A CASE-CONTROL STUDY OF RISK FACTORS FOR POST-POLIOMYELITIS SYNDROME

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ABSTRACT

Post-poliomyelitis syndrome (PPS) is a clinical syndrome of new weakness, fatigue, and pain in individuals who have previously recovered from acute paralytic poliomyelitis. The primary objective of this study was to identify factors which predict subsequent PPS. Among patients with prior polio, cases were those with new weakness and fatigue, and controls were those without these complaints. A chart review of 353 patients evaluated at the Montreal Neurological Institute post-polio clinic identified 127 cases and 39 controls. In univariate analyses, significant risk factors for PPS were a greater current age (odds ratio of 1.8 per decade, 95% confidence interval 1.3 to 2.6), a longer time since acute polio (odds ratio of 1.6 per decade, 95% confidence interval 1.1 to 2.3), more weakness at acute polio (odds ratio 1.5, 95% confidence interval 1.1 to 2.0), a recent weight gain (odds ratio 3.8, 95% confidence interval 1.6 to 9.4), muscle pain with exercise (odds ratio 3.8, 95% confidence interval 1.5 to 9.5), muscle pain (odds ratio 2.6, 95% confidence interval 1.3 to 5.5), and joint pain (odds ratio 2.3, 95% confidence interval 1.1 to to 5.3). The multivariate analyses revealed that a model containing current age (odds ratio 1.7 per decade, 95% confidence interval 1.1 to 2.6), weakness at acute polio (odds ratio 1.6, 95% confidence interval 1.1 to 2.5), muscle pain with exercise (odds ratio 4.9, 95% confidence interval 1.6 to 15.6), recent weight gain (odds ratio 6.4, 95% confidence interval 2.02 to 20.3), and joint pain (odds ratio 2.33, 95% confidence interval 0.8 to 7.1) was the most effective in predicting who would develop PPS. Age at acute polio, degree of recovery after polio, weakness at best point after polio, physical activity, and sex were not contributing factors.

RESUME

Le syndrome post-polio (SPP) est un syndrome clinique de nouvelle faiblesse, fatigue, et douleur chez des individus s'étant remis d'une poliomyélite paralytique aigue. Le but principal du projet de recherche était d'identifier des facteurs de prédiction au SPP. Parmi les patients ayant eu une poliomyélite antérieure, les cas de SPP ont été choisis parmi ceux présentant avec des symptômes de nouvelle faiblesse et fatigue et les patients témoins parmi ceux ne présentant pas ces symptômes. Une revue des dossiers de 353 patients évalués à la clinique post-polio de l'Institut neurologique de Montréal identifia 127 cas de SPP et 39 patients témoins. Lors des analyses à univariance, les facteurs de risque significatifs pour le SPP s'avérèrent être l'âge plus avancé (risque relatif de 1.8 par décennie, intervalle de confiance de 95% de 1.3 à 2.6), la période de temps depuis la poliomyélite aigue (risque relatif de 1.6 par décennie, intervalle de confiance de 95% de 1.1 à 2.3), faiblesse plus prononcée lors de la phase aigue de la poliomyélite (risque relatif 1.5, intervalle de confiance de 95% de 1.1 à 2.0), gain de poids récent (risque relatif de 3.8, intervalle de confiance de 95% de 1.6 à 9.4), douleur musculaire accompagnant l'exercise (risque relatif de 2.6, intervalle de confiance de 95% de 1.5 à 9.5), et douleur articulaire (risque relatif de 2.3, intervalle de confiance de 95% de 1.1 à 5.3). Les analyses à multivariances révèlent qu'un modèle composé de l'âge actuel (risque relatif 1.7 par décennie, intervalle de confiance de 95% de 1.1 à 2.6), faiblesse lors de la phase aigue de la poliomyélite (risque relatif de 1.6, intervalle de confiance de 95% de 1.1 de 2.6), douleur musculaire accompagnant l'exercise (risque relatif de 4.9, intervalle de confiance de 95% de 1.6 à 15.6), gain de poids récent (risque relatif de 6.5, intervalle de confiance de 95% de 2.02 à 20.03), et douleur articulaire (risque relatif de 2.33, intervalle de confiance de 95% 0.8 à 7.1) furent les plus efficaces pour prédire qui manifesterait les sumptômes du SPP. L'âge à la phase aigue de la poliomyélite, degré de récupération après la poliomyélite, faiblesse à l'étape la plus favorable suivant la poliomyélite, activité physique et sexe ne furent pas des facteurs contribuants.

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PREFACE

All the work presented in this manuscript is my original work, and has not been published to this time. The Montreal Neurological Institute post-polio clinic and the data collection form for the clinic were developed by Dr Neil Cashman. The idea for the study came from preliminary work (for course requirements) performed by Ms. Cathy Tansey, a former student in the Department.

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OBJECTIVE

The primary objective of this study is to identify risk factors for post-poliomyelitis syndrome in patients who have recovered from acute paralytic poliomyelitis. The risk factors of interest are age at acute polio, severity of acute polio, degree of revovery after polio, time in years between acute polio and clinic evaluation, present age, severity of weakness at best point after polio, physical activity, recent weight gain, recent major trauma, muscle pain with exercise, joint pain, and muscle pain Secondary objectives are to determine if increased weakness in cases occurs to a greater degree in the lower extremities than the upper extremities, to determine the difference in frequency with which increased weakness occurs in previously affected and previously unaffected extremities, to evaluate the effect of time on the development of symptoms in PPS, and to evaluate three different weakness severity measures.

INTRODUCTION

Through the development of effective vaccinations, acute poliomyelitis is now a rare disease in North America. However, it is still a common disease in some third world countries, and a large number of individuals (640,000 in the U.S.A.) who have recovered from acute paralytic poliomyelitis are alive today (1). As many as 50% of this population may develop post-poliomyelitis syndrome (PPS) later on in life (2-6). Thus, PPS is the most prevalent motor neuron disease in North America.

Post-poliomyelitis syndrome is a clinical syndrome of new weakness, fatigue, and pain in individuals who have experienced at least 10 years of neurological and functional stability after recovery from acute paralytic poliomyelitis (5,7). Paralytic poliomyelitis is an illness characterized by high fever, followed by muscular paralysis, and is caused by infection with the poliovirus. Although, a wide variety of new symptoms are reported by individuals with antecedent poliomyelitis, these three are the most frequently mentioned and appear to constitute a true "syndrome," or concurrence of symptoms. This study is concerned primarily with new weakness and fatigue, as these are the most frequently reported and appear to be the most disabling to the patients involved (1-5,7). It is also unclear at the present time, how or if pain is related to the original acute illness and to PPS.

The most likely etiology of new weakness and fatigue many years after recovery from paralytic polio is a distal degeneration of massively enlarged motor units which are present as a result of the recovery process after acute paralytic poliomyelitis (8,9). Overuse is thought to be a contributing factor (10). A motor unit, as originally defined by Sherrington, consists of a motor neuron and all the muscle fibers that it innervates or supports. Motor neuron invasion by poliovirus during acute poliomyelitis may result in permanent loss of a number of motor neurons, together with denervation of their

associated muscle fibers with subsequent clinical weakness. The recovery process is characterized by reinnervation of denervated muscle fibers by terminal axonal sprouting from remaining motor neurons. This process results in enlargement of motor units up to 7 times normal size (11). It is thought that with time, these enlarged motor units are unable to support such a large number of muscle fibers, possibly because of overuse (10), and that a degeneration of terminal axons may occur. This process can produce neuromuscular junction transmission defects, a possible cause of fatigue (12-17), and denervation, with subsequent increased weakness in the muscle involved (8,9). Thus, the development of PPS may be dependent upon the severity of the initial infection, the recovery process after paralytic poliomyelitis, the time elapsed since acute polio, and overuse.

