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Predictive Factors for Post-Poliomyelitis Syndrome

Daria A. Trojan, MD, MSc, Neil R. Cashman, MD, Stanley Shapiro, PhD, Catherine M. Tansey, MSc, John M. Esdaile, MD

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From the Department of Neurology (Drs. Trojan, Cashman), Montreal Neurological Institute and Hospital, the Department of Medicine (Dr. Esdaile), Montreal General Hospital, and the Department of Epidemiology and Biostatistics (Dr. Shapiro, Ms. Tansey), McGill University, Montreal, Quebec, Canada.

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Reprint requests: Daria A. Trojan, M.D., Montreal Neurological Institute, 3801 University, Montreal, Quebec, Canada H3A 2B4, Canada.

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ABSTRACT Trojan DA, Cashman NR, Shapiro S, Tansey CM, Esdaile JM. Predictive factors for post-poliomyelitis syndrome. Arch Phys Med Rehabil 1994;75:770-7.
Post-poliomyelitis syndrome (PPS) is generally defined as a clinical syndrome of new weakness, fatigue, and pain in individuals who have previously recovered from acute paralytic poliomyelitis. The purpose of this study was to identify, through a case-control study design, factors that predict subsequent PPS in patients with prior paralytic poliomyelitis. Among patients attending a university-affiliate hospital post-polio clinic, "cases" were patients with new weakness and fatigue, and "controls" were patients without these complaints. A chart review of 353 patients identified 127 cases and 39 controls. Logistic regression modeling was used to calculate adjusted and unadjusted odds ratios. In univariate analyses, significant risk factors for PPS were a greater age at time of presentation to clinic ($p = 0.01$), a longer time since acute polio ($p = 0.01$), and more weakness at acute polio ($p = 0.02$). Other significant associated, but not necessarily causal factors were a recent weight gain ($p = 0.005$), muscle pain ($p = 0.01$) particularly that associated with exercise ($p = 0.005$), and joint pain ($p = 0.04$). Multivariate analyses revealed that a model containing age at presentation to clinic, severity of weakness at acute polio, muscle pain with exercise, recent weight gain, and joint

pain best distinguished cases from controls. Age at acute polio, degree of recovery after polio, weakness at best point after polio, physical activity, and sex were not contributing factors. These findings suggest that the degree of initial motor unit involvement as measured by weakness at acute polio, and possibly the aging process and overuse are important in predicting PPS.
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Although acute poliomyelitis is now relatively uncommon in North America,*[1]* approximately 640,000 individuals who have recovered from acute paralytic poliomyelitis are alive today.*[2]* Subsequently, as many as half of these individuals may develop post-poliomyelitis syndrome (PPS).*[3-7]* PPS is defined as a clinical syndrome of new weakness, fatigue, and pain in those who have recovered from acute paralytic poliomyelitis.*[2,8,9]* Even though PPS is the most prevalent progressive motor neuron disease in North America today, there are few epidemiologic studies that evaluate possible predictors for this condition.

PPS is believed to be caused by a distal degeneration of massively enlarged motor units from axonal sprouting after acute paralytic poliomyelitis.*[10,11]* Overuse is thought to be a contributing factor.*[12,13]* This degenerative process can produce neuromuscular junction transmission defects, a possible cause of fatigue,*[14-19]* and permanent denervation with resultant clinical weakness.*[10,11,14,20]* Because it is currently unclear how or if pain is referable to disease of the motor unit, this study is concerned with new weakness and fatigue as part of PPS. Pain is studied as a predictor, but not as part of PPS.

The object of this study was to identify factors that predict and are associated with PPS (new weakness and fatigue) in patients with antecedent paralytic poliomyelitis. Previous studies have shown that potential risk factors for PPS include a more advanced age at acute polio,*[21,22]* a greater severity of initial acute poliomyelitis,*[4,6,21,22]* a greater recovery in muscular strength after poliomyelitis,*[22]* presence of permanent impairment after recovery after poliomyelitis,*[7]* lower disability at presentation to clinic,*[21]* female sex,*[7]* a greater length of time since acute polio,*[7]* and possibly increased recent physical activity.*[22]* In addition to studying these risk factors, our study evaluated a number of previously evaluated predictors including age at time of presentation to the clinic, usual physical activity prior to development of PPS, and joint pain, and a number of novel predictors including weakness at the time of maximum strength ("best point") after polio, recent weight gain, and muscle pain (at rest or with exercise). The identification of potentially preventable factors may result in better management of patients with previous polio

METHODS

Study Design

Because of the long delay between acute polio and PPS, a case-control design was used. Based on the numbers of cases and controls identified, this study should have been able to detect an odds ratio of 2.5 for an exposure rate of $p = 0.4$.*[23]* Institutional ethics committee approval was ottained for the study.

