromuscular disease; Fatigue

Summary

Generalized fatigue and muscle fatiguability are major symptoms of post-poliomyelitis syndrome (PPS), and may be due to neuromuscular junction transmission defects, as suggested by increased jitter on single fiber electromyography (SFEMG). To determine the etiology of this defect, we studied jitter at low (1, 5 Hz) and high (10, 15, 20 Hz) frequency stimulation with stimulation SFEMG in 17 post-polio patients with muscle fatiguability, and in 9 normal controls. In 5 of 17 PPS patients and in 1 of 9 controls, jitter was significantly higher (unpaired *t*-test, $P < 0.05$) at high frequency stimulation (HFS). In the remaining PPS patients and controls there was no significant difference in jitter at high and low stimulation frequencies. PPS patients with increased jitter at HFS had a significantly longer time interval since acute polio (mean 48.5 years) than PPS patients without increased jitter at HFS (mean 40 years; $P < 0.05$), but were not distinguished by other historical or clinical criteria. We conclude that the neuromuscular junction defect in post-polio patients is similar to that observed in amyotrophic lateral sclerosis, and is probably due to ineffective conduction along immature nerve sprouts and exhaustion of acetylcholine stores. The

appearance of an increase in jitter with HFS in post-polio patients may be dependent upon time after acute polio.

Introduction

Post-poliomyelitis syndrome (PPS) is a clinical syndrome of new weakness, fatigue, and pain in individuals who have previously recovered from paralytic poliomyelitis *(Codd et al. 1985; Halstead et al. 1985; Jubelt and Cashman 1987; Munsat 1991; Speier et al. 1987; Windebank et al. 1987)*. Fatigue is a major symptom in PPS, occurring in 59 to 89% of patients *(Codd et al. 1985; Halstead et al. 1985; Halstead et al. 1987; Trojan and Cashman 1989)* and is frequently cited as the most disabling symptom. A recent study showed that symptoms of generalized fatigue may occur equally commonly in PPS and normal controls, whereas symptoms attributable to muscle fatiguability are significantly more common in PPS patients *(Berlly et al. 1991)*. Although the etiology of PPS is unknown, the most likely hypothesis attributes it to a distal degeneration of massively enlarged motor units from axonal sprouting following paralytic polio *(Wiechers 1988; Wiechers and Hubbell 1981)*. Previous studies in postpolio patients have suggested the presence of neuromuscular junction defects by demonstrating decrement of the compound motor action potential on repetitive stimulation *(Hodes 1948)* and increased jitter on single fiber electromyography (SFEMG) *(Cashman et al. 1987; Dalakas et al. 1986; Wiechers 1988; Wiechers and Hubbell 1981; reviewed in Trojan et al. 1991)*. These neuromuscular junction transmission defects may be due to both a remodeling process characterized by continuous denervation and reinnervation of muscle fibers in enlarged motor units *(Cashman et al. 1987; Lange et al. 1989; Wiechers 1988; Wiechers and Hubbell 1981)*, and/or to ongoing "permanent" terminal axonal degeneration *(Wiechers 1988; Wiechers and Hubbell 1981)*. Thus, evidence for neuromuscular junction transmission defects occurs at all stages following paralytic poliomyelitis, including asymptomatic postpolio patients *(Cashman et al. 1987; Wiechers 1988)*. Because of clinical and electrophysiological similarities of PPS with other disorders characterized by muscle fatiguability and increased jitter, fatigue in PPS may be attributable to neuromuscular junction transmission defects *(Bernstein and Antel 1981; Denys and Norris 1979; Engel 1986; Mulder et al. 1959; Stalberg et al. 1974, 1975; Trojan et al. 1993)*.

The electrophysiological abnormality of increased jitter in disorders of the neuromuscular junction is relatively nonspecific, and may be due to both pre-synaptic and post- synaptic abnormalities *(Stalberg and Trontelj 1979)*. It has been previously shown that the changes in jitter with rate of stimulation frequency provide some information regarding the location and etiology of neuromuscular junction transmission defects *(Chaudry et al. 1991; Sanders and Howard 1986; Schiller and Stalberg 1978; Schwartz and Stalberg 1975; Stalberg et al. 1974; Stalberg et al. 1975)*. For example, in botulism and myasthenic syndrome, jitter decreases with high frequency stimulation (HFS) through a partial correction of the presynaptic defect with higher nerve terminal calcium concentrations at greater discharge rates *(Chaudry et al. 1991; McArdle 1984; Sanders and Howard 1986; Schiller and Stalberg 1978; Schwartz and Stalberg 1978; Swift 1981)*. In amyotrophic lateral sclerosis (ALS), jitter increases with HFS probably secondary to ineffective conduction along immature nerve sprouts or exhaustion of acetylcholine (ACh) stores at higher stimulation rates *(Miller 1984; Stalberg 1982; Stalberg et al. 1975; Swift and Greenberg 1984)*.

To determine the possible etiology of the neuromuscular junction transmission defects in patients with past poliomyelitis, we studied the response of jitter to different stimulation frequencies in 17 fatigued post-polio patients and in 9 normal controls. The technique of stimulation SFEMG *(Jabre et al. 1989; Trontelj et al. 1986)* was used for this study because it allows distal motor nerve depolarization and muscle fiber activation by a stimulating needle electrode at a constant stimulation frequency determined by the electromyographer.