Several studies have been performed which have identified potential risk factors for PPS. These include greater severity of initial acute poliomyelitis, a greater recovery in muscular strength after poliomyelitis, a higher age at acute polio, a lower present disability, and possibly increased recent physical activity (4,6,18,19). Age at time of acute polio may actually be a measure of severity of polio since it is known that individuals who develop acute poliomyelitis at a later age usually have a more severe illness (5). In the study in which greater recovery was identified as a risk factor (19), the degree of recovery was not adjusted for the severity of weakness at acute polio, therefore it is not known whether or not PPS is more likely to occur in patients with a greater recovery, but a similar degree of weakness at acute polio. Because the degree of recovery is dependent upon the degree of initial weakness, a greater degree of recovery in PPS patients may actually be a reflection of the increased severity of weakness at acute polio in PPS patients as compared to controls. Because PPS is thought to be due to the disintegration of enlarged post-polio motor units possibly through overuse, severity of

acute polio as a measure of initial motor unit involvement, recovery after polio as a measure of motor unit enlargement after acute polio, and physical activity (and a lower current disability) as a measure of overuse are all risk factors which are reasonable physiologically based on the proposed etiology for PPS.

In addition to studying the previously noted risk factors, the present study has evaluated the following: severity of weakness at best point after polio, current age, time since acute polio to present, usual physical activity prior to development of PPS, muscle pain with exercise, history of recent trauma, recent weight gain, muscle pain, and joint pain.

BACKGROUND

Acute poliomyelitis.

Introduction

The introduction of effective vaccinations for poliomyelitis in 1955 (the Salk vaccine) and 1961 (the oral Sabin vaccine) has made acute poliomyelitis almost entirely preventable (7). Because of this, poliomyelitis has been largely forgotten by many members of the medical community. Unfortunately, acute poliomyelitis is still common in many areas of the world, and a number of individuals who survived this disease are still alive today. Even though acute polio is now a rare disease in North America, it is still endemic in the underdeveloped areas of Central and South America, Asia, and Africa (20). The World Health Organization estimated that in the year 1990 alone there were 116,000 new cases of paralytic poliomyelitis worldwide (21). In addition, a Household Survey of Disabling Conditions conducted by the National Center for Health Statistics in 1987 estimated that there were over 640,000 people who had survived paralytic polio in the U.S.A. (1).

The virus.

Acute paralytic poliomyelitis is produced by motor neuron invasion by poliovirus. Any one of the three polioviruses (types 1, 2, or 3) can produce the illness. The polioviruses are classified in the genus enterovirus within the family picornavirus. They are small, RNA-containing viruses (20).

Transmission.

Poliovirus infection usually occurs by the fecal/oral route. The poliovirus is acquired orally. The virus replicates in the gastrointestinal tract, where it can penetrate the gastric

mucosa, and can be carried via blood to all parts of the body. It can be excreted in orapharyngeal secretions and stool. After infection, fecal secretion continues for up to several weeks' time, and in areas with poor sanitation and over-crowding, transmission occurs easily to other individuals (20).

Clinical features.

Acute paralytic poliomyelitis as a result of poliovirus infection is rare. Ninety to 95% of all poliovirus infections are asymptomatic. In most individuals infected with poliovirus, only a minor illness occurs, characterized by no symptoms, or minor symptoms of sore throat, gastrointestinal upset, low-grade fever, malaise, and mild headache. These symptoms resolve in 1 to 4 days. In a small proportion of individuals (1 to 2%), a major illness occurs. A major illness begins with symptoms typical of a minor illness (fever and malaise), followed by generalized headache and vomiting, and then by the development of neck and back stiffness. Drowsiness may be present. Paralysis may occur 2 to 5 days after onset of headache. It can develop rapidly or in a more stuttering fashion, over a period of time ranging from less than 2 days to greater than 1 week. It results from the preferential damage of large motor neurons by the poliovirus (20,22).

Most patients (90 to 95%) survive acute paralytic poliomyelitis, and a majority of the survivors experience at least some recovery of muscle function. Most of the recovery occurs within the first few months, but further recovery, especially functional recovery, can continue for years following the initial infection (22).

Pathophysiology.

Acute paralytic poliomyelitis is primarily a disease of the motor unit. A motor unit

consists of a motor neuron and all the muscle fibers it innervates or supports. Electrical excitation of a motor neuron in the central nervous system is followed by conduction of an impulse in the axon and its terminal branches, synaptic transmission at the neuromuscular junction mediated by the neurotransmitter acetylcholine (ACh), and the depolarization and contraction of the muscle fibers it innervates. If enough motor units are stimulated, a clinically apparent muscle contraction will be produced in the individual. The number of muscle fibers innervated by a motor neuron varies both within a muscle and between muscles, and can range from 6 to 10 muscle fibers in extraocular muscles to 2000 muscle fibers in the gastrocnemius muscle (23) In general, muscles that require a finer degree of movement control have smaller motor units

During acute poliomyelitis, motor unit invasion by poliovirus can result either in motor neuron death or injury with partial or complete recovery (20). Motor neuron death will cause denervation of muscle fibers with a resultant loss of voluntary activation of the involved muscle fibers If only a few motor neurons innervating a muscle are affected, no weakness will be perceived by the patient because of the normal reserve present in human beings Thus, it is possible to have motor neuron invasion by poliovirus with destruction of motor neurons without a clinically apparent weakness (17) Pathological studies have revealed that in limbs with minimal paralysis or normal function, only about 20% of the motor neurons were destroyed (24). A more severe loss of motor neurons from acute polio will result in partial or complete denervation of the muscles involved, and will be perceived as weakness or complete loss of voluntary muscle contraction by the patient

Recovery of muscular force after acute polio can occur by sprouting from remaining motor neurons or by muscle fiber hypertrophy of innervated muscle. Sprouting can start within 3 to 4 weeks after poliovirus infection from the terminal axonal branches of motor

neurons (25-28). This process can produce reinnervation of some or all denervated muscle fibers with restoration of the ability to produce muscle contraction. It has been estimated that even with a loss of 50% of motor neurons supplying a muscle, the surviving motor neurons can achieve complete reinnervation resulting in normal muscle strength (29). Muscle biopsy studies have shown that after recovery from acute paralytic poliomyelitis, motor neurons may be innervating up to 7 times the number of muscle fibers they would normally supply (11). In addition to sprouting with reinnervation, muscle fiber hypertrophy can augment the restoration of muscle strength during the recovery process from acute polio (30). Thus, most individuals who have survived acute paralytic poliomyelitis can expect a variable degree of recovery of muscle function.

Post-poliomyelitis syndrome.

Definition.

Individuals who have recovered from paralytic poliomyelitis are at risk for developing new difficulties related to their original illness later on in life. Progressive new weakness following decades of motor stability in this population was first described in the late nineteenth century (31). Recently, investigators have stressed generalized fatigue and pain as additional features of a "post- poliomyelitis syndrome (PPS)" (2,5,7). Thus, PPS is defined as new weakness, fatigue, and pain in individuals who have recovered from antecedent acute paralytic poliomyelitis. Patients may complain of a wide variety of new symptoms, however these three are most frequently reported, and appear to constitute a true syndrome, or concurrence of symptoms (1-7). Other terms that have been used to describe some or all of the possible symptoms which patients describe many years after polio are post-poliomyelitis muscular atrophy (PPMA), the late sequela of poliomyelitis, or the late effects of poliomyelitis (1,3,5,13).

Frequency.

There are approximately 640,000 survivors of acute paralytic poliomyelitis in the U S A (1). Canada is expected to have a similar proportion of such individuals within its population Studies from the Mayo Clinic indicate that at least one half of this population may develop PPS later on in life (3,6) Thus, PPS is now recognized as a major public health problem in North America.

Manifestations of post-poliomyelitis syndrome.