Study Population

Cases and controls were identified through a chart review of 353 patients evaluated at a university affiliated-hospital post-polio clinic between 1986 and March, 1992. Patients are referred to the clinic for evaluation and treatment of specific problems, however a proportion of patients come simply to obtain information about PPS and on methods for reducing the risk for PPS. A prerequisite for evaluation in the clinic is a history of paralytic polio, therefore virtually all patients have had paralytic polio. In a few cases, the diagnosis of acute paralytic polio was questionable, and electrodiagnostic testing was done in an

attempt to confirm the history. On the initial visit, a standardized history and physical examination form was completed (NRC or DAT) for each patient, and a thorough medical history, physical examination, and appropriate diagnostic tests were performed. Some patients were seen only once, others were seen more frequently. To prevent any bias from use of data obtained on follow-up visits, data obtained from the initial interview and the immediately following laboratory investigations were used. The study was conceived after clinic visits had occurred, but a standardized evaluation form was used on all patients.

Inclusion criteria for cases in the study were based on those suggested by Mulder and colleagues.*[24]* They were (1) a history of past paralytic poliomyelitis (an illness characterized by high fever, followed by muscular weakness), (2) initial partial or complete recovery of function, (3) at least 10 years of functional stability following initial recovery, and (4) new symptoms of increased or new muscular weakness, *and* fatigue (muscular and/or general). Muscular fatigue was defined as increasing muscular weakness on exertion, which improves with rest. General fatigue was defined as an overwhelming, "flu-like" exhaustion.*[8]* Exclusion criteria were (1) presence of past and concurrent medical conditions that could produce weakness and fatigue at initial visit (eg, significant cardiac disease that requires treatment with medication), chronic obstructive pulmonary disease, cancer, cirrhosis, depression, hypothyroidism, anemia, connective tissue disease, chronic infection, diabetes mellitus, and chronic renal failure), (2) presence of other past or concurrent neurological disorders that could produce weakness and fatigue at initial visit (eg, peripheral neuropathy, head injury, stroke, Parkinson's disease, radiculopathies, spinal stenosis with myelopathy), and (3) presence of severe pain at initial visit that could make differentiation between pain and muscular weakness difficult. One hundred twenty-seven cases were identified.

Inclusion criteria for controls in the study were (1) a history of past paralytic poliomyelitis (an illness characterized by high fever, followed by muscular weakness), (2) initial partial or complete recovery of function, and (3) at least 10 years of functional stability following initial recovery. Exclusion criteria were (1) presence of past and concurrent medical conditions that could produce weakness and fatigue at initial visit leg, significant cardiac disease [that requiring treatment with medication]), chronic obstructive pulmonary disease, cancer, cirrhosis, depression, hypothyroidism, anemia, connective tissue disease, chronic infection, diabetes mellitus, and chronic renal failure), (2) presence of other past or concurrent neurological disorders that could produce weakness and fatigue at initial visit leg, peripheral neuropathy, head injury, stroke, Parkinson's disease, radiculopathies, spinal stenosis with myelopathy), (3) presence of severe pain at initial visit that could make differentiation between pain and muscular weakness difficult, and (4) presence of new symptoms of increased or new muscular weakness, and/or fatigue (muscular and/or general). Thirty-nine controls were identified.

Data Collection

Data were obtained from a chart review of patients included in the study. Data on the following independent variables were obtained: age (at time of presentation to clinic), sex, age at acute polio, latency or time in years between acute polio and presentation to clinic, presence of pain (muscular and/or joint; muscular pain included pain with exercise and/or pain at rest), weakness at acute polio, weakness at "best point" after acute polio, weakness at time of presentation to clinic, recovery after polio, hospitalization at time of acute polio, ambulation disability index at "best point" after acute polio and at presentation to clinic, reported recent weight gain (within last 5 years), physical activity index, and motor strength score at presentation to clinic in each of four extremities. The scales used are described below.

Degree of weakness was estimated on the same 0 to 6 scale at three different time periods: at time of acute polio, at "best point" after acute polio, and at presentation to clinic. The measure was based on subjective patient estimates of percent weakness in each of four limbs, respiratory muscle weakness, and

speech/swallowing dysfunction. During the initial interview, each patient was asked to rate the amount of weakness in each of four limbs from 0 to 100 (0 being normal or not paralyzed, and 100 being completely paralyzed) at each of three time periods. For respiratory muscle function, a 50 was assigned for some weakness, and a 100 for weakness requiring use of a ventilator. A 50 was assigned for some speech and/or swallowing dysfunction, and a 100 for complete loss of speech and/or swallowing. The sum total score of all six figures was divided by 100 to make the final scale easier to interpret in further analyses. In this way, a scale ranging from 0 to 6 was produced.

