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RESEARCH REPORT

Electrophysiological findings in a cohort of old polio survivors

Eric J. Sorenson, Jasper R. Daube, and Anthony J. Windebank

Department of Neurology, Mayo Clinic, Rochester, MN, USA

Abstract A population-based cohort of poliomyelitis survivors was established and followed for 15 years (mean time since polio was 40 years). Over time, the cohort demonstrated a modest decline in summated compound muscle action potential amplitudes (CMAP) and a moderate decline in the summated motor unit number estimates (MUNE). There was no association between symptoms of late deterioration and magnitude of decline. Rather, the presence of these symptoms was associated with the magnitude of the residual deficits. Two patterns of neuron loss were modeled (linear and proportional decline). The summated MUNE was a more sensitive measure of loss of motor units than was the summated CMAP and appears to be a more valid measure of attritional loss of anterior horn cells. Of these two models of neuron loss, the proportional loss of motor neurons was a better fit of the data than a linear loss.

Key words: electrophysiology, epidemiology, neuromuscular disease, poliomyelitis

Introduction

Progressive neurological deficits in patients with a remote history of poliomyelitis have been reported for many years *(Mulder et al., 1972)*. Recently, we have shown that over a prolonged period of follow-up (15 years), there is a modest decline in neuromuscular function in a cohort of subjects with a remote history of polio *(Sorenson et al., 2005)*. Others have reported a moderate functional decline in polio survivors as well *(Jubelt and Cashman, 1987; Wiechers, 1987; Jubelt and Drucker, 1993; Stolwijk-Swuste et al., 2005)*. The etiology of this decline remains debated. It has been proposed that poor collateral reinnervation from the terminal axonal sprouts in massively reinnervated muscles is the main causative factor *(Dalakas, 1988)*. An inflammatory response within the affected muscles has been shown in some instances *(Dalakas, 1988)*. It has been shown that denervation may continue years after the acute polio infection in symptomatic and asymptomatic subjects *(Cashman et al., 1987; Grimby et al., 1998)*. McComas has previously reported a drop in motor unit number estimates (MUNE) counts in late survivors of poliomyelitis *(McComas et al., 1997)*.

Our population-based cohort was established in 1987 and consisted of 50 subjects with a remote history of paralytic poliomyelitis. The majority of the cohort complained of progressive weakness during the follow-up period. However, the presence of symptoms had no association with the magnitude of decline with time, rather it was associated with the residual weakness following the polio infection. As part of the cohort studies, we completed electrophysiological testing on the cohort subjects, including bilateral median (thenar) and peroneal (extensor digitorum brevis, EDB) compound muscle action potentials (CMAP) and MUNE, for those same muscles. We report here a detailed analysis of the electrophysiological data.

Methods

The cohort has been previously described *(Windebank et al., 1991; 1996)*. Fifty representative subjects were randomly chosen from 298 patients with

Address correspondence to: Dr. Eric J. Sorenson, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: 507-284-8729; Fax: 507-284-1013; E-mail: sorenson.eric@mayo.edu

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a documented history of paralytic poliomyelitis residing in Olmsted County at the time of the infection. At baseline, 5 years, and 15 years, the electrophysiological testing was performed in addition to the strength and timed functional tasks. This included bilateral median CMAP recording over the thenar muscles and bilateral peroneal CMAP recording over extensor digitorum brevis. For these same four nerves, MUNE were calculated. The statistical method described by Daube (1995) was used. For both CMAP and MUNE, a uniform methodology was utilized for all three time points. For each subject, the CMAP amplitudes and MUNE were summated into a composite CMAP and MUNE score, respectively. Each subject completed a questionnaire inquiring into the presence of any symptoms of progressive weakness at baseline and at follow-up.