The 3 most common symptoms of PPS are new weakness, fatigue and pain (1-7). New weakness can occur both in muscles previously clinically involved and uninvolved at the time of acute polio, however it occurs more frequently in those muscles previously involved (7) This finding can be explained by the fact that previously unaffected muscles may have had subclinical motor neuron involvement by poliovirus (24). New weakness can be described as permanent or transient, which is related to activity. We believe that transient new weakness is actually muscular fatigue or decreased endurance. Fatigue in PPS can be either general or muscular Frequently, both occur concurrently. General fatigue is usually described as generalized exhaustion, such as occurs with the "flu " Manifestations include decreased concentration, and requirement for rest periods during the day and increased sleep Muscular fatigue (fatiguability) can be defined as a difficulty with muscular endurance, or increased weakness with exertion that improves with rest Pain in PPS is usually localized to the muscle or joints. Muscle pain is usually described as an aching or sore feeling which occurs after light physical activity It may also have a burning quality, similar to that felt by the patients during denervation from acute polio These muscle pains frequently improve with rest (7). Joint pains may be chronic or intermittent, and are also frequently aggravated by activity. They may be a

result of osteoarthritis, bursitis, and tendonitis from the chronic overuse or abnormal use of weak, unstable limbs. New atrophy, or loss of muscle bulk is also described by PPS patients, and has been reported in 28% of patients attending a post polio clinic (18). It is probably a relatively late phenomenon in PPS (32). Other less frequently reported complaints include respiratory insufficiency from progressive muscular weakness, dysarthria (difficulty with articulation), dysphagia (difficulty swallowing), muscle cramps, fasciculations, and new or progressive joint deformities (7). These difficulties can produce functional problems such as decreased mobility with the need for assistive devices, with difficulty dressing, difficulty with bathing and performing personal hygiene, and change or cessation of occupation (7).

Time of onset.

The time of onset of PPS ranges from 8 to 71 years following acute poliomyelitis. The average interval from several studies is 36 years (7).

Course.

The course of PPS is characterized by a slow progression of weakness, frequently interspersed with periods of stabilization. Death as a result of PPS is rare, and tends to occur in those with borderline respiratory function. On average, the rate of decline in muscle strength using a clinical measure of muscle strength (part of a normal neurological examination) has been estimated as only 1% per year by Dalakas (13). Munsat followed 16 PPS patients for a period of 2 to 9 years with regular assessments of isometric strength (using an electronic strain-gauge myometer), and found a small, but statistically significant decline in muscle strength (33).

Diagnosis

The diagnosis of PPS is clinical. Currently, there is no known diagnostic test which can distinguish symptomatic from asymptomatic post-polio patients (14) Therefore, other conditions which can produce the patients' symptoms need to be excluded before the diagnosis can be made (1) The following criteria have been proposed for diagnosis: 1) a credible history of acute paralytic poliomyelitis, 2) partial or complete recovery of function, 3) a period of stability of at least 10 years' duration, and 4) the later development of progressive new weakness (with or without fatigue and pain) for which there is no other neurological or medical cause (34).

Etiology of post-poliomyelitis syndrome.

The etiology of PPS, or new weakness and fatigue, is unknown. Many possible etiologies and contributing factors have been proposed. As hypothesized by Wiechers and Hubbell (8,9), the most likely etiology of new weakness and fatigue many years after recovery from paralytic polio is a distal degeneration of the abnormally enlarged motor units which are found after recovery from polio In this way, PPS may be a result of the recovery process itself. The surviving motor neurons, which may have permanent abnormalities as a result of polio, now innervate many more muscle fibers than normal, and may be unable to sustain a greatly increased metabolic demand. With time, terminal axonal sprouts may degenerate, with subsequent denervation of individual muscle fibers. Some of these denervated muscle fibers may become reinnervated by sprouts from neighboring motor neurons, producing a continuous "remodeling" process of the post-polio motor unit (9,14,35,36). However, some of the muscle fibers will become permanently denervated, and thus produce permanent progressive weakness (8,9). Evidence for this theory is provided by the finding of smaller macro motor unit potentials

(a measure of motor unit size) on macro-electromyography (a specialized clinical electrophysiological technique) in newly weakened patients (37) and angular atrophic muscle fibers (indicative of ongoing denervation) on muscle biopsy (14). This degenerative and remodeling process can also produce neuromuscular junction transmission defects which may be a cause of muscular fatigue. Evidence for neuromuscular junction transmission defects is provided by the electrophysiological techniques of repetitive stimulation and single fiber electromyography. Both a decrement of the compound muscle action potential and increased jitter on single fiber electromyography are commonly found in post-polio patients, and are indicative of neuromuscular junction transmission defects (12-17,35).

However, evidence for neuromuscular junction transmission defects and for ongoing denervation is commonly found in both symptomatic and asymptomatic patients (14). There appears to be a relationship between the degree of neuromuscular junction deficits and the degree of motor unit enlargement after polio. Therefore, the extent of initial recovery may predict the degree of the electrophysiological deficits later on in life (38). Whether or not these observed abnormalities actually produce symptoms in the patient as a whole, may be due to a combination of factors. These may include degree of motor unit deterioration, the reserve present in the muscle affected, the functional importance of the muscle involved, and the general activity level of the patient (17).

Other possible etiologies for PPS that have been proposed are (1) chronic poliovirus infection, (2) death of remaining motor neurons with normal ageing, coupled with previous loss from polio, (3) premature ageing of cells permanently damaged by poliovirus, (4) predisposition of motor neurons to degeneration because of glial, vascular, and lymphatic changes caused by poliovirus, (5) poliomyelitis-induced vulnerability of motor neurons to secondary insults, (6) genetic predisposition of motor neurons to both

poliomyelitis and premature degeneration, and (7) an immune-mediated syndrome. These hypotheses are reviewed in detail elsewhere (7)

Possible contributing factors to the theory of distal degeneration of enlarged motor units proposed by Wiechers include the normal dropout of motor units with ageing, growth hormone deficiency, overuse myopathy, and disuse atrophy. Anatomic and electrophysiological studies have demonstrated a loss of spinal cord motor neurons with the normal ageing process This loss becomes prominent after age 60 (39-41). 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 (7). Somatomedin C has been found to be low in 9 of 10 patients with PPS and normal in 12 polio survivors without PPS (42) Both growth hormone and somatomedin C stimulate the synthesis of protein and nucleic acids in muscle cells, and the regeneration of peripheral nerves after nerve injury including the sprouting of neurons. Growth hormone stimulates the production of somatomedin C in the liver and from a variety of extrahepatic sites (43,44). Thus, the normal cessation of growth hormone and somatomedin C production in a proportion of the population with loss of this hormonal support for muscle hypertrophy and motor neuron sprouting may be important in the development of PPS (43,45-47). Overuse of muscle may also be a contributing factor This theory is supported by evidence of overuse of specific lower extremity muscles during gait analysis of post-polio patients (10), and by the finding of increased creatinine phosphokinase levels in newly symptomatic post-polio patients and normal creatinine phosphokinase levels in equally weak non-symptomatic post-polio patients (6). Elevated creatinine phosphokinase can be a marker of muscle injury, and has been reported in many neuromuscular diseases as a result of muscle damage and necrosis (48). Thus, the elevated creatinine phosphokinase levels observed in PPS may indicate muscle injury and overuse (49), which could

certainly contribute to increased weakness and fatigue. Finally, disuse atrophy is a well-known cause of muscle weakness in patients with a wide variety of diseases, and can also be a contributing factor to the development of PPS (1).

This study is concerned primarily with the symptoms of new weakness and fatigue as part of PPS. These two symptoms are probably related to motor unit dysfunction and the original poliovirus infection as explained above. Pain is also part of PPS, but may be either a primary or secondary symptom of this disorder (discussed in the following section). Because it is unclear at the present time how or if it is related to the original poliovirus infection and to PPS, it will not be used as an inclusion criterion for PPS cases.