Materials and methods

Patients and controls

All post-poliomyelitis patients were evaluated with a standard history and physical examination *(Cashman et al. 1987)*. Data obtained in all patients and used in further analyses included present age, sex, age at time of acute polio, time since acute polio, duration of new symptoms, and presence of other difficulties (new weakness and pain), in addition to fatigue. An index of initial polio severity, a fatigue index, the Barthel ADL index *(Granger 1982)*, and a mobility index were also computed for each patient. A modified Klingman initial polio severity index was used *(Klingman et al. 1988)*. A score from 0 to 6 was obtained on each patient. One point was given for involvement of each of four extremities (partial or complete paralysis), one point for involvement of speech and/or swallowing, and one point for respiratory involvement. The subjective Hare fatigue scale *(Hare et al. 1985)* was used to measure fatigue. This is a 0 to 4 scale where 0 represents no symptoms from fatigue, 1 is mild, 2 is moderate, 3 is severe, and 4 is unbearable symptoms from fatigue. A modified Klingman mobility index *(Klingman et al. 1988)* with possible scores ranging from 0 to 6 was also used. Zero 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 nonambulatory, wheelchair-bound (manual), 5 is non-ambulatory, wheelchair-bound (electric), and 6 is bedridden.

All 17 patients provided a history consistent with prior paralytic poliomyelitis, followed by recovery, and at least 25 years of functional stability. All patients presented with complaints of new muscle fatiguability, defined as increased weakness on exertion, improving with rest. Other complaints included increased weakness in 14 patients, and pain in 12 patients. No patient had concurrent medical or neurological disorders which could have interfered with the results of the electrophysiological evaluation. Age range was 33 to 69 years, with a mean of 52 years. Nine normal controls, without known neurological or medical disorders were also studied. Age range was 30 to 37 years, with a mean of 33 years. All patients and controls provided informed consent for participation in the study.

SFEMG studies

Muscles examined in patients had been previously affected by acute paralytic poliomyelitis, and were present in an extremity where the patient reported new muscle fatiguability. All muscles studied in PPS patients with stimulation SFEMG showed evidence of impairment of neuromuscular transmission. These muscles had increased jitter in at least 2 out of 20 or fewer muscle fibers sampled by conventional SFEMG, in comparison to the published limits for normal *(Stalberg and Trontelj 1979)*. The muscles studied in patients included the vastus medialis (15 patients), biceps (1 patient), and extensor digitorum communis (1 patient), whereas muscles studied in controls were the vastus medialis (4 subjects), and extensor digitorum communis (5 subjects). The data obtained from the one patient studied in the biceps muscle was pooled with data obtained from subjects studied in the extensor digitorum communis muscle in the appropriate analyses.

All 17 patients and 9 normal controls were studied with stimulation SFEMG, an electrophysiological technique similar to conventional SFEMG, which differs in the manner of muscle fiber activation. Both techniques permit the measurement of jitter and blocking. In conventional SFEMG, jitter is the variability in the time of firing of two muscle fibers when both are being repetitively activated by the same motor neuron. An increase in normal jitter occurs with abnormalities in terminal axonal impulse propagation, in the neuromuscular junction, and in the motor end-plate. When the abnormality at any one of these sites is more severe, actual transmission failure or blocking can occur *(Stalberg and Trontelj 1979)*. During

stimulation SFEMG, muscle fiber activation is produced by electrical stimulation of the axon terminal with a monopolar needle electrode, whereas during conventional SFEMG, muscle fiber activation occurs voluntarily by the patient. Because of this, jitter values obtained with stimulation SFEMG reflect the neuromuscular transmission of only 1 muscle fiber, rather than 2, and for this reason they are lower than those obtained by conventional SFEMG *(Jabre et al. 1989; Trontelj et al. 1986)*. On stimulation SFEMG, jitter and blocking can be measured at constant, predetermined stimulation frequencies. In contrast, during conventional SFEMG muscle fiber activation occurs at variable stimulation frequencies since stimulation is under the voluntary control of the patient.

Stimulation SFEMG was performed in a manner similar to previously published reports *(Jabre et al. 1989; Trontelj et al. 1986)*. The motor point of the muscle studied was located with a surface stimulating electrode by finding the area of the muscle over which stimulation produced the greatest muscular contraction with the least voltage. Muscle fiber activation was produced by a rectangular pulse of 0.05 msec duration with a pair of monopolar electrodes, one placed near the motor point and the other subcutaneously, a few centimeters away. The current was adjusted to obtain the greatest twitch at the lowest stimulus intensity. A 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 less than 300 μsec and an amplitude of greater than 200 μV. To assure suprathreshold stimulation (and thus avoid false "stimulus-jitter"), the voltage was raised gradually to confirm steadiness of the amplitude and shape of the muscle fiber potential from one stimulus to the next. Jitter was automatically 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 prevent the use of fibers activated by direct muscle fiber stimulation (and thus bypassing the nerve and the neuromuscular junction), muscle fibers with jitter values of 5 μsec or less were not utilized in the analyses. A stimulation frequency of 10 Hz was used while searching for appropriate fibers to study. Once an appropriate fiber was located, jitter values were obtained at stimulation frequencies of 1, 5, 10, 15, and 20 Hz in each single muscle fiber. Inclusion criteria for selection of muscle fibers 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 difficulties in following them for the length of time necessary for the study. Because the fibers selected had little if any blocking, we were unable to assess the effect of stimulation frequency on blocking. Despite these precautions, we were unable to obtain jitter values at all 5 stimulation frequencies for all fibers identified. Therefore, only those fibers for which jitter values were available at 4 or 5 stimulation frequencies were utilized for further analyses. Data on 2 to 10 muscle fibers each studied at 4 to 5 stimulation frequencies was obtained on all patients and controls.

Statistical analysis

Neuromuscular transmission as measured by jitter was compared between PPS patients and controls at each of 5 stimulation frequencies in 2 separate muscle groups (quadriceps, biceps and extensor digitorum communis) with the unpaired *t*-test. The unpaired *t*-test was also used to compare mean jitter at low (1 and 5 Hz) and high (10, 15, 20 Hz) stimulation frequencies for each subject, to compare mean jitter at 1 Hz in those patients with and without increased jitter with HFS, and to compare mean jitter (calculated from average jitter at each stimulation frequency for each patient) at low and high frequency stimulation for all PPS patients and all controls. The non-parametric Mann-Whitney U-test was utilized to compare data from ordinal measurement scales between groups of patients. Fisher's exact test was utilized to compare proportions of patients. Statistical significance was accepted at $P < 0.05$.