Recovery after acute polio was measured as the difference between severity of weakness at time of acute polio and severity of weakness at "best point" after acute polio.

A motor strength index at time of presentation to clinic was estimated for each of four extremities. This index was based on motor strength determined on physical examination in each of five muscle groups in the upper extremities (deltoid, biceps, triceps, wrist extensors, hand intrinsics) and in each of five muscle groups in the lower extremities (hip flexors, quadriceps, hamstrings, dorsiflexors, plantarflexors) by a 0 to 5 Medical Research Council (MRC) scale.*[25]* The results obtained for each muscle group in a particular limb were summed to arrive at a motor strength index for each extremity.

An ambulation disability index, modified from one developed by Klingman and coworkers,*[22]* was also computed at "best point" after acute polio, and at presentation to clinic. It ranged from 0 to 5; 0 = no functional disability, 1 = mild difficulty with ambulation without need for braces, 2 = moderate difficulty with ambulation with need for braces, 3 = severe difficulty with ambulation with need for braces for short distances, and a wheelchair for longer distances, 4 = severe disability, wheelchair bound, and 5 total disability and bedridden.

Physical activity before onset of PPS for cases, and recent physical activity for controls (within last 5 years) were calculated in the following manner, similar to that used by Klingman and associates*[22]*: 1 = little or no regular participation in sports, manual labor, or walking, 2 = occasional moderate sports activity (greater than or equal to 20 min one or two times per week), and/or mild to moderate demands at work and at home (eg, frequent ambulation for several hours at a time or occasional light lifting), 3 = frequent participation in sports (greater than or equal to 20 min two or more times per week), and/or moderate to heavy activities at work or home (eg, frequent heavy lifting or manual labor).

Some of the variables had a large number of missing values. Because at least some data were available on most subjects, estimates for the two variables of weakness at acute polio, and consequently the degree of recovery were made during the chart review (for 36 and 28 patients, respectively) if some information were present. If a patient stated that an extremity, speech/swallowing function, or respiratory muscles were involved, but that degree of involvement was not known (eg, partial vs complete), a 75 was imputed for that limb, a 50 for speech/swallowing dysfunction, and a 50 for respiratory muscle weakness. If a limb, respiratory muscles, or speech/swallowing function were partially involved, a 50 was ascribed. If a patient had no knowledge as to involvement of limbs in the past, no estimates were imputed.

Reliability and Validity of Variables

Inter-rater reliability of the dependent variable (case/control status) was estimated by having another rater (NRC) review a random sample of 10% (n = 16) of charts, and assign case/control status to these patients. Percent agreement between the two raters was 94%. Coefficient Kappa,*[26]* which corrects the percent agreement score for chance agreement, was 87.5%.

The reliability of the variables weakness at time of acute polio and age at acute polio were assessed. This

was determined by a review of all available medical records of patients hospitalized in the Montreal area at the time of acute polio. From the information available in the old records, a weakness score (using a 0 to 6 scale) at time of acute polio was estimated for each patient in a manner similar to that described above. This weakness score was based on information on degree of weakness in each of four limbs, respiratory muscle weakness, and speech/swallowing function. If a limb was unaffected, a 0 was assigned, if mildly weakened (MRC grade 4) a 10, if moderately weakened a 50, if severely weakened (MRC grade 1 to 2) a 90, and if completely paralyzed a 100 was assigned. For respiratory muscle function a 50 was assigned for some weakness, and a 100 for weakness requiring use of a ventilator. For speech/swallowing function, a 50 was assigned for some speech/swallowing dysfunction, and a 100 for complete loss of speech and/or swallowing. The sum total of all six figures was then divided by 100 to arrive at a 0 to 6 score for each subject. Patients tended to overestimate their weakness at acute polio; however, their assessment of age at which they had acute polio was accurate. Patient estimates of weakness at acute polio was 2.98 ± 1.49 (mean ± SD) compared with data from old charts of 2.11 ± 1.16 ($p = 0.05$, $n = 19$, mean difference 0.86 ± 1.47). Patient estimates of age at acute polio was 8.72 ± 9.46 years compared with 8.95 ± 9.36 years from old records ($p = 0.9$, $n = 28$, mean difference 0.23 ± 0.49). The effect of case/control status on recall of these variables is unknown because old records were available on only two controls.