Possible risk factors for post-poliomyelitis syndrome.

Previous studies have identified several possible risk factors for PPS. These include severity of weakness at acute polio, degree of recovery after acute polio, present disability, age at acute polio, and recent physical activity. Only four studies have attempted to identify risk factors for PPS.

Halstead and Rossi (18) defined variables which could predict who developed PPS at a shorter time interval. From a clinic population of 174 persons evaluated over a one year period of time, 132 patients who fulfilled the criteria for PPS (new health problems probably related to paralytic polio) were identified. An unknown number of variables were evaluated with a modified life-table analysis. The four variables at time of acute polio which were strongly associated with development of new health problems many years later at a significantly shorter time interval (Mantel-Cox test) were hospitalization at acute polio, paralysis of all four limbs (versus only one limb), age 7 years or older (versus under 7 years), and requirement of a respirator. Sex was not a contributing factor.

These four variables may actually reflect severity of acute polio. People who are hospitalized and who require the use of a respirator probably have a more severe illness. Patients who develop acute poliomyelitis at a later age are also known to have more severe involvement. Because this study did not compare PPS patients with asymptomatic post-polio patients, it is difficult to consider the variables identified as true "risk factors" for the development of PPS.

Speier and co-workers (4) completed a study with the aim of determining the percentage of people previously affected by paralytic polio who would develop PPS, and of identifying possible risk factors for PPS. Six hundred and seventy persons from a population of 1619 patients hospitalized at the Sister Kenny Institute, Sheltering Arms Hospital, and the University of Minnesota hospitals in Minneapolis, Minnesota between July 1, 1952 and June 30, 1953 were located. A 30-item questionnaire which included questions regarding sex, date of birth, present age, date of polio, education and employment history, dates and localization of hospitalization, need for aids and degree of function for upper and lower limbs at discharge from acute polio rehabilitation and at present, breathing and swallowing problems at acute polio and at present, the presence of other new problems including increased weakness in polio-affected and in previously unaffected areas, level of endurance, loss of functional activities, and presence of pain or cramping. Forty-nine percent (n=327) of the questionnaires, from 21% of the original population were received. New problems were reported by 41% of those questioned, with pain being the most common new difficulty (in 47% of patients with new difficulties), followed by decreased endurance (42%), and increased weakness (40%). A chi-square test was used to evaluate proportions of patients. There was no significant relationship between sex and age at acute polio with the development of new problems many years after the original illness. However, severity of acute polio as measured by lower limb

weakness requiring the use of ambulatory aids (with or without a history of bulbar and/or respiratory problems) was found to be significantly associated with the development of new problems. Thus, severity of acute polio was again shown to be an important variable in the future occurrence of PPS.

In another study, Klingman and co-workers (19) performed a case-control study to identify risk factors for PPS. From a chart review of 288 patients evaluated in the Polio Clinic at Ranchos Los Amigos Medical Center, 57 patients with PPS were found (credible history of poliomyelitis, initial partial recovery of function, at least 10 years of clinical stability following recovery, subsequent development of progressive muscular weakness). Forty-nine patients with a history of poliomyelitis, but without a history of recent progressive weakness served as the control group. One hundred eighty-two patients were excluded; 78 because of medical or orthopedic problems which could have explained their increased weakness, and 104 because of inadequate information or a questionable history of polio. Risk factors evaluated were interval in years since acute polio, age at acute polio, initial severity of weakness, residual disability, recovery, and level of recent physical activity. Severity of initial polio was measured on a scale of 1 to 6 where one point was given for involvement of each of 4 limbs, one for back involvement, and one for respiratory involvement. Residual weakness severity score was computed in the same way as severity of initial polio. Residual disability was measured on a 5 point scale with 0 = no functional deficit, 1 = mild disability without need for braces, 2 = more severe disability with need for braces, 3 = severe disability and wheelchair-bound, and 4 = total disability and bedridden. Recovery index was calculated as the difference between initial severity and residual disability. Recent activity was measured on a 3-point scale as follows: 1 = little or no regular participation in sports, manual labor or walking, 2 = occasional to moderate sports activity (e.g. >20 minutes of sustained activity 1 to 3 times

per week), 3 = frequent participation in sports (>20 minutes of sustained activity two or more times per week) and/or moderate to heavy activities at work or at home (e.g. frequent heavy lifting or manual labor) MANOVA was used to find a significant multivariate solution Recovery was excluded in this analysis because it was a linear combination of two other variables These variables (with the addition of recovery) were then analyzed with ANOVA. No significant differences between cases and controls were found in terms of sex, or in the number of years since acute polio. However, univariate analyses revealed that patients with PPS were significantly older at acute polio, had a greater initial involvement, had a lower residual disability score, had a greater recovery, and were more physically active than controls. The greatest degree of variance between the two groups could be accounted for by the recovery index (79%), followed by initial severity (65%), and residual disability (47%). Age at acute polio and recent physical activity accounted for only 9 and 5% of the variance, respectively, between the two groups. Because recovery was not adjusted for initial severity of polio, it is impossible to know whether or not a greater recovery in patients with a similar degree of weakness at acute polio was important in the development of PPS. A greater recovery would tend to occur in those patients with a more severe involvement at acute polio, and may thus simply reflect initial polio severity. In addition, odds ratios with their 95% confidence limits were not provided

In a more recent study completed by Windebank and co-workers at the Mayo Clinic (6), a cohort of 300 individuals who had paralytic polio between 1935 and 1955 were identified. From 247 survivors, 50 subjects who had lived closest to Rochester were selected for a detailed historical, functional, psychological, clinical, and electrophysiological evaluation. The purpose of this study was to identify the prevalence of specific symptoms many years after acute polio, and to identify risk factors for the

development of late symptoms. Sixty-four percent of these survivors complained of new symptoms of muscle pain, fatigue, and weakness after a period of prolonged stability. However, these difficulties led to changes in lifestyle or activity in only 18% of patients. Possible risk factors evaluated were present age, age at time of polio, time interval since polio, severity of acute polio (measured by a Neurological Disability Score based on a standardized physical examination in the old records, NDS-max), present severity of weakness (also measured by a Neurological Disability Score, NDS-now), and recovery (difference between NDS-now and NDS-max). Comparisons between cases and controls were made with an unpaired t-test. The likelihood of expressing new complaints was not related to age at polio, current age, time interval since polio, or recovery. The development of new difficulties in a limb was most strongly predicted by the severity of weakness in that limb at acute polio. In addition, they found that patients with leg weakness at acute polio were twice as likely to complain of new problems compared to those with arm weakness. Thus, severity of acute polio was again found to be an important factor in determining who would develop PPS. The main advantage of this study in comparison to previous studies (which relied on patient recall) is the accuracy in assessing severity of weakness at acute polio because of the standardized examinations performed and the detailed records available at the Mayo Clinic. In addition, this study has virtually no referral bias because it used a population-based resource available at the Mayo Clinic. The difficulties with this study include the small patient numbers used, the omission of calculation of odds ratios with 95% confidence intervals, and an inadequate assessment of recovery after polio. Recovery after polio should be measured as the difference between weakness at acute polio and weakness at best after acute polio, and not as the difference between weakness at acute polio (NDS-max) and current weakness (NDS-now). Because PPS patients are currently weaker than previously (by definition),

their recovery may have been underestimated by these investigators. In addition, as in the previous study, degree of recovery was not analyzed in patients with similar degrees of weakness. Therefore, it is impossible to know whether or not recovery is an important factor.

These four studies indicate that initial polio severity, and possibly recovery are the most important factors in predicting future development of PPS. These findings are consistent with the previously described hypothesis for the etiology of PPS because the severity of the original motor neuron poliovirus invasion as estimated by the degree of weakness at acute polio is hypothesized to be important for the development of PPS. The degree of motor unit enlargement during the recovery process after acute polio as estimated by the degree of recovery of muscular strength may also by an important factor because greatly enlarged or overextended motor units may be at greater risk for developing a distal degeneration over time.