Results

We studied neuromuscular junction transmission by SFEMG in PPS patients and in normal controls. Jitter was measured by stimulation SFEMG at 5 stimulation frequencies in 2-10 muscle fibers in 17 post-polio patients with muscle fatiguability, and in 9 normal controls. Jitter was significantly higher in PPS muscle fibers than in normal controls at all 5 stimulation frequencies in the 2 muscle groups studied, quadriceps and extensor digitorum communis (not shown; *Trojan et al. 1993*).

The effect of stimulation frequency on neuromuscular transmission in PPS and normal controls was then evaluated. This was done by comparing mean jitter measurements of all fibers (each studied at greater than or equal to 4 stimulation frequencies) at low frequency (1, 5 Hz) and high frequency (10, 15, 20 Hz) stimulation in each patient and control. The data are presented in Table 1. We found that in 5 of 17 PPS patients and in 1 of 9 controls, jitter was significantly higher at high stimulation frequencies (10, 15, 20 Hz) than at low stimulation frequencies (1, 5 Hz) (unpaired *t*-test, $P < 0.05$). Fig. 1 illustrates the marked increase in jitter observed with increasing stimulation frequency in the 10 muscle fibers studied in 1 patient. In the remaining 12 PPS patients and in 8 controls, there was no significant difference in jitter at high and low stimulation frequencies. A representative jitter response at different stimulation frequencies in a normal control is illustrated in Fig. 2. The actual data for the patients presented in Figs. 1 and 2 are displayed in Table 2. The effect of baseline jitter (at 1 Hz) on jitter response to HFS was also assessed. There was no significant difference in mean jitter at 1 Hz between groups of patients with and without increased jitter with HFS (28.79 ± 17.79 μsec (n = 24) and 35.73 ± 28.26 μsec (n = 43), respectively).

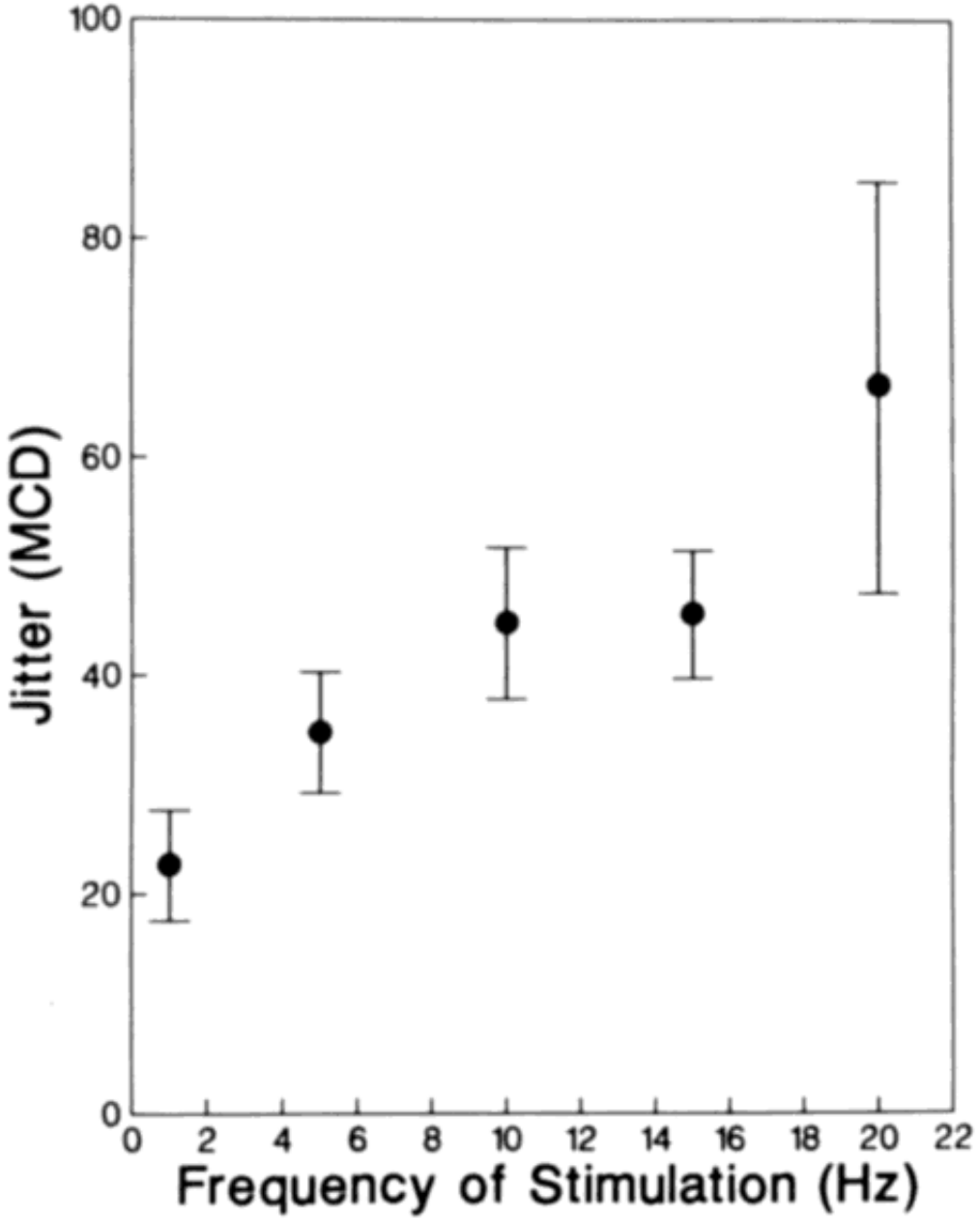

Fig. 1. Increase in jitter with increased stimulation frequency in 10 quadriceps muscle fibers of a PPS patient. Jitter (mean ± SEM) for each of 5 stimulation frequencies is illustrated. Mean jitter at high frequency stimulation (81.9 ± 27.0 μsec, mean ± SD) was significantly higher ($P < 0.001$) than mean jitter at low frequency stimulation (39.9 ± 22.5 μsec).