An ANOVA for repeated measures was completed for the baseline, 5-year, and 15-year summated CMAP amplitudes and MUNE to determine if there was a decline over time. Wilcoxon rank sum tests were completed to determine if there was an association between the subject's symptom status and the magnitude of decline or the magnitude of baseline deficits. The Wilcoxon rank sum test was chosen because it is the most conservative of the tests available and requires no assumptions of normality or linearity.

One theory behind the post-polio syndrome is the dying back of overworked massively reinnervated motor neurons. If true, one would predict a correlation between baseline weakness and subsequent loss of motor units. To test this possibility, we correlated the baseline weakness scores on the neurological disability scale (NDS-w) and the decline in MUNE and CMAP amplitude.

Because there was a larger proportional drop in the MUNE relative to the CMAP amplitudes, the relationship between the MUNE and the CMAP was explored further. We plotted individual thenar MUNE against thenar CMAP amplitudes and peroneal MUNE against peroneal CMAP amplitudes. Additionally, we modeled the rate of loss of the MUNE after two biologically plausible patterns: linear loss or proportional loss. These are analogous to zero-order kinetic and first-order kinetic models, respectively, in pharmacological rates of decay. By comparing these models, one can assess if the rate of loss follows a linear (zero-order) pathway or a proportional (first-order) pathway. To model the linear pathway, the baseline and 5-year MUNE data were used to generate a linear regression formula that was then used to 'predict' the 15-year result. For the proportional model, the baseline and 5-year MUNE data were applied to the first-order kinetic formula: $\ln MUNE_5 = (\ln MUNE_0)(-kT)$ where $MUNE_5$ is the 5-year MUNE value, $MUNE_0$ is the baseline MUNE value, and T represents the time, 5 years. The equation is solved for k (k represents the velocity constant for the equation and is directly proportional to the half-life of the MUNE counts with the following relationship: $k = -0.693/t_{1/2}$, where $t_{1/2}$ is the time for the MUNE to drop in half, i.e., the half-life of the MUNE). By substituting the calculated k back into the original formula, the 15-year MUNE value was predicted. Both the linear and the proportional models were regressed against the actual 15-year MUNE data to determine if a correlation was present for either.

Results

Of the original 50 subjects to begin the cohort, 3 subjects died during the 15-year follow-up period. Nine of the remaining 47 refused further participation. Thirty-eight subjects of the original 50 completed the 15-year follow-up. The mean age of the 38 participants was 53 years (range 36–71 years) in 1987 at the inception of the cohort. The mean age at the time of the acute poliomyelitis was 15 years (range 1.5–36 years). There were 22 women and 16 men. Of these, 31 reported symptoms of progressive weakness during the follow-up period. 7 remained asymptomatic throughout the study. The demographics of the original cohort and the 38 patients completing the study are summarized in Table 1.

Overall, there was a decline in the summated CMAP amplitude and MUNE over the 15-year follow-up period. The summated CMAP amplitude declined from a mean of 26.0 (SD 2.5) at baseline to a mean of

Table 1. The demographics of the original cohort and the 38 patients completing the study.

Baseline characteristics of the cohort	All subjects enrolled	Thirty-eight subjects completing the cohort
Age at inception of cohort (1987) in years	49 (range 36–71)	53 (range 36–71)
Age at time of polio in years	13 (range 1.5–36)	15 (range 1.5–36)
Gender ratio	23 male: 27 female	16 male: 22 female
Baseline NDS	18 (range 0–103)	17 (range 0–103)
Residual bulbar weakness	6 of 50	4 of 38
Residual upper extremity weakness	24 of 50	16 of 38
Residual lower extremity weakness	29 of 50	18 of 38

NDS, neurological disability score for weakness.

19.0 (SD 3.7) at the 15-year follow-up point ($p < 0.001$). The summated MUNE declined from a mean of 407 (SD 67) at baseline to a mean of 226 (SD 64) at the 15-year follow-up point ($p < 0.001$). These data are summarized numerically in Tables 2 and 3. Individual thenar and peroneal MUNE and CMAP data are summarized in Tables 4 and 5.