Other possible risk factors include time interval since acute polio, current age, severity of weakness after complete recovery from polio, past physical activity (rather than recent physical activity), weight gain prior to onset of PPS, muscle pain with exercise, muscle pain, and joint pain. Although Klingman et al (19) and Windebank et al (6) found no difference between cases and controls in terms of years since acute polio, the study of Halstead and Rossi (18) suggests that it is actually the time since acute polio to present or to development of PPS that is more important than age in predicting who will develop PPS. This finding would be consistent with the previous hypothesis for PPS (8,9) which implies that it is actually the time since polio rather than the chronological age of the subject (with the normal ageing process) that is most important in determining PPS. However, current age should also be studied because of its association with the normal dropout of motor neurons (39-41) and with the decline in growth hormone and

somatomedin C with the ageing process (42,43,45-47).

Actual severity of weakness at the subject's best point after polio has never been evaluated. A patient's perception of increased weakness may be dependent upon chronic weakness. Also, patients who were strongest after their recovery from polio may also have been more active, and may be at greater risk for developing PPS. Current severity of weakness would not be a true "risk factor" because it is not occurring prior to development of PPS. In addition, PPS patients will probably be currently weaker than controls because of their definition (i.e. PPS cases have new or increased weakness whereas controls do not). Therefore, current weakness can be evaluated for descriptive purposes, however it is not a true risk factor in the epidemiological sense.

Chronic muscular overuse has also been been suggested as a possible contributing factor to PPS because of "overwork" of the already overly-engaged post-polio motor neurons (10). Thus, physical activity, obesity, muscle pain with exercise, and recent trauma may be possible risk factors. Klingman et al (19) found that recent physical activity was greater and that residual disability was lower in PPS patients than controls, but that physical activity contributed little to the variance between the two groups. A lower residual disability may be an indicator of overuse (with a lesser use of orthotic devices) or even greater activity. However, recent physical activity is probably not as important as chronic physical activity since with the development of PPS, patients may reduce their activity levels. Obesity or weight gain has been suggested as a risk factor, but has never been evaluated (7). Exercising to the point of muscle pain with possible subsequent muscular injury may also be an indicator of overuse. Creatinine phosphokinase which is known to be released by injured muscle has been found to be higher in symptomatic post-polio patients than in asymptomatic controls (6). In addition, it may be interesting to know where increased weakness is most likely to develop. If

increased weakness develops more frequently in the lower extremities, which are presumably at greater risk for being overworked than the upper extremities, then it may be possible that activity is a contributing factor. New symptoms have been found to develop twice as frequently in patients with weak lower extremities than upper extremities (6) Recent trauma may also contribute to overuse, and may be important to study.

Muscle pain and joint pain will also be evaluated in this study Both may be indirect measures of use because pain, especially joint pain as a result of osteoarthritis may be related to obesity in certain joints, and to increased activity (50,51). Alternatively, pain may precipitate increased weakness in an extremity because of the tendency of patients not to use painful extremities with the consequent development of disuse atrophy in the involved extremity (51)

Thus, a few studies have been completed which have identified variables of importance for the development of PPS, however further work in this area is indicated. This study will attempt to substantiate the previous work performed on PPS, and to analyze possible additional risk factors for this newly recognized syndrome. In addition, because relatively little is known about PPS, a few descriptive analyses on PPS will be performed.

METHODS

Selection of a study design.

A case-control design was used for this study. This type of design was chosen primarily because it allowed efficient use of data already available and the study of multiple potential risk factors for PPS. Both cases and controls were identified from a physician-referred post-polio clinic at the Montreal Neurological Institute and Hospital, Montreal, Quebec. Controls were chosen from the same population of patients as cases to allow the study of risk factors to which both groups of patients were susceptible. Because most patients evaluated in the clinic came with a specific complaint(s), more cases than controls were available for the study.

The main disadvantages of this study design are selection bias in the identification of cases and controls, and inaccuracy in the recall of potential risk factors (52). Because subjects were chosen from a hospital-based clinic, there may have been an overrepresentation of individuals with the highest level of disability or need. This may have been an advantage for the selection of cases since they were presumably those more involved, but made the identification of asymptomatic controls difficult. Another difficulty was inaccuracy in the recall of events which occurred 20 or more years ago. In addition, ascertainment of information on acute polio, one of the main potential risk factors, was problematic because of the age at which it occurred in many individuals (i.e. at 1 to 2 years of age). It is obviously difficult or impossible to recall such events, and some patients may have had to rely on information given to them by family members. However, acute polio and events surrounding this illness constituted a very traumatic time period in the lives of most patients, and are fairly well remembered. Clinical experience indicates that even though some patients may not know the exact degree of weakness which occurred, they do know which limbs or functions were affected. Kaulen et al (53)

validated 3 self-reported measures of functional status (respiratory status, mobility, and activities of daily living (ADL)) at one year post-acute polio (provided by patients 20 to 30 years after acute polio) with medical record audit data (from hospital charts from time of acute polio) in a group of post-polio patients and found that the correlation between the two was relatively high (0.73 to 0.83). The main difficulty was not assessment of whether or not a deficit in a particular function had been present, but in the degree of that deficit (53). Thus, some inaccuracy in assesment of the risk factors is present, but not to such a degree as to make their study impossible. To evaluate the degree of recall inaccuracy in this study, patient recall for some of the variables was correlated with data obtained from old hospital charts.

Study Population.

Cases and controls were identified from a population of patients evaluated in a post-polio clinic at the Montreal Neurological Institute and Hospital (in operation since 1986). 353 patient charts of all patients evaluated at the clinic between 1986 and March, 1992 were reviewed for the study. Patients were either referred by other physicians or self-referred to this clinic. The primary reason why patients came to the clinic was to obtain information and treatment for any symptoms which they were having. Many patients did have PPS (increased weakness and fatigue), but some came with only pain (such as low back pain or foot pain). In addition, some asymptomatic patients came to the clinic for the purpose of obtaining information about PPS, and about any possible preventive measures. A prerequisite for evaluation in the clinic is a history of paralytic polio, therefore virtually all patients have had acute polio. In a few cases the diagnosis of past acute paralytic polio was questionable, and confirmatory electrodiagnostic testing was performed. A standardized history and physical examination form (13) was completed

for each patient at the time of the initial visit (see Appendix), and a thorough medical history and physical examination was performed on each patient at that time. This provided standardized information on all patients evaluated in the clinic. When appropriate, diagnostic tests were also performed to rule out other causes for the patient's symptoms as part of this initial evaluation. This initial data collection was performed by either Dr. Daria Trojan, a clinical and research fellow, or Dr. Neil Cashman, a well-recognized expert in the area. A small proportion (< 10%) of patient data collections were performed by a neurology resident, however all patients (including those seen by Dr. Daria Trojan) were also reviewed with Dr. Neil Cashman. Information for eligibility criteria, for criteria for determination of case/control status, and for risk factors was obtained from the standardized history and physical examination forms completed for each patient, and the initial detailed history and physical examination. The results of any necessary laboratory investigations (which were performed immediately after this extensive initial evaluation) were used for exclusion of cases and controls from the study. Some patients in the clinic were seen only once, whereas others were seen on a more regular or frequent basis. To prevent any bias arising from use of data obtained on follow-up visits on a proportion of the clinic population, only data obtained from the initial interview and the immediately following laboratory investigations were used for the study.

Identification of cases.