We also analyzed the effect of stimulation frequency on neuromuscular transmission on pooled data from all patients and all controls. Mean jitter (obtained from average jitter for each stimulation frequency for each subject) at low and high frequency stimulation was compared for all PPS patients and all controls. Despite the fact than only approximately 1/3 of PPS patients displayed significantly increased jitter on HFS, a significant difference was found between low and high frequency stimulation for all PPS patients (37.07 ± 16.53 μsec at low frequency stimulation, 48.58 ± 19.61 μsec at high frequency stimulation; $P < 0.006$), but not in all normal controls (18.39 ± 5.72 μsec at low frequency stimulation, 21.65 ± 7.25 μsec at high frequency stimulation; $P = 0.1170$).

To evaluate the clinical significance of this neuromuscular junction response to HFS in a proportion of PPS patients, clinical data from patients with significantly higher jitter at HFS was compared with that from patients who had no difference in jitter at low and high stimulation frequencies. There were no

significant differences between these two groups of patients with respect to age at study, sex, age at acute polio, severity of acute polio, duration of new symptoms, fatigue index, Barthel ADL index, or mobility index. However, a significant difference was noted with the variable of time since acute polio. Patients who had increased jitter at HFS had a significantly longer time since acute polio than patients without this electromyographic finding ($P < 0.05$). A summary of the clinical data is presented in Table 3.

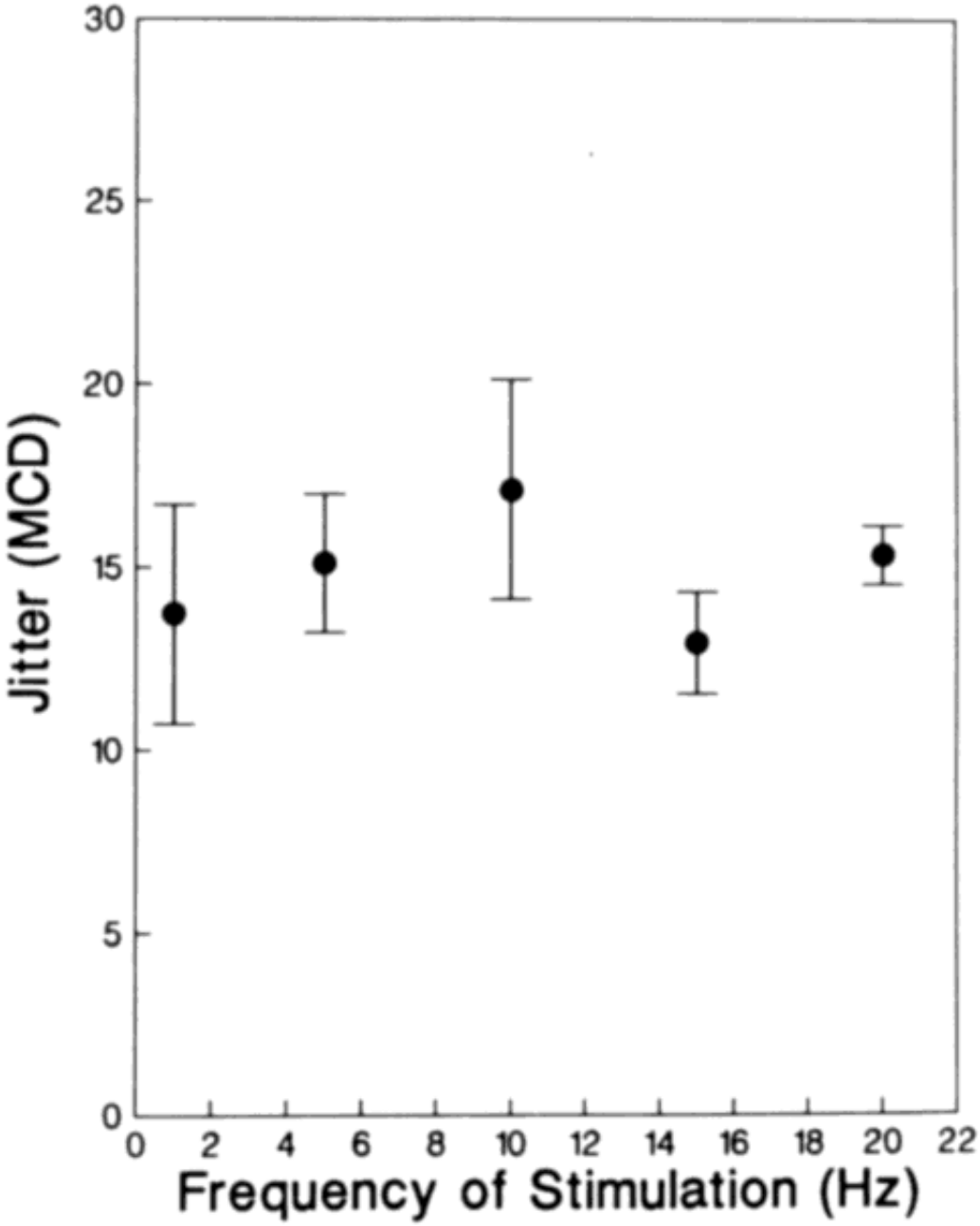

Fig. 2. Jitter response to increased stimulation frequency in 5 quadriceps muscle fibers of a normal control. Jitter (mean ± SEM) for each of 5 stimulation frequencies is illustrated. There was no significant difference between mean jitter at high frequency stimulation (15.1 ± 4.43 μsec, mean ± SD) than at low frequency stimulation (14.4 ± 5.38 μsec).