There was no association between the magnitude of decline in either the summated CMAP amplitude or the summated MUNE and the presence of symptomatic progression. There was a mean decline in the CMAP amplitude of 6.8 mV (SD 2.8) for the asymptomatic group and a mean decline of 7.2 mV (SD 1.5) for the symptomatic group ($p = 0.90$). There was a mean decline in MUNE of 229 (SD 43) for the asymptomatic group and a mean decline of 120 (SD 24) for the symptomatic group ($p = 0.09$).

There was an association identified between the baseline values and the presence of symptomatic progression. The more severe the baseline deficit, the more likely the subjects were to be symptomatic. The mean baseline summated CMAP amplitude was 31.8 mV (SD 3.8) for the asymptomatic group and was 24.8 mV (SD 1.8) for the symptomatic group ($p = 0.08$). The mean baseline summated MUNE was 540 (SD 61) for the asymptomatic group and was 376 (SD 30) for the symptomatic group ($p = 0.04$). These data are summarized numerically in Tables 2 and 3.

Addressing the hypothesis of accelerated motor unit loss due to metabolic exhaustion, there was no correlation between the change in the summated CMAP amplitude or summated MUNE and the baseline weakness. Regression analysis comparing the baseline NDS-w score with the change in summated MUNE demonstrated an insignificant r^2 of 0.07 ($p = 0.20$). Regression analysis comparing the baseline NDS-w score with the change in summated CMAP amplitude demonstrated an insignificant r^2 of 0.05 ($p = 0.28$).

Interestingly, the mean MUNE had the larger proportional drop from the baseline relative to the CMAP amplitude. There was a change in the mean MUNE counts of 44% over the 15 years compared with 27% for the summated CMAP. Attritional loss of the anterior horn cells is one of the leading theories for late deterioration in these subjects and could explain our change in MUNE counts. To explore why the MUNE counts may decline out of proportion to the CMAP amplitude, we compared individual MUNE counts and CMAP amplitudes to determine if there was an association between them. We plotted thenar MUNE against thenar CMAP amplitudes and peroneal MUNE against peroneal CMAP amplitudes (Fig. 1). From these graphs, it is apparent that the CMAP amplitudes remain preserved until there has been a large loss of motor neurons. It is not until the MUNE counts drop below 50 that there is any appreciable decline in the CMAP amplitude. Comparing the change in MUNE counts with the change in CMAP amplitude failed to identify any significant correlation ($r^2 = 0.07$, $p = 0.18$).

Regression of the linear and the proportional models was completed as described in the Methods. For the linear model, no significant correlation was identified between the 'predicted' MUNE and the actual MUNE ($r = 0.35$, $p = 0.08$). For the proportional model, there was a significant correlation identified between the predicted MUNE and the actual MUNE ($r = 0.49$, $p = 0.01$). In neither model did the slope of decline approximate 1. These are summarized graphically in Fig. 2. The coefficient of variation was 3.6 for the proportional model and 9.0 for the linear model.

Discussion

The summated CMAP amplitudes and the summated MUNE do demonstrate a modest decline with time. This decline is more apparent with the MUNE data where a larger proportional change is demonstrated. While these do decline with time, there is no association between those symptomatic and the magnitude of change. Rather, the presence of symptoms of progressive weakness is associated with the magnitude of deficit at the start of the cohort. These findings concur with the strength and functional testing previously reported from this cohort *(Sorenson et al., 2005)*. In this same group of subjects, there was a modest decline in their strength (both quantitative and semiquantitative testing), timed walking tests, and hand manipulation tests *(Sorenson et al., 2005)*. Furthermore, these findings agree with other

Table 2. Summated motor unit number estimates for the three tested time periods and their change with time.