Cases of PPS were identified by a chart review of patients evaluated at the Montreal Neurological Institute. A total of 127 cases were found. Criteria for PPS cases were based on those suggested by Mulder et al (34), and included the following:

1. A credible history of past paralytic poliomyelitis (i.e. 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.

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 improved with rest. Symptoms of pain may or may not have been present

Exclusion criteria:

1. Presence of medical conditions which could produce weakness and fatigue. These included significant cardiac disease (that requiring treatment with medications), chronic obstructive pulmonary disease, cancer, cirrhosis, depression, hypothyroidism, anemia, connective tissue diseases, chronic infection, diabetes mellitus, and chronic renal failure.

2. Presence of other concurrent neurological disorders which could produce weakness and fatigue (e.g. peripheral neuropathy, stroke, Parkinson's disease, radiculopathies, spinal stenosis with myelopathy).

3. Presence of severe pain which could make the differentiation between pain and muscular weakness difficult The presence of this difficulty would have been mentioned in the impression as part of the initial evaluation.

4. Symptoms of either new weakness or fatigue (muscular and/or general). (i.e. if a patient had either new weakness or fatigue, they were not considered to be a case).

Identification of borderline cases.

A group of borderline cases was also identified. Borderline cases met the usual

criteria for cases as previously described, but had new symptoms of either weakness or fatigue (i.e. not both). The total number of borderline cases identified was 25. five of these patients complained of only new weakness (i.e. no fatigue), and 20 complained of only new fatigue. Thus criteria for borderline cases were the following

1. A credible history of past paralytic poliomyelitis (i.e. 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
4. New symptoms of increased or new muscular weakness, or fatigue (muscular and/or general) Muscular fatigue was defined as increasing muscular weakness on exertion, which improves with rest. Symptoms of pain may or may not have been present.

Exclusion criteria:

1. Presence of medical conditions which could produce weakness and fatigue.
2. Presence of other concurrent neurological disorders which could produce weakness and fatigue.
3. Presence of severe pain.
4. Symptoms of both new weakness and fatigue (muscular and/or general)

Identification of controls.

Controls were also identified through a chart review of patients evaluated at the post-polio clinic at the Montreal Neurological Institute. Inclusion and exclusion criteria for controls were the same as those for cases with the exception of the presence of new symptoms of increased or new muscular weakness, and fatigue as an inclusion criteria. Therefore, selection criteria for controls were the following:

Inclusion criteria:

1. A credible history of past paralytic poliomyelitis (i.e. 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.
4. Pain may or may not have been present.

Exclusion criteria

1. New symptoms of increased or new muscular weakness, and fatigue (muscular and/or general) Fatigue secondary to fibromyalgia may have been present.
2. Presence of medical conditions which could produce weakness and fatigue. These included significant cardiac disease (that requiring treatment with medications), chronic obstructive pulmonary disease, cancer, cirrhosis, depression, hypothyroidism, anemia, connective tissue disease, chronic infection, diabetes mellitus, and chronic renal failure.
3. Presence of other concurrent neurological disorders which could produce weakness and fatigue (e.g. peripheral neuropathy, stroke, Parkinson's disease, radiculopathies, spinal stenosis with myelopathy).
4. Presence of severe pain which could make the differentiation between pain and muscular weakness difficult The presence of this difficulty would have been mentioned in the impression as part of the initial evaluation.

A copy of the form used to determine eligibility for the study, and for determination of case/control status is included in the Appendix.

Data collection.

Data were obtained from a chart review of patients seen at the Montreal Neurological

Institute post-polio clinic. A log of excluded cases and controls was kept, along with information on reasons for exclusion. One hundred and sixty-two patients from a total of 353 were excluded. Data on the following independent variables was obtained:

1. Date of birth.
2. Sex.
3. Date of initial evaluation.
4. Rater who performed the initial interview and physical examination.
5. Age at acute polio.
6. Age (at time of initial evaluation).
7. Latency or time in years between acute polio and present (time of initial evaluation).
8. Time new symptoms have been present (as of initial evaluation).
9. Presence of pain (muscular and/or joint, yes or no).
10. Location of pain (i.e. in which of four extremities or back).
11. Presence of new muscular atrophy (yes or no).
12. Location of atrophy (in which of four extremities).
13. Severity of weakness at acute polio (measured on a 0 to 6 scale). Degree of weakness in each of 4 extremities and for respiratory, speech/swallowing function was also recorded.
14. Severity of weakness at best point after acute polio (measured on a 0 to 6 scale). Degree of weakness in each of 4 extremities and for respiratory, speech/swallowing function was also recorded.
15. Current severity of weakness (at time of initial evaluation, measured on a 0 to 6 scale). Degree of weakness in each of 4 extremities and for respiratory, speech/swallowing function was also recorded.

16. Recovery after polio (difference between weakness at time of acute polio and weakness at best point after polio)

17. Hospitalization at time of acute polio (yes or no).

18. Respiratory involvement at time of acute polio (yes or no).

19. Length of hospitalization at time of acute polio (in months).

20 Presence of muscle pain with exercise (yes or no).

21 Disability index at best point after acute polio (measured on a 0 to 5 scale).

22 Disability index at present (measured on a 0 to 5 scale).

23 Reported recent weight gain (within the last 5 years; yes or no).

24 Physical activity index (usual activity before onset of PPS for cases, usual activity for controls).

25. Recent major trauma (within last 5 years; yes or no).

26 Present motor strength score in each of 4 extremities (based on physical examination at time of initial visit).

Severity of weakness was measured with three different weakness severity scores (with decreasing degree of accuracy) at each of three times: at time of acute polio, at best point after acute polio, and at present The primary method was "the most accurate," and was used for the main analyses in the study All three measures produced scores ranging from 0 to 6, where 0 referred to a normal individual, and 6 to a completely paralyzed individual Three different weakness severity scales were computed for each patient to provide data for a preliminary analysis of the usefulness and validity of varying degrees of accuracy in estimating weakness (as a subanalysis for this study) and for any future analyses

The primary method for calculation of severity of weakness (and that considered to be the primary method for data analysis) was based on patient estimates of percent

weakness in each of four limbs, and for impairment of speech/swallowing and respiratory function. 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 completely paralyzed, and 100 being normal or not paralyzed) at each of three time periods. A 50 was assigned for some respiratory involvement, and a 0 for respiratory involvement requiring use of a ventilator. A 50 was assigned for some loss of speech and/or swallowing, and a 0 for complete loss of speech and/or swallowing. Each of these six figures was subtracted from 100, and a sum total of all six obtained. This total score was then 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. A sample calculation of this weakness severity score is presented in Table 1.

For the second method of calculation of severity of weakness, patient estimates of severity of weakness in each of four limbs were divided into quartiles. For the first quartile (0 - 25) a value of 12.5 was assigned, for the second quartile (26 - 50) a 37.5 was assigned, for the third quartile (51 - 75) a 62.5 was assigned, and for the fourth quartile an 87.5 was be assigned. A 50 was assigned for some respiratory involvement, and a 0 for respiratory involvement requiring use of a ventilator. A 50 was assigned for some loss of speech and/or swallowing, and a 0 for complete loss of speech and/or swallowing. These six figures were subtracted from 100, and a sum total of all six obtained. This total score was then divided by 100 to arrive at the final total second severity of weakness measure.

For the third method of calculation of severity of weakness, a 1 was assigned for any weakness in any of four limbs (i.e. a patient estimate of weakness of less than 100), and for any dysfunction of speech and/or swallowing, and respiratory function. Thus, a score of 0 to 6 was obtained by this method, and for the two methods previously described

The recovery score was also measured on a 0 to 6 scale where 0 referred to no recovery, and 6 referred to complete recovery following complete paralysis at time of acute polio. This score was arrived at by calculating the difference between severity of weakness at time of acute polio with severity of weakness at best point after acute polio. Three recovery scores were obtained because three measures of severity of weakness were calculated

An ambulation disability index (modified from one developed by Klingman and co-workers (19)) was also computed at reported best point after acute polio, and at time of initial evaluation It ranged from 0 to 5, and was calculated as follows: 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, 5 = total disability and bedridden

Physical activity before onset of PPS for cases, and recent physical activity for controls was calculated in the following manner (similar to that used by Klingman et al (19): 1 = little or no regular participation in sports, manual labor, or walking, 2 = occasional moderate sports activity (≥ 20 mins) one to two times per week, and/or mild to moderate demands at work and at home (frequent ambulation for several hours at a time or occasional light lifting), 3 = frequent participation in sports (≥ to 20 mins or more two or more times per week), and/or moderate to heavy activities at work or home (e.g. frequent heavy lifting or manual labor).