TABLE 1

JITTER AT LOW AND HIGH FREQUENCY STIMULATION IN PPS PATIENTS AND NORMAL CONTROLS

Case	Jitter (mean ± SD)		*P*-value
	Low frequency	High frequency	
Patient 1	48.3 ± 29.7 (n = 12)	69.17 ± 37.0 (n = 18)	0.11
Patient 2	44.7 ± 29.5 (n = 7)	39.8 ± 19.6 (n = 12)	0.67
Patient 3	29.5 ± 13.2 (n = 6)	30.2 ± 9.24 (n = 9)	0.91
Patient 4	48.1 ± 7.11 (n = 4)	52.4 ± 12.7 (n = 5)	0.57
Patient 5	32.6 ± 16.0 (n = 5)	28.7 ± 11.6 (n = 12)	0.58
Patient 6	70.7 ± 14.4 (n = 4)	61.3 ± 10.1 (n = 6)	0.26
Patient 7	38.5 ± 15.3 (n = 8)	46.7 ± 18.9 (n = 10)	0.34
Patient 8	68.2 ± 45.3 (n = 10)	62.0 ± 47.7 (n = 15)	0.75
Patient 9	14.5 ± 3.5 (n = 4)	32.5 ± 18.1 (n = 6)	0.09
Patient 10	33 ± 20.3 (n = 8)	49.8 ± 41.8 (n = 12)	0.31
Patient 11	21.3 ± 13.0 (n = 10)	23.6 ± 6.3 (n = 15)	0.56
Patient 12	27.0 ± 18.8 (n = 12)	30.4 ± 12.5 (n = 18)	0.56
Patient 13	28.7 ± 17.5 (n = 20)	52.3 ± 38.3 (n = 30)	0.01
Patient 14	48 ± 27.4 (n = 12)	66.9 ± 21.5 (n = 17)	< 0.05
Patient 15	39.9 ± 22.5 (n = 10)	81.9 ± 27.0 (n = 14)	< 0.01
Patient 16	22.9 ± 8.1 (n = 4)	67.1 ± 36.8 (n = 6)	< 0.05
Patient 17	18.3 ± 2.2 (n = 4)	27.3 ± 2.7 (n = 6)	< 0.05
Control 1	23.6 ± 14.4 (n = 4)	24.5 ± 7 (n = 6)	0.90
Control 2	26.8 ± 8.4 (n = 8)	28.3 ± 6.7 (n = 12)	0.66
Control 3	20.6 ± 7.3 (n = 6)	24.5 ± 6.2 (n = 9)	0.29
Control 4	14.9 ± 7.4 (n = 8)	16.9 ± 5.6 (n = 12)	0.50
Control 5	12 ± 9.2 (n = 6)	9.7 ± 4.9 (n = 9)	0.54
Control 6	18.2 ± 14.1 (n = 6)	29.39 ± 13.3 (n = 9)	0.14
Control 7	14.4 ± 5.4 (n = 10)	15.1 ± 4.4 (n = 15)	0.73
Control 8	18.5 ± 5.11 (n = 10)	25.7 ± 8.1 (n = 15)	0.02
Control 9	16.6 ± 7.2 (n = 8)	21.4 ± 5.3 (n = 11)	0.11

Low frequency = 1, 5 Hertz (Hz) stimulation; High frequency = 10, 15, 20 Hz stimulation; SD =

standard deviation; Mean values are average jitter measurements obtained in individual muscle fibers (each studied at greater than or equal to 4 stimulation frequencies) at low and high frequency stimulation. Jitter is measured as the mean consecutive difference (MCD) of latency of the stimulation artifact to the depolarization of the muscle fiber being studied in μsec; *P*-value = two-tailed *P*-value for unpaired *t*-statistic for difference between jitter means at high and low frequency stimulation.

TABLE 2

JITTER MEASUREMENTS FOR CASES PRESENTED IN FIGS. 1 AND 2

Case	Muscle fiber	Stimulation rate (Hz)				
		1	5	10	15	20
Patient 13	I	N/A	42	58	77	215
	II	15	30	49	59	61
	III	16	21	27	47	36
	IV	16	14	20	15	23
	V	25	33	87	65	126
	VI	27	43	36	42	45
	VII	18	21	33	52	46
	VIII	20	26	18	33	32
	IX	25	76	55	29	31
	X	63	42	65	37	49
Control 7	I	23	17	12	12	17
	II	8	13.5	26.5	18.5	16
	III	7.5	12.5	19	12	14
	IV	18.5	21.5	18.5	10.5	16.5
	V	11.5	11	9.5	11.5	13

NA = not available; Hz = Hertz; jitter is measured as the mean consecutive difference (MCD) of latency from stimulation artifact to muscle fiber being studied and is measured in μsec. The quadriceps muscle was evaluated in both subjects.

TABLE 3

COMPARISON OF CLINICAL DATA BETWEEN PATIENT GROUPS

Patient group	Age (yrs)	Sex (% male)	Age at acute polio (yrs)	Severity of acute polio	Time since acute polio * (yrs)	Duration of New Symptoms (yrs)
1 (n = 12)	50.3 ± 14.2	50%	10.3 ± 12.5	2.9 ± 1.4	40.0 ± 7.6	5.0 ± 1.5
2 (n = 5)	56.0 ± 4.6	80%	7.5 ± 3.9	3.2 ± 1.8	48.5 ± 6.0	6.4 ± 2.3

* $P < 0.05$; group 1 = patients with no significant difference in jitter at low and high stimulation frequencies; group 2 = patients with significantly higher jitter at high stimulation frequencies; severity of acute polio was measured on a 0-6 modified Klingman initial polio severity index *(Klingman et al. 1988)*. One point was given for involvement of each of four extremities, one point for involvement of speech and/or swallowing, and one point for respiratory involvement.