The concurrent criterion-oriented validity of patient estimates of weakness at time of presentation to clinic was evaluated by correlating percent scores of weakness in each limb with the motor strength score (estimated from the physical examination performed at that time) for each extremity for each patient. The correlation coefficients for the left and right upper extremities, and for the left and right lower extremities were -0.67 ($n = 184$), -0.75 ($n = 183$), -0.81 ($n = 163$), and -0.79 ($n = 167$), respectively.

The construct validity of the weakness measure was evaluated by comparing mean weakness at acute polio in those patients who were and were not hospitalized. Mean weakness was 2.58 ± 1.43 ($n = 128$) in hospitalized patients and 1.79 ± 1.15 ($n = 42$) in unhospitalized patients ($p < 0.002$).

Statistical Analysis

Preliminary analysis involved univariate and bivariate analyses with standard parametric procedures. Continuous independent variables were examined to determine whether they would be used as continuous or categorical variables in the logistic regression model.*[27]* Age at presentation to clinic, latency, weakness at acute polio, and weakness at presentation were entered as continuous variables. Age at polio (less than or equal to 7, and greater than 7.0 years), weakness at best after acute polio (less than or equal to 0.6, and greater than 0.6), and recovery (less than or equal to 0.6, 0.61-1.6, 1.61-2.6, and 2.61-5) were entered as categorical variables. The variables that were collinear with each other (as identified by high correlation coefficients, and by eigenvalue and condition index analyses) were not entered together in the same multivariate analyses.*[28]*

A crude odds ratio, with 95% confidence intervals was calculated for each independent variable by univariate logistic regression modeling. Multivariate logistic regression models were computed by a stepwise approach, and adjusted odds ratios with 95% confidence intervals were calculated for all variables. A significance level of p less than or equal to 0.10 for improvement in the loglikelihood ratio test was required for entry of a term and a value of p less than or equal to 0.15 was required for a term to stay in the model. Specific interaction terms of interest were the relationship of: (1) weakness at acute polio to recovery; (2) physical activity to weakness at best point after acute polio; (3) recent weight gain to weakness at presentation to clinic; (4) weakness at acute polio to latency; and (5) recovery to latency.

The stability of the calculated odds ratios was evaluated by assessing the effect of removal of outliers (influential observations) on some of the univariate and multivariate analyses.*[28]* These analyses showed

that the four outliers identified produced only small changes (in either direction) in the computed odds ratios and their associated confidence intervals. The extreme values that resulted in the identification of the outliers were for the variables age at acute polio, latency, and recovery. In addition, the effect of the imputed missing values on some of the univariate and multivariate odds ratios was assessed by comparing odds ratios both with and without imputed missing values. The addition of imputed missing values did not produce important changes in the odds ratios obtained. They were well within the margin of error.

The statistical analyses were done without correction for the relatively large number of analyses performed. Because the probability of finding a statistically significant finding increases with the number of analyses performed, the *p* values presented may be underestimations of the true *p* values.

The statistical packages used for data analyses were SAS[a] and BMDP (1988 version).[b] SAS was used for calculation of descriptive statistics, a-tests, XZ tests, correlation coefficients, collinearity analysis, and outlier analysis. BMDP was used for univariate and multivariate logistic regression modeling.

RESULTS

Three hundred fifty-three charts from a university-affiliated post-polio clinic were reviewed. One hundred eighty-seven patients were excluded. Reasons for exclusion included no history of past paralytic polio in 31 patients, history of two episodes of past paralytic polio in 2 patients, no period of at least 10 years of functional stability following initial recovery in one patient, presence of new fatigue (without weakness) in 39 patients, presence of new weakness (without fatigue) in 11 patients, presence of severe pain in 14 patients, presence of other past or concurrent neurological disorders that could produce weakness and fatigue in 40 patients, and presence of past or concurrent medical disorders that could produce weakness and fatigue in 49 patients. In the patients excluded from the study, age at acute polio ranged from 0 to 43 years (mean ± SD, 9.18 ± 10.14 years), age at presentation to clinic ranged from 27 to 87 years (52.37 ± 13.51 years), and 63% were female. One hundred and twenty-seven cases and 39 controls were identified. For the patients included in the study, age at acute polio ranged from 0.05 to 39 years (mean ± SD, 5.98 ± 6.8 years), age at presentation to clinic ranged from 18.9 to 79.5 years (49.4 ± 12.08), 63% were female, 54% complained of muscle pain, and 77% complained of joint pain. The mean length of time that cases had new symptoms was 5.7 ± 5.94 years (mean ± SD).