	Baseline MUNE mean (SD)	5-year MUNE mean (SD)	15-year MUNE mean (SD)	MUNE reduction (SD)
All subjects ($n = 38$)	407 (67)	331 (61)	226 (64)	181 (114)
Symptomatic ($n = 31$)	376 (30)	315 (33)	147 (19)	229 (43)
Asymptomatic ($n = 7$)	540 (61)	488 (66)	420 (38)	120 (24)

MUNE, motor unit number estimate.

Table 3. Summated compound muscle action potential amplitudes for the three tested time period and their change with time.

	Baseline CMAP in mV, mean (SD)	5-year CMAP in mV, mean (SD)	15-year CMAP in mV, mean (SD)	CMAP reduction (SD) in mV
All subjects ($n = 38$)	26.0 (2.5)	27.8 (2.9)	19.0 (3.7)	7.0 (5.8)
Symptomatic ($n = 31$)	24.8 (1.8)	27.2 (2.2)	17.6 (1.9)	7.2 (1.5)
Asymptomatic ($n = 7$)	31.8 (3.8)	35.2 (4.5)	25.0 (3.9)	6.8 (2.8)

CMAP, compound muscle action potential.

population-based studies *(Nollet et al., 2003)*. This suggests that the polio population declines uniformly and that there is a threshold below which the subjects may become symptomatic. Those subjects with larger deficits at baseline have a greater probability of crossing that threshold.

We are able to confirm the loss of motor units late in polio survivors as reported by McComas *et al. (1997)*. In that study, there was a loss of motor units over a 2-year follow-up of 13.4%, or 6.7% per year studied. Our subjects lost about 3% of their motor units per year. Cashman *et al. (1987)* have demonstrated that the highly reinnervated motor units in subjects with old polio are unstable. The magnitude of this instability was directly proportional to the degree of reinnervation. Muscle pathology in those subjects, both symptomatic and asymptomatic, demonstrated changes typical of old and recent denervation *(McComas et al., 1997)*. They proposed that late denervation and weakness may be the result of a dying back phenomena of the highly sprouted axon terminals. While this process may occur, the results of others and our study provide strong evidence for the loss of motor units in addition to the dying back of the terminal axonal sprouts.

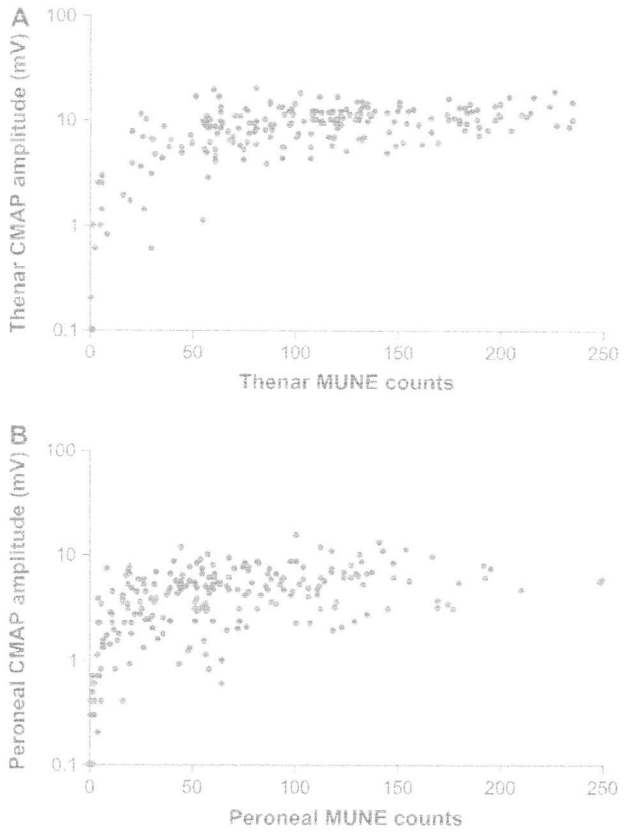

Figure 1. Motor unit number estimates (MUNE) values (x-axis) plotted against the compound muscle action potential (CMAP) amplitude (y-axis). The median (thenar) MUNE appears in the upper graph (A), the peroneal (EDB) MUNE appears in the lower graph (B). Note the preservation of the CMAP amplitude until there is a prominent drop in the MUNE count. Data represent pooled data points for all subjects from all three time points.