Discussion

We have confirmed the presence of neuromuscular junction transmission defects in patients with a history of antecedent paralytic poliomyelitis by stimulation SFEMG. Significantly increased jitter was present in PPS patients as compared to normal controls at all 5 stimulation frequencies studied. We have also found that in a proportion of fatigued post-polio patients (approximately 1/3) jitter can increase with HFS. This finding was observed in only 1 normal control, and may thus provide further evidence for a defect in neuromuscular transmission in post-polio patients. The fact that patients with this finding were characterized by a significantly greater time since acute polio may indicate that this defect evolves over time after acute paralytic polio.

Increased jitter on SFEMG or stimulation SFEMG can be indicative of a neuromuscular junction transmission defect *(Stalberg and Trontelj 1979)*. The finding of increased jitter in disorders such as myasthenic syndrome, botulism, ALS, myasthenia gravis (MG), and PPS can be due to a variety of either pre-synaptic or post-synaptic abnormalities of the neuromuscular junction. However, jitter can respond differently to HFS in disorders of the neuromuscular junction. In myasthenic syndrome, a reduced number of functional voltage-gated calcium channels is present, secondary to antibodies directed against calcium channels at motor nerve terminals *(Vincent et al. 1989)*. In botulism, the primary defect is an abnormality in the ACh release process, due to reduced sensitivity of vesicles to calcium-triggered exocytosis *(Cull-Candy et al. 1976; Howard and Gundersen 1980; Kao et al. 1976; Schiavo et al. 1992; Simpson 1986; Swift and Greenberg 1984)*. In both myasthenic syndrome and botulism, jitter can decrease with HFS *(Chaudry et al. 1991; Schiller and Stalberg 1978; Schwartz and Stalberg 1978)* presumably because of summation of calcium transients in the nerve terminal *(Sanders and Howard 1986; McArdle 1984; Swift 1981)*. HFS may thus partially correct the pre-synaptic defect present in these two disorders. In ALS, the neuromuscular defect may be due to the presence of immature axonal sprouts or to limitations in quantal number or content of ACh vesicles at motor neuron terminals *(Stalberg et al. 1975; Swift and Greenberg 1984)*. Jitter has been observed to increase with HFS in ALS probably as a result of ineffective conduction along immature terminal nerve sprouts or depletion of available ACh stores at rapid rates of stimulation *(Miller 1984; Stalberg 1982; Stalberg et al. 1975; Swift and Greenberg 1984)*.

Several mechanisms might be applicable to neuromuscular junction transmission defects in patients with past poliomyelitis. The recovery process after acute paralytic poliomyelitis is characterized by reinnervation by axonal sprouting *(Coers and Woolf 1959; Wiechers 1988; Wiechers and Hubbell 1981)*, a process which can enlarge motor units to 7 times normal size by pathological criteria *(Coers and Woolf 1959)*. Electrophysiological studies in patients with antecedent paralytic poliomyelitis suggest that the

grossly enlarged post-polio motor unit is undergoing continuous remodeling, or ongoing denervation and reinnervation. In addition, electron microscopic, light microscopic, and in vitro microelectrode studies of motor nerve terminals in post-polio patients have shown abnormalities involving the pre-synaptic region of the neuromuscular junction, which are consistent with reinnervation and denervation *(Maselli et al. 1992)*. Thus, immature sprouts may be present at all stages after paralytic polio *(Cashman et al. 1987, 1991; Lange et al. 1989; Wiechers 1988; Wiechers and Hubbell 1981)*. Immature nerve terminals have been found to release smaller amounts of ACh in experimental studies *(Swift and Greenberg 1984)*, and also exhibit abnormal transmission properties, which would certainly contribute to neuromuscular junction transmission defects. Microelectrode studies performed in two symptomatic post-polio patients were suggestive of a reduction in quanta available for immediate release at the motor nerve terminal, and a reduction in the average endplate potential quantal content *(Maselli et al. 1992)*. Thus, massively sprouted post-polio motor neurons may be unable to provide normal quantities of ACh at nerve terminals through a variety of mechanisms. Our findings of increased jitter with HFS in approximately 1/3 of PPS patients, and significantly increased jitter with HFS in the entire population of PPS patients and not in normal controls, indicates that of presynaptic disorders, the neuromuscular defect in patients with past poliomyelitis is most similar to ALS. In addition, because jitter response to HFS in patients with antecedent paralytic polio differs from that in myasthenic syndrome and botulism, defective calcium influx is unlikely to account for impaired release of ACh in post-polio motor units. We have also found that increased jitter with HFS within a particular patient is a later phenomenon, suggesting that this finding may be due to acquired, late factors other than remodeling of enlarged motor units, which occurs at all stages after polio. Thus, a new, unknown, superimposed abnormality in the post-polio motor unit may be present which could account for our observations.

The reason why only certain post-polio patients with muscle fatiguability were found to have increased jitter with HFS and why one normal control also displayed this phenomenon is speculative. To our knowledge, the response of jitter to stimulation frequency in normal controls has never been published. Because an increase in jitter with HFS was found in only one control, further studies are indicated in normals prior to drawing any conclusions. There may be several reasons for the finding of increased jitter with HFS in only 1/3 of PPS patients. First, because the occurrence of this phenomenon was found to be related to time after polio, its absence in a proportion of PPS patients may simply be due to an inadequate length of time after the acute illness. In addition, we studied only limited numbers of fibers and only one muscle in each patient. A more thorough examination may have resulted in the identification of this phenomenon in a greater number of patients. Because this study did not include stable post-polio patients, it is not known whether stimulation frequency-dependent neuromuscular junction transmission defects are specific for PPS, or whether they occur after poliomyelitis which is not complicated by new symptoms. Clearly, further study as to the nature, location, and clinical significance of the neuromuscular defects in post- polio patients is indicated.

Acknowledgements This work was supported in part by the Fonds de la recherche en santé du Québec, The Quebec March of Dimes, and the Association Polio Québec. We are indebted to EMG technicians Lora Tombari and Susan Murray for their expert technical assistance, to the reviewers for constructive criticism, and to the patients who participated in the study.