Descriptive statistics (including means, proportions, standard deviations), along with *t*-tests, X^2 tests, 95% confidence intervals of differences in means and proportions between cases and controls are presented in tables 1 and 2. Cases were significantly different ($p < 0.05$) from controls with respect to an older age at time of presentation to clinic, a longer time since acute polio, a greater weakness at acute polio, and a greater weakness and a greater disability at presentation to clinic. In addition, cases were significantly more likely to have experienced a recent weight gain, muscle pain (at rest and/or with exercise), joint pain, and muscle pain with exercise than controls. There were no significant differences between cases and controls in terms of sex, age at acute polio, weakness at "best point" after acute polio, disability at "best point" after acute polio, recovery, and physical activity.

Table 1: Comparison of Means of Independent Variables in Cases and Controls (continuous

variables)					
		Mean ± SD			
Variable	Scale	Cases	Controls	*p* Value	95% CI of Difference
Age at presentation	Years	51.26 ± 11.68 (*n* = 127)	43.31 ± 11.45 (*n* = 39)	<0.001	3.8, 12.1
Latency	Years	44.83 ± 11.94 (*n* = 127)	38.82 ± 11.70 (*n* = 39)	0.006	1.8, 10.2
Age at polio	Years	6.44 ± 7.37 (*n* = 127)	4.49 ± 3.89 (*n* = 39)	0.12	0.2, 3.7
Weakness at acute polio	Weakness measure	2.53 ± 1.46 (*n* = 126)	1.83 ± 1.18 (*n* = 36)	0.009	0.2, 1.2
Weakness at best after polio	Weakness measure	0.87 ± 0.67 (*n* = 119)	0.63 ± 0.58 (*n* = 29)	0.08	-0.005, 0.5
Weakness at presentation	Weakness measure	1.52 ± 0.90 (*n* = 103)	0.63 ± 0.58 (*n* = 29)	<0.001	0.6, 1.2
Recovery	Weakness measure	1.71 ± 1.26 (*n* = 118)	1.40 ± 1.22 (*n* = 27)	0.26	-0.1, 0.9
Disability index at best after polio	Disability index	0.99 ± 0.77 (*n* = 123)	0.73 ± 0.65 (*n* = 37)	0.06	0.005, 0.5
Disability at presentation	Disability index	1.61 ± 1.03 (*n* = 124)	0.87 ± 0.88 (*n* = 38)	<0.001	0.4, 1.1
Physical activity	Physical activity index	1.57 ± 0.61 (*n* = 118)	1.64 ± 0.67 (*n* = 39)	0.52	-0.2, 0.3

p value = two-tailed *p* value for unpaired *t*-statistic for cases and controls.
Abbreviations: Latency = difference between age at presentation to clinic and age at polio; SD, standard deviation; yrs, years; 95% CI of difference = 95% confidence interval of difference in means between cases and controls.

The variables weakness at acute polio and recovery had imputed values for 36 and 28 patients, respectively if some information was available. Please refer to text for description of computation of Weakness Measure, Disability Index, and Physical Activity Index.

Table 2: Comparison of Proportions of Independent Variables in Cases and Controls (categorical variables)

	Proportions (%)			
Variable	**Cases**	**Controls**	***X²* *p*value**	**95% CI of Difference**
Sex (female)	82/127 (65)	22/39 (56)	0.36	-9, 17
Recent weight gain	57/121 (47)	7/37 (19)	0.002	14, 42
Muscle pain	75/126 (60)	14/39 (36)	0.01	14.3, 45.7
Joint pain	103/127 (81)	25/39 (19)	0.03	1.3, 33
Muscle pain with exercise	50/104 (48)	7/36 (19)	0.003	13.3, 44.7

95% CI of difference = 95% confidence interval of difference in proportions between cases and controls (measured in percent); X^2 *p* value presented is not continuity adjusted.

Univariate (unadjusted) odds ratios with their 95% confidence intervals for each independent variable were calculated by logistic regression modeling. The results are presented in table 3. The variables with significant odds ratios are age at presentation to clinic, latency, weakness at acute polio, weakness at presentation to clinic, disability index at presentation to clinic, recent weight gain, muscle pain, joint pain, and muscle pain with exercise. The risk for PPS increased by 1.8 for each decade of life, and increased by 1.6 for each decade after acute polio. The odds ratio for PPS was 1.5 and 7, respectively, for each increment of 1 on the weakness measure at acute polio and at presentation to clinic. In addition, patients with a greater disability at presentation to clinic were significantly more likely to have PPS (odds ratios ranging from 6.4 to 31.7 for each increment on the disability index). Patients with a recent weight gain (in the last 5 years) were 3.8 times as likely to have PPS, whereas patients reporting muscle pain with exercise were also 3.8 times more likely to have PPS. The odds ratios for muscle pain and joint pain were 2.6 and 2.4, respectively.