Motor strength at time of initial evaluation in each of two upper extremities was estimated. During the initial physical examination, motor strength in each of 5 muscle groups (deltoid, biceps, triceps, wrist extensors, hand intrinsics) was measured on a 0 to 5 Medical Research Council (MRC) scale (53). The MRC scale is a commonly used

measure of muscular strength which is applied during a clinical neurological examination of a patient. The motor strength in the hand intrinsic muscles was multiplied by 2 since the hand is by far the most important part of the entire upper extremity for patients and in any disability evaluation, and its contribution to perceived total upper extremity weakness will be the greatest. The results obtained for each muscle group were added for each upper extremity for a total possible score ranging from 0 to 30 with 0 being completely paralyzed and 30 being normal motor strength

Motor strength at time of initial evaluation in each of two lower extremities was also estimated by an index. During the initial physical examination, motor strength in each of 5 muscle groups (hip flexors, quadriceps, hamstrings, dorsiflexors, plantarflexors) was measured on a 0 to 5 MRC scale. The results obtained for each muscle group for each lower extremity were added for a total possible score ranging from 0 to 25, with 0 being completely paralyzed, and 25 being normal motor strength

Missing values for independent variables.

A preliminary analysis done by the author on the first 127 patients seen at the Montreal Neurological Institute post-polio clinic (these 127 patients were not the PPS cases used in the present study) revealed that for three variables, weakness at acute polio, weakness at best point after acute polio, and consequently the recovery score, approximately 30% of patients had missing values The other variables had essentially no missing values This was understandable in view of the fact that for many patients, acute polio occurred at a very young age. Also, for some patients it was impossible to quantitate amount of weakness on a 0 to 100 scale However, because at least some data were available on most subjects, estimates of weakness at acute polio were made during this study if some information was present If a patient stated that an extremity was

involved, but that degree of involvement was not known (e.g. partial vs complete), then a 25 was imputed for that limb, and a 50 for speech/swallowing or respiratory function. If a limb or function was 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 of selection of case/control status and validity of some independent variables.

The reliability of the assessment of whether a patient was a PPS case or post-polio control without PPS was estimated Case ascertainment for PPS can be difficult in some situations since no definitive diagnostic test is currently available (14) In addition, because the same individual was determining case/control status, and performing the analysis, some selection bias may have been present. For these reasons, in order to determine agreement between two assessors (inter-rater reliability), a random sample of 10% of the cases and controls were reviewed by Dr Neil Cashman, and case/control status was assigned to these patients by him

The validity of a few of the risk factors was estimated. Independent variables that were validated included severity of weakness at time of acute polio, age at acute polio, length of hospitalization, and current severity of weakness. The first three variables were validated by requesting old hospital records for all cases and controls who were hospitalized or possibly hospitalized in the Montreal area. Only charts on patients hospitalized in Montreal were used in this analysis to improve the efficiency and feasibility of this sub-study. Letters and consent forms for permission to review old hospital records were sent to 87 patients. Fifty-two patients returned signed consent forms to allow the author to review old hospital charts. Requests for copies of old

hospital charts were submitted for 43 patients hospitalized in Montreal hospitals at the time of acute polio. Responses from the hospitals were received for 41 patients. Unfortunately, some of the data obtained were very incomplete. In some cases (approximately 10) old hospital records for hospitalizations before 1960 had been destroyed. The author reviewed microfiches of records on 8 patients hospitalized at the Montreal Children's Hospital. Thus, data on actual degree of weakness at acute polio was available on 19 patients. Because most of the old hospital charts obtained did not include accurate assessments of muscle strength (i.e. MRC (53) measurements of muscular strength in muscle groups), but only general descriptions of degree of paralysis, it was impossible to calculate motor strength scores for all patients. Therefore, only a percent weakness score at time of acute polio was calculated for each of four limbs, and for impairment of respiration and speech/swallowing. If old hospital records indicated that a limb was completely paralyzed, a 0 was assigned, if almost completely paralyzed with trace muscular movements a 10, if partially paralyzed a 50, if almost normal in strength a 90, and if normal in strength a 100 was assigned. Degree of involvement of respiratory function and speech/swallowing function from old hospital records was estimated in the same manner as described for the weakness severity scores. The percent scores obtained for each limb and function from old hospital charts were used to compute a weakness severity score (as described earlier in the Methods section), and then this score was correlated with patient estimates of degree of weakness for each limb and function. Age at acute polio and length of hospitalization were readily available from old records. Present severity of weakness (percent score) reported by each case and control was correlated with the motor strength score (obtained from the physical examination at time of initial evaluation) for each extremity for each patient. Thus, the concurrent criterion-oriented validity of some of the retrospectively gathered and currently available data was

estimated.

The construct validity of the severity of weakness measure itself was also evaluated. This was done by correlating severity of weakness at time of acute polio with length of hospitalization at time of acute polio In addition, the mean severity of weakness at time of acute polio for those patients who were hospitalized was compared with those who were not hospitalized.

Data analysis.

The statistical packages used for data analysis were SAS (SAS Institute Inc., SAS Circle, P.O Box 8000, Cary, NC 27512 USA), and BMDP (1988 version, BMDP Statistical Software, Inc., 1440 Sepulveda Blvd, Los Angeles, CA 90025 USA). SAS was used for calculation of descriptive statistics, t-tests, X^2 tests, correlation coefficients, collinearity analysis, and outlier analysis. BMDP was used for univariate and multivariate logistic regression modeling.

1. Reliability of case/control status and validity of some of risk factors.

To assess the inter-rater reliability of case/control status, 10% (n = 16) of the chosen cases and controls were reviewed by Dr Neil Cashman, and case/control status was also assigned by him The percent agreement score was corrected for chance agreement by calculating coefficient Kappa (54)

$$K = \frac{\text{(observed proportion - expected proportion)}}{\text{(1.0 - expected proportion)}}$$

An inter-rater percent agreement score of at least 90% was expected prior to continuation of the study.

The concurrent criterion-oriented validity of a few of the risk factors (severity of

weakness at time of acute polio, age at acute polio, length of hospitalization, and current severity of weakness) was assessed by correlating patient assessments of these variables with data obtained from old hospital records (for cases and controls hospitalized in the Montreal area), and physical examination at initial evaluation for all cases and controls. For current severity of weakness, each extremity was treated separately. A Pearson correlation coefficient was calculated for each of these 4 variables. In addition, the means of patient estimates and means of estimates obtained from old hospital charts on the first 3 variables were compared with the unpaired t-test.

The construct validity of the measure of severity of weakness at acute polio measure was evaluated by calculating a Pearson correlation coefficient for the two variables of severity of weakness at time of acute polio with length of hospitalization. In addition, mean severity of weakness at time of acute polio was compared between those patients hospitalized and not hospitalized with an unpaired t-test.

The relationship between the two variables of length of time since acute polio and age at acute polio, and recall inaccuracy of severity of acute polio was also evaluated. Recall inaccuracy was measured as the difference in the weakness severity score (based on patient estimates) and weakness severity score (based on old hospital records). Univariate linear regression of length of time since acute polio on recall inaccuracy, and of age at acute polio on recall inaccuracy was performed. Unfortunately, the effect of case/control status on recall inaccuracy was impossible to evaluate because weakness severity scores (based on old hospital records) were available on only 2 controls (and 17 cases).