REFERENCES

Berlly, M.H., Strauser, W.W. and Hall, K.M. (1991) Fatigue in postpolio syndrome. Arch. Phys. Med. Rehabil., 72: 115-118. [PubMed Abstract]

Bernstein, L.P. and Antel, J.P. (1981) Motor neuron disease: decremental responses to repetitive stimulation. Neurology, 31: 202- 204. [PubMed Abstract]

Cashman, N.R., Maselli, R., Wollman, R.L., Roos, R., Simon, R., Antel, J.P. (1987) Late denervation in patients with antecedent paralytic poliomyelitis. New Engl. J. Med., 317: 7-12. [PubMed Abstract]

Cashman, N.R., Maselli, R.A., Wollman, R.L. and Antel, J.P. (1991) Electromyographic and muscle biopsy features of post-polio syndrome. In: Munsat, T.L. (Ed.), Post-Polio Syndrome, Butterworth-Heinemann, Boston, MA, pp. 83-89.

Chaudry, V., Watson, D.F., Bird, S.J. and Cornblath, D.R. (1991) Stimulated single-fiber electromyography in Lambert-Eaton myasthenic syndrome. Muscle Nerve; 14: 1227-1230. [PubMed Abstract]

Codd, M.B., Mulder, D.W., Kurland, L.T., Beard, C.M., O'Fallon, W.M. (1985) Poliomyelitis in Rochester, Minnesota, 1935-1955: epidemiology and long-term sequelae: a preliminary report. In: Halstead, L.S. and Wiechers, D.O. (Eds.), Late Effects of Poliomyelitis, Symposia Foundation, Miami, FL, pp. 121-134.

Coers, C. and Woolf, A.L. (1959) The Innervation of Muscle: a biopsy study. Blackwell Scientific, Oxford.

Cull-Candy, S.G., Lundh, H. and Thesleff, S. (1976) Effects of botulinum toxin on neuromuscular transmission in the rat. J. Physiol., 260: 177-203. [PubMed Abstract]

Dalakas, M.C., Elder, G., Hallett, M. et al. (1986) A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms. New Engl. J. Med., 314: 959-963. [PubMed Abstract]

Denys, E.H. and Norris, F.H. (1979) Amyotrophic lateral sclerosis impairment of neuromuscular transmission. Arch. Neurol., 36: 202-205. [PubMed Abstract]

Engel, A.G. (1986) Acquired autoimmune myasthenia gravis. In: Engel, A.G. and Banker, B.Q. (Eds.), Myology, McGraw Hill Inc, New York, NY, pp. 1925-1954.

Granger, C.V. (1982) Health accounting: functional assessment of the long-term patient. In: Kottke, F.J., Stillwell, G.K. and Lehmann, J.F. (Eds.), Krussen's Handbook of Physical Medicine and Rehabilitation, W.B. Saunders, Philadelphia, PA, pp. 253-274.

Halstead, L.S. (1991) Post-polio syndrome: definition of an elusive concept. In: Munsat, T.L. (Ed.), Post-Polio Syndrome, Butterworth- Heinemann, Boston, MA, pp. 23-38.

Halstead, L.S. and Rossi, C.D. (1987) Post-polio syndrome: clinical experience with 132 consecutive outpatients. In: Halstead, L.S. and Wiechers, D.O. (Eds.) Clinical and Research Aspects of the Late Effects of Poliomyelitis, March of Dimes Birth Defects Foundation, White Plains, NY, pp. 13-26. [PubMed Abstract]

Halstead, L.S., Wiechers, D.O. and Rossi, C.D. (1985) Late effects of poliomyelitis: a national survey. In: Halstead, L.S. and Wiechers, D.O. (Eds.), Late Effects of Poliomyelitis, Symposia Foundation, Miami, FL, pp. 11-31.

Hare, TW., Hakki, A.H., Lowenthan, D.T., Iskandrian, A.S. and Segal, B.L. (1985) Simplified scale for rating perceived exertion in patients with coronary artery disease. Ann. Sports Med., 2: 64-68.

Hodes, R. (1948) Electromyographic study of defects of neuromuscular transmission in human

poliomyelitis. Arch. Neurol. Psychiat., 60: 457-473.

Howard, B.D., Gundersen, C.B., Jr. (1980) Effects and mechanisms of polypeptide neurotoxins that act presynaptically. Annu. Rev. Pharmacol. Toxicol., 20: 307-336. [PubMed Abstract]

Jabre, J.F., Chiroco-Post, J. and Wiener, M. (1989) Stimulation SFEMG in myasthenia gravis. Muscle Nerve, 12: 38-42. [PubMed Abstract]

Jubelt, B. and Cashman, N.R. (1987) Neurologic manifestations of the post-polio syndrome. Crit. Rev. Neurobiol., 3: 199-220. [PubMed Abstract]

Kao, L, Drachman, D.B. and Price, D.L. (1976) Botulinum toxin: mechanism of presynaptic blockade. Science, 193: 1256-1258. [PubMed Abstract]

Klingman, J., Chui, H., Corgiat, M. and Perry, J. (1988) Functional recovery: a major risk factor for development of post-poliomyelitis muscular atrophy. Arch. Neurol., 45: 645-647. [PubMed Abstract]

Lange, D.J., Smith, T. and Lovelace, R.E. (1989) Postpolio muscular atrophy: diagnostic utility of macroelectromyography. Arch. Neurol., 46: 502-506. [PubMed Abstract]

Maselli, R.A., Davis, C.A., Wollman, R. et al. (1992) Neurophysiological and morphological abnormalities at the neuromuscular junction in patients with post-poliomyelitis syndrome. Neurology, 42 (Suppl. 13): 231 (abstract).

McArdle, J.J. (1984) Overview of the physiology of the neuromuscular junction. In: Brumback, R.A. and Gerst, J. (Eds.), The Neuromuscular Junction, Futura Publishing Company, Mount Kisco, NY, pp. 96-100.