Others have suggested that these massively reinnervated motor units die prematurely due to excessive metabolic demands. This theory suggests that those subjects most severely affected by polio are at greatest risk for progressive deficits late in life. While we did identify an association between the severity of baseline deficits and the development of subjective complaints late in life, there was no association between these baseline deficits and any of the measured changes in neuromuscular function. These findings do not support this theory of motor neuron exhaustion.

Others have reported attritional loss of motor unit with aging in normal populations *(Doherty et al., 2003)*. McComas reported that the loss of motor units in their subjects was approximately twice that seen in their normal population *(McComas et al., 1997)*. Unfortunately, these were not age- or gender-matched controls, which limits the value of this comparison. The rate of decline in our polio cohort was approximately the same as the normal population in the study of McComas but about half that in their polio patients. At the establishment of our cohort, a normal age- and gender-matched control group was not included. Without such a control group, one cannot reliably compare the changes in the polio group with those in a normal aging population. However, in a cross-sectional study of normal subjects, there was a decline in the thenar MUNE counts from a mean of 288 to 139 between the ages of 40 and 60 years *(Doherty et al., 2003)*. This represents approximately a 50% decline, or 2–3% per year. This is commensurate with the rate

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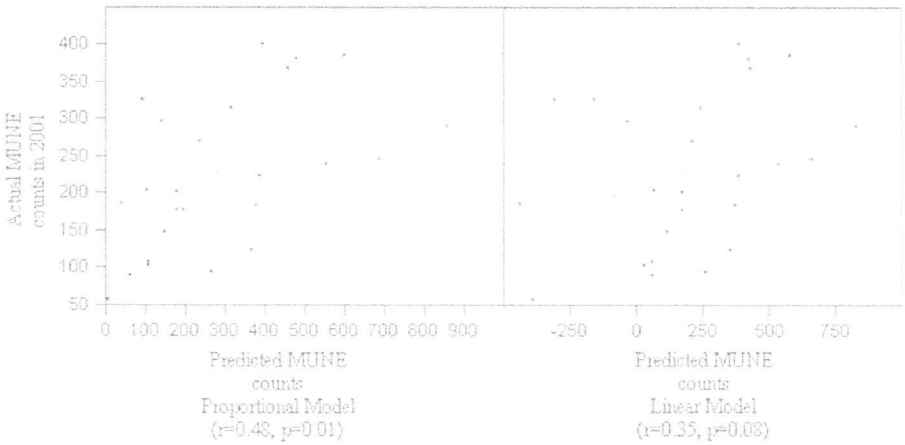

Figure 2. Regression analysis for the two models of motor neuron loss. The graph on the right represents the predicted motor unit number estimates (MUNE) following a proportional rate of loss regressed against the actual MUNE value obtained at the end of the study period (coefficient of variation 3.6). The left graph represents the predicted MUNE following the linear rate of loss regressed against the actual MUNE value obtained at the end of the study period (coefficient of variation 9.0).

of decline in our study population of 2.9% annually. Additionally, in that same cross-sectional study, there was a drop in the CMAP area from 38.2 to 25.9 mV-ms over the same age range. This represents a decline of 1.6% per year compared with 1.8% identified in our cohort study. While the methods of these two studies differ, the similarity of these results suggests that our polio cohort did not age any differently than a normal population. This suggests that the most likely cause for the decline in our polio survivors is aging alone.