2 Outlier analysis.

To check the data for errors in data entry, and for outliers, an outlier analysis was performed by looking at ranges of independent variables, and by calculating leverage for each observation. Outliers were defined as those patients with significant leverage values (>.146 for α=.05 and n=191) (55). Any outliers were checked for errors in data entry, and errors found were corrected. Some of the following analyses were then calculated both with and without the remaining outliers to determine their impact on the results.

3. Information on missing values.

The variables of severity of weakness at time of acute polio, weakness at best point after acute polio, and recovery index were frequently missing. For example, the severity of weakness at acute polio score 1 had 40 of 166 cases and controls (24%) with missing values, and recovery score 1 for cases and controls had 49 (29%) missing values. The variables concerned with age and time had few, if any, missing values. When possible, values were imputed to the missing data for weakness at acute polio as previously discussed, and some of the subsequent analyses were calculated both with and without the imputed missing values to assess their impact on the results. Severity of weakness at acute polio and recovery scores A are those without imputed missing values, and those marked B are with imputed missing values. The weakness and recovery scores with ascribed missing values were the primary ones used in further calculations. The number of missing values (with percentages) for each of the independent variables are presented in Table 2.

4. Preliminary statistical analysis.

Frequency histograms of all continuous independent variables were plotted to evaluate the distribution of these variables. Descriptive statistics including means, proportions, standard deviations, and ranges, were calculated for the entire population of cases and controls. Subsequently, means, proportions, two-sample t-tests, and X^2 tests were calculated for cases, borderline cases, and controls separately.

The primary variables of interest in this and the following analyses are:

1. Present age
2. Sex.
3. Age at acute polio.
4. Latency or time in years between acute polio and present (as of initial evaluation).
5. Severity of acute polio as determined by the 0 to 6 severity of weakness score.
6. Recovery score.
7. Severity of weakness at best point after acute polio.
8. Current severity of weakness (as of initial evaluation).
9. Reported recent weight gain (within last 5 years; yes or no).
10. Physical activity index (usual physical activity for controls, and usual physical activity prior to onset of PPS for cases).
11. Recent major trauma (within last 5 years; yes or no).
12. Disability index at best point after acute polio.
13. Current disability index.
14. Muscle pain with exercise (yes or no).

15. Joint pain (yes or no).

16. Muscle pain (yes or no).

5. Collinearity analysis.

All continuous independent variables were evaluated for the presence of collinearity by computing a correlation coefficient matrix for all variables, and by eigenvalue and condition index analysis. Any variables that were collinear with each other were not entered together in the same multivariate analyses.

6. Linearity of continuous variables.

Prior to the utilization of logistic regression modeling, all continuous independent variables were examined for the assumption of linearity in the logistic regression model. This was done by calculating the log odds for each quartile for each variable. For each variable, a plot of logit (p) for each quartile vs. midpoint of each quartile was made. Based on these plots, the variables were entered either as continuous or categorical variables into subsequent logistic regression models.

7. Univariate logistic regression models.

Univariate logistic regression models were estimated for each independent variable. From these calculations, an odds ratio, with 95% confidence intervals, was calculated for each variable. Because it was mathematically impossible to calculate an odds ratio for trauma (no controls had experienced recent trauma), 0.5 was assigned as the number of

controls with recent trauma to permit an estimate of the odds ratio. Some calculations were done both with and without imputed missing values to assess their effect on the results.

8. Multivariate logistic regression models.

Multivariate logistic regression models were computed by a stepwise approach. A significance level of p=0.10 for improvement in the loglikelihood ratio test was used for entry of a term and a value of p=0.15 was used for a term to stay in the model. Specific interaction terms of interest were (1) severity of weakness at acute polio X recovery, (2) physical activity X severity of weakness at best point after acute polio, (3) recent weight gain X current severity of weakness, (4) severity of weakness at acute polio X latency, and (5) recovery X latency. The analyses included calculation of adjusted odds ratios with 95% confidence intervals for all significant variables. Significant models were computed both with and without imputed missing values.

9. Subanalyses:

a. Comparison of proportions of lower extremities with upper extremities currently exhibiting increased weakness.

An analysis was performed to determine if increased weakness occurs more frequently in the lower extremities than in the upper extremities in ambulatory PPS cases (defined as those with a present disability index of < 3). The proportions of previously involved

upper extremities at time of acute polio presently exhibiting increased weakness with the proportions of previously involved lower extremities presently exhibiting increased weakness was compared with a X^2 test. A similar analysis was performed in patients using their upper extremities to aid them in mobility (those with a present disability index of >2). This analysis may provide some further information on the importance of activity in the development of PPS because the lower extremities are presumably at greater risk for increased physical activity than the upper extremities in ambulatory patients. Conversely, the upper extremities may be at greater risk for increased physical activity in patients using wheelchairs for mobility.

b. Comparison of proportions of previously involved and uninvolved extremities currently exhibiting increased weakness

An analysis was performed to determine whether increased weakness is more likely to occur in previously involved or uninvolved extremities in cases. Previously involved extremities were defined as those with patient weakness estimates of less than 100 at time of acute polio, and previously uninvolved extremities were defined as those with patient estimates of 100 at time of acute polio. A comparison of the proportions of extremities in these two groups currently exhibiting increased weakness was done to provide descriptive information about PPS, as well as information regarding where increased weakness is most likely to occur.

c. Evaluation of the effect of time on development of symptoms in PPS

An analysis was performed to evaluate the importance of time in the development of certain symptoms considered to be part of PPS. It has been hypothesized that PPS may be a progressive disease, beginning with fatigue, followed by the addition of weakness, and finally atrophy (32). To test this hypothesis, and also to determine the importance of weakness at acute polio, the means (and standard deviations) of latency, current age, and weakness at acute polio were computed for four groups of patients. An analysis of variance (ANOVA) was performed to evaluate differences between the four groups of patients. Patients were divided into the following 4 groups:

Group 1: post-polio controls (no new symptoms)

Group 2: post-polio patients with new fatigue only (borderline cases)

Group 3: post-polio patients with new fatigue and weakness (cases)

Group 4: post-polio patients with new fatigue, weakness, and atrophy (one patient had no fatigue).

d. Evaluation of the three weakness severity scores.

The ability of the three different weakness severity scores to accurately describe weakness as a result of polio and to be used for statistical analyses was assessed. Means and standard deviations for all three severity scores were calculated for cases and controls. In addition, as stated previously, the concurrent criterion-oriented validity of the three weakness scores at time of acute polio was assessed by calculating correlation coefficients beween patient estimates of weakness at time of acute polio and percent weakness scores

from old hospital charts

Sample size calculations

The primary risk factor of interest in this study was severity of weakness at acute polio. Secondary risk factors considered were recovery after polio, latency, age, and muscle pain with exercise. Other variables which were measured by very crude methods in the present study, but which may be important to study in future studies are physical activity and obesity (which would contribute to overuse of enlarged motor units). A presumed clinically relevant odds ratio was estimated to be 2.5 (a small odds ratio such as 1.1 would not be very meaningful in the clinical management of these patients with the types of variables that were being considered). The odds ratio for initial severity obtained from a previous study in our clinic had been 4.1 (95% confidence intervals 1.9 to 8.8). Initial severity had been dichotomized as either less than 195 or greater than 195 on a 0 to 600 scale as previously described. One hundred and ninety-five was chosen as a result of calculations for the assessment of linearity of continuous variables in the logistic regression model (the details of these calculations are described in the Methods and Results sections). For $\alpha = 0.05$ (one sided), $\beta = 0.20$, OR = 2.5, and $p_0 = 0.4$ (where p_0 = exposure rate among controls, based on previous work), it was determined that 60 cases and controls would be needed (52). If one had wished to detect an OR of 2.0, 104 cases and controls would have been necessary. For