Table 3: Unadjusted (univariate model) Odds Ratios for PPS

Variable	**Scale**	***n***	**Odds Ratio**	**95% CI**	***p* Value**
Age at presentation	Decade	166	1.8	1.3, 2.59	<0.001
Latency	Decade	166	1.6	0.13, 2.25	0.01
Age at polio	>7 years	166	1.2	0.5, 2.88	0.69
Weakness at acute polio	Weakness measure	162	1.5	1.09, 2.04	0.01

Weakness at best after polio		Weakness measure (>0.6)	148	1.8	0.77, 4.08	0.18
Weakness at presentation		Weakness measure	132	7.0	2.75, 17.94	<0.001
Recovery						
	(1) (0.61-1.6)	Weakness measure	145	2.0	0.63, 6.38	0.51
	(2) (1.61-2.6)			1.6	0.52, 4.94	
	(3) (>2.6)			2.4	0.71, 8.08	
Disability index at best after polio						
	(1)	Disability index	160	2.0	0.86, 4.45	0.47
	(2)			4.7	0.53, 41	
	(3)			1.6	0.15, 16.5	
	(4)			14,030	*	
Disability index at presentation						
	(1)	Disability index	162	6.4	2.25, 18.21	0.001
	(2)			13.6	2.9, 62	
	(3)			31.7	3.44, 289	
	(4)			16.7	1.74, 161	
Physical Activity						
	(1)	Physical activity index	157	0.93	0.43, 1.99	0.69
	(2)			0.6	0.15, 2.11	
Sex		Female/Male	166	1.4	0.68, 2.92	0.36
Recent weight gain		Yes/No	158	3.8	1.56, 9.36	0.0004
Muscle pain		Yes/No	165	2.6	1.25, 5.53	0.01
Joint pain		Yes/No	166	2.4	1.09, 5.3	0.03
Muscle pain with exercise		Yes/No	140	3.8	1.54, 9.54	0.005

95% CI = 95% confidence interval of the odds ratio; Latency = difference between age at presentation to clinic and age at polio.
* Mathematically impossible to calculate confidence intervals. The variables weakness at acute polio and recovery had imputed values for 36 and 28 patients, respectively if some information was available. Please refer to text for description of computation of Weakness Measure, Disability Index, and Physical Activity Index.

Multivariate models were calculated using a stepwise approach with logistic regression modeling. The best multivariate model for predicting who would develop PPS (using all possible predictive factors with the exception of weakness and disability index at presentation to clinic) was one that included the variables current age, weakness at acute polio, muscle pain with exercise, recent weight gain, and joint pain. The adjusted odds ratios with their 95% confidence intervals for the variables in this model are presented in table 4. If age at presentation to clinic was excluded from the model, the variable time from acute polio to presentation to clinic, entered the model in its place with only a slight loss of statistical efficiency. Both age and time from acute polio could not be included in the same model because they were correlated with each other. The addition of recovery did not significantly improve the model, even if weakness at acute polio was excluded. None of the interaction terms proved to be statistically significant.

Table 4: Adjusted (multivariate model) Odds Ratios for PPS

Variable	Scale	Odds Ratio	95% CI	*p* Value
Age	Decade	1.7	1.1, 2.6	0.01
Weakness at acute polio	Weakness severity measure	1.6	1.06, 2.52	0.02
Muscle pain with exercise	Yes/No	5.0	1.6, 15.6	0.003
Recent weight gain	Yes/No	6.4	2.02, 20.3	<0.001
Joint pain	Yes/No	2.3	0.77, 7.06	0.10

95% CI = 95% confidence interval of the odds ratio. This model is based on 132 cases and controls. The variable weakness at acute polio had imputed values for 32 patients if some information was available. Please refer to text for computation of Weakness Measure.

DISCUSSION

The best multivariate model for predicting who will develop PPS indicates that patients who had a greater weakness at acute polio, are currently older, have muscle pain with exercise, a recent weight gain, and joint pain are those most likely to develop PPS. Other factors shown to be important in univariate analyses are a longer time since acute polio, and muscle pain (at rest or with exercise). Age at acute polio, recovery after polio, weakness at "best point" after polio, physical activity, and sex were not contributing factors.