Miller, R.G. (1984) The effects of nerve injury on the neuromuscular junction. In: Brumback, R.A. and Gerst, J. (Eds.), The Neuromuscular Junction, Futura Publishing Company, Mount Kisco, NY, pp. 235-237.

Mulder, D.W., Lambert, E.H. and Eaton, L.M. (1959) Myasthenic syndrome in patients with amyotrophic lateral sclerosis. Neurology, 9: 627-631.

Munsat, T.L. (1991) Post-Polio Syndrome, Butterworth-Heinemann, Boston, MA.

Sanders, D.B. and Howard, J.F. (1986) AAEE Minimonograph #25: Single-fiber electromyography in myasthenia gravis. Muscle Nerve, 9: 809-819. [PubMed Abstract]

Schiavo, G., Benfenati, F., Poulain, B. et al. (1992) Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. Nature, 359: 832-835. [PubMed Abstract]

Schiller, H.H. and Stalberg, E. (1978) Human botulism studied with single-fiber electromyography. Arch. Neurol., 35:346-349. [PubMed Abstract]

Schwartz, M.S. and Stalberg, E. (1975) Myasthenic syndrome studied with single-fiber electromyography. Arch. Neurol., 32: 815-817. [PubMed Abstract]

Simpson, L.L. (1986) Molecular pharmacology of botulinum toxin and tetanus toxin. Annu. Rev. Pharmacol. Toxicol., 26: 427-453. [PubMed Abstract]

Speier, J.L., Owen, R.R., Knapp, M. and Canine, J.K. (1987) Occurrence of post-polio sequelae in an epidemic population. In: Halstead, L.S. and Wiechers, D.O. (Eds.), Research and Clinical Aspects of the Late Effects of Poliomyelitis, March of Dimes Birth Defects Foundation, White Plains, NY, pp. 39-48. [PubMed Abstract]

Stalberg, E. (1982) Electrophysiological studies of reinnervation in ALS. In: Rowland, L.P. (Ed.), Human Motor Neuron Diseases, Raven Press, New York, pp. 47-57.

Stalberg, E. and Trontelj, J.V. (1979) Single Fiber Electromyography, The Mirvalle Press Ltd., Old Woking, Surrey.

Stalberg, E., Ekstedt, J. and Broman, A. (1974) Neuromuscular transmission in myasthenia gravis studied with single fiber electromyography. J. Neurol. Neurosurg. Psychiat., 37: 540-547. [PubMed Abstract]

Stalberg, E., Schwartz, M.S. and Trontelj, J.V. (1975) Single fiber electromyography in various processes affecting the anterior horn cell. J. Neurol. Sci., 24: 403-415. [PubMed Abstract]

Swift, T.R. (1981) Disorders of neuromuscular transmission other than myasthenia gravis. Muscle Nerve, 4: 334-353. [PubMed Abstract]

Swift, T.R. and Greenberg, M.K. (1984) Miscellaneous neuromuscular transmission disorders. In: Brumback, R.A. and Gerst, J. (Eds.), The Neuromuscular Junction, Futura Publishing Company, Mount Kisco, NY, pp. 305-309, 303-304.

Trojan, D.A. and Cashman, N.R. (1989) Treatment of fatigue in post-poliomyelitis syndrome with pyridostigmine. Arch. Phys. Med. Rehabil., 70: A-42.

Trojan, D.A., Gendron, D. and Cashman, N.R. (1991) Electrophysiology and electrodiagnosis of the post-polio motor unit. Orthopedics, 14: 1353-1361. **[Lincolnshire Library Full Text]**

Trojan, D.A., Gendron, D. and Cashman, N.R. (1993) Anticholinesterase responsive neuromuscular junction defects in post- poliomyelitis fatigue. J. Neurol. Sci., 114: 170-177. **[Lincolnshire Library Full Text]**

Trontelj, J.V., Milhelin, M., Fernandez, J.M. and Stalberg, E. (1986) Axonal stimulation for end-plate jitter studies. J. Neurol. Neurosurg. Psychiat., 49: 677-685. [PubMed Abstract]

Vincent, A., Lang, B. and Newsom-Davis, J. (1989) Autoimmunity to the voltage-gated calcium channels underlies the Lambert-Eaton myasthenic syndrome, a paraneoplastic disorder. Trends Neurosci., 12: 496-502. [PubMed Abstract]

Wiechers, D.O. (1988) New concepts of the reinnervated motor unit revealed by vaccine-associated poliomyelitis. Muscle Nerve, 11: 356- 368. [PubMed Abstract]

Wiechers, D.O. and Hubbell, S.L. (1981) Late changes in the motor unit after acute poliomyelitis. Muscle Nerve, 4: 524-528. [PubMed Abstract]

Windebank, A.J., Daube, J.R., Litchy, W.J. et al. (1987) Late sequelae of paralytic poliomyelitis in Olmsted County, Minnesota. In: Halstead, L.S. and Wiechers, D.O. (Eds.), Research and Clinical Aspects of the Late Effects of Poliomyelitis, March of Dimes Birth Defects Foundation, White Plains, NY, pp. 27-38. [PubMed Abstract]

The Lincolnshire Post-Polio Network
Registered Charity No. 1064177
An Information Service for Polio Survivors and Medical Professionals

All enquiries, book requests, medical article requests, membership fees, items for newsletters and donations to
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

The Lincolnshire Post-Polio Network takes great care in the transcription of all information that appears at this site. However, we do not accept liability for any damage resulting directly or otherwise from any errors introduced in the transcription. Neither do we accept liability for any damage resulting directly or otherwise from the information available at this site. The opinions expressed in the documents available at this site are those of the individual authors and do not necessarily constitute endorsement or approval by the Lincolnshire Post-Polio Network.

Document preparation: Chris Salter, Original Think-tank, Cornwall, United Kingdom.
Document Reference: <URL:http://www.zynet.co.uk/ott/polio/lincolnshire/library/trojan/stimulation_fdrnjtd.html>
Created: 16th April 1999
Last modification: 30th January 2010.