One needs to be cautious in generalizing the results from a small number of distal muscles to the remaining muscles throughout the body. We have reported the data as summated CMAP amplitudes and MUNE to minimize the concern of limb-to-limb variation and the variability inherent from measurement error. Nevertheless, these precautions do not eliminate the potential of a sampling bias. However, these electrophysiological studies demonstrate considerable internal consistency with our other strength and functional assessments that do study the performance of a wider range of muscles and functions. This consistency adds to the validity of our electrophysiological findings and conclusions.

The summated MUNE in our population demonstrated a larger magnitude of decline than the summated CMAP amplitude. The graphs in Fig. 2 convincingly show that there may be a substantial loss of motor units before there is any appreciable change in the CMAP amplitude. This is almost certainly due to the effects of reinnervation. The CMAP amplitude remains preserved due to collateral reinnervation even in the setting of progressive anterior horn cell loss. It is only after the loss of motor neurons has progressed beyond the capacity of reinnervation that there will be a concomitant loss of the CMAP amplitude. In our data, this limit of reinnervation does not occur until the number of motor units in the thenar and peroneal group drops below 50. Until then, reinnervation is sufficient to maintain the CMAP unchanged. These data suggest that the summated MUNE is a more valid measure to detect neuron loss over time than the summated CMAP.

While neither model of loss (proportional or linear) closely matches the data, the stronger correlation and better coefficient of variation would favor the proportional model over the linear model. The large degree

Table 4. Motor unit number estimates for individual muscle groups at all three time points.

	Mean thenar MUNE	Mean peroneal MUNE
Baseline	123	81
5 year	100	66
15 year	68	45
Significance	$p = 0.001$	$p = 0.01$

MUNE, motor unit number estimate.

Table 5. Compound muscle action potential amplitudes for individual muscle groups at all three time points.

	Mean thenar CMAP (mV)	Mean peroneal CMAP (mV)
Baseline	8.5	4.5
5 year	9.4	4.5
15 year	6.5	3.0
Significance	$p = 0.001$	$p = 0.003$

CMAP, compound muscle action potential.

of variation seen in both models may be a reflection of the underlying variation known to occur with most MUNE techniques available currently. Nonetheless, these findings raise doubts about linear assumptions of decline for motor neuron loss in polio.

Limitations of our study are that of the 50 original subjects, only 38 were available for the follow-up testing and only 7 remained asymptomatic for the duration of the study. There is no evidence that the 38 subjects studied are systematically different from the 9 who declined participation or the 3 who died (Table 1). The fact that only seven subjects remained asymptomatic does limit our power to correlate progression with time to the development of the post-polio syndrome. However, given the associations identified in this study, it appears that the severity of the residual deficits is the strongest predictor of its development rather than the rate of decline late in life.

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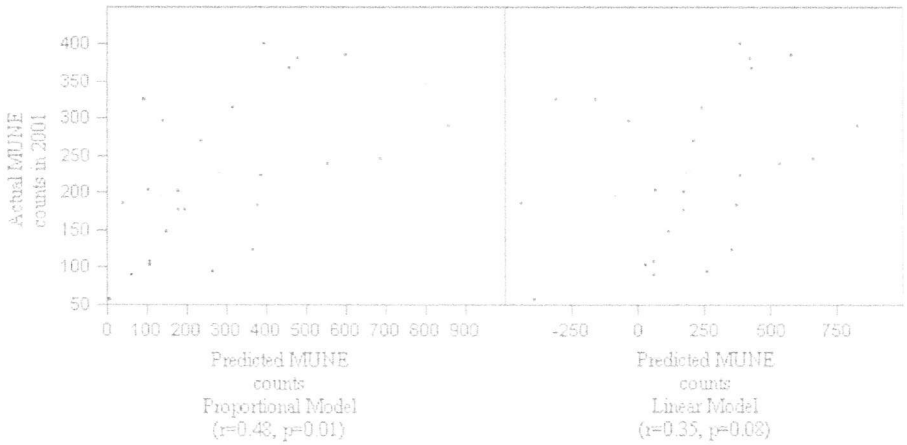

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