Our sample of patients was similar to that of previous epidemiologic studies, which evaluated possible predictive factors for PPS. The mean age at acute polio in our patients was 6 years as compared to a range of a mean of 7 to 13 years in other studies.*[6,7,21,22]* Mean age at presentation to clinic was 49.4 years in our study, and ranged from a mean of 41.9 to 49.1 years in previously published reports.*[6,7,21,22]* Our patient sample was predominantly female (63%), similar to the patient sample in two previous studies (65%*[21]* and 54% female*[6]*), but different from one previous study characterized by male predominance (46% female*[7]*). Thus, any differences in our results are probably not due to a large disparity in basic demographic characteristics of our patient sample compared to those in previously published reports.

Case-control studies are subject to bias in the identification of cases and controls, and in the assessment of exposures (usually assessed by recall). These sources of bias are not all unique to case-control studies.*[23]*

The controls in our study were identified from a university-aftiliated post-polio clinic. Because these patients may have had a more severe paralytic poliomyelitis, and may have been more likely to be symptomatic than controls with a history of past paralytic poliomyelitis not evaluated at the clinic, the odds ratios calculated in this study may be underestimations. However, unlike a previous population-based study that used a self-reported questionnaire for case ascertainment,*[7]* our study had more stringent criteria for identification of cases and controls, which included a standardized clinical evaluation and laboratory testing, as indicated. We excluded approximately 50% of patients evaluated primarily because of the presence of concurrent medical and other neurological conditions that could produce weakness and fatigue. Most variables considered in our study as possible predictive factors were assessed by recall. This may have produced error because of the length of time since passage of events (with resultant decreased study power), and bias. Cases may overestimate or be more likely to remember certain factors than controls, producing an overestimation of the odds ratios.*[23]* In addition, recall of time sequence of events may be faulty. For example, cases may be more apt to note increased physical activity prior to onset of PPS than controls, producing an overestimation of the odds ratio for this variable. To evaluate some possible sources of error in our study, we assessed the reliability of case/control selection, and the reliability and validity of some of the potential predictive factors. We determined that inter-rater reliability of case/control status was excellent. Patient recall of age at acute polio and thus length of time since acute polio was accurate. Although patients tended to overestimate the degree of weakness at acute polio as compared to data available from old hospital charts, the weakness measure used correlated well with other weakness estimates. Assuming that cases overestimated their initial involvement to a greater degree than controls, a smaller odds ratio with a higher statistical significance would have been obtained for this variable had more accurate data been available.

Despite the possible sources of error in our study, our findings on the important predictive factors for PPS are consistent with previously proposed hypotheses for PPS. The severity of the original motor neuron destruction during acute polio, as estimated by weakness at acute polio, has been proposed to be important for the development of PPS by other investigators.*[4,6,21,22]* Because PPS is thought to result from a distal degeneration of enlarged motor units (as a result of the recovery process from acute paralytic polio through axonal sprouting),*[10,11]* the degree of motor unit enlargement as measured by the degree of muscular recovery after polio may also be a risk factor for PPS.*[22]* In addition, factors that result in overuse of these enlarged motor units could contribute to the development of PPS.*[12,13]* Our study confirmed the findings of previous investigators who noted that an increased severity of acute poliomyelitis,*[4,6,21,22]* and greater length of time since acute polio*[7]* are risk factors for PPS. Although recovery after paralytic poliomyelitis,*[22]* age at acute polio,*[21,22]* recent physical activity,*[22]* and sex*[7]* were noted to be significant predictive factors for PPS in previous studies, our data did not confirm these findings. Degree of recovery and age at acute polio were higher in PPS patients than controls (table 1), but the differences were not statistically significant (tables 1 and 3). Physical activity was minimally higher in PPS cases than stable patients after acute poiiomyelitis, and did not result in a significant odds ratio (tables 1 and 3). This lack of association of physical activity with PPS was also noted in a recent study.*[7]* It is possible that a study with greater power or with the use of more accurate measures may have identitied these variables as significant predictors for PPS. In contrast to the findings of a previous study,*[22]* we found that the degree of disability at time of presentation to clinic was higher in cases than controls. This may be a reflection of their increased weakness, a diagnostic criterion for PPS. The new findings from our study are that a greater age is important in the development of PPS. In addition, we found that factors that may be signs of overuse (or alternatively consequences of increased weakness) such as recent weight gain, muscle pain particularily that associated with exercise, and joint pain are significantly associated with PPS.

Unlike most previous studies, we evaluated specific interaction terms that may be of clinical relevance in

the prediction of PPS. The possible association between permanent impairment after acute polio and severity of acute polio in predicting PPS has been previously evaluated. The incidence of PPS increased significantly with increasing impairment in both mild and moderate categories of acute polio severity, but not in the severe category.*[7]* Our study did not evaluate this particular association. We found no significant interaction or association between weakness at polio to recovery, physical activity to weakness at best point after acute polio, recent weight gain to weakness at presentation to clinic, weakness at acute polio to latency, and recovery to latency. This indicates that the presence of PPS did not vary significantly with different levels of the variables considered. For example, degree of recovery was not significantly dependent upon severity of acute polio in predicting PPS. Because our population was relatively small for such evaluations, it is possible that a larger study with a greater number of observations in different categories would have resulted in the finding of significant interaction terms.

Age at presentation to clinic, as a measure of the normal ageing process has been proposed as a possible contributor to PPS.*[9]* Our finding that age at presentation to clinic is a significant risk factor for PPS provides support for this hypothesis. However, other explanations are also possible. For example, the likelihood of having PPS may simply increase with the passage of time since acute polio (and thus age). The normal progressive dropout of motor neurons*[9,29-31]* and the decrease in growth hormone and somatomedin C levels with greater age*[32-34]* may be precipitating factors for PPS. Anatomic and electrophysiological studies have demonstrated a loss of spinal cord motor neurons with ageing. This loss becomes prominent after age 60.*[29-31]* It is possible that the superimposition of this process over the already limited number of motor neurons present after polio contributes to the development of PPS.*[9]* Somatomedin C has been found to be low in 9 of 10 patients with PPS and normal in 12 polio survivors without PPS.*[35]* The growth hormone/somatomedin C axis stimulates the synthesis of protein and nucleic acids in muscle cells,*[36-38]* and the regeneration of peripheral nerves after injury including sprouting.*[39-41]* In a proportion of the population, growth hormone and somatomedin C production ceases with age.*[32-34]* Thus, aging with progressive loss of motor neurons, and with absence of growth hormone and somatomedin C may be important in the development of PPS.*[8,35]*

Chronic overuse has also been proposed as a contributing factor to PPS.*[12,13]* Thus, variables such as length of time since acute polio, joint and muscle pain, physical activity, and weight gain may be possible predictive factors. We found that length of time since acute polio is a risk factor for PPS, and that recent weight gain, muscle pain especially that occurring with exercise, and joint pain are associated factors with PPS, thus providing some evidence for this hypothesis. A greater length of time since acute polio may be a measure of overuse, or it may reflect the greater likelihood of having more patients with PPS with the passage of time since acute polio. Recent weight gain can contribute to overuse, but it may also be a consequence of decreased physical activity resulting from weakness and fatigue. The fact that muscle and joint pain were found to be significantly associated with PPS may reflect the fact that pain is considered to be the third component of PPS,*[2,9]* or it may be another measure of overuse or even disuse. Joint and muscle pain can be related to exercise, and in this way be indirect measures of overuse.*[42-44]* Our finding that muscle pain with exercise (as a clinical measure of muscular damage) is significantly associated with PPS is consistent with a previous report of increased creatinine kinase levels in PPS patients and not in asymptomatic post-polio controls.*[6]* The fact that physical activity was not significantly associated with PPS may indicate that the amount of physical activity is not as important as the intensity at which activities are conducted. Frequent periods of activity, if interspersed with rest and with the avoidance of pain may be safe.*[13]* The occurrence of pain can also lead to decreased use of certain muscles with the consequent development of disuse atrophy and weakness.*[46]* Alternatively, increasing weakness may itself cause symptoms of joint and muscle pain. Thus, pain and weight gain can precede or follow the development of new weakness, and may or may not be measures of overuse. Further study should be performed to clarify this issue.

In conclusion, the results from this study provide insight on predictive factors for PPS, and can be applied in the clinical management of patients who have recovered from paralytic poliomyelitis. Our findings support the hypothesis that the severity of initial motor unit involvement as estimated by weakness at acute polio, and possibly the normal ageing process and overuse are important in predicting PPS. Even though patients have no control over the severity of weakness as a result of acute polio, they do have control over some predictive factors for PPS. Patients can be advised that they should avoid gaining weight and exercising to the point of muscle pain because these variables have been found to be strongly associated with PPS. The exact role of physical activity will still need further evaluation; however, the usual recommendations of low-level aerobic exercise with avoidance of muscle pain and fatigue appear valid. Thus, this study can provide the basis for physiologically reasonable and practical advice to post-polio patients to minimize or delay the risk of PPS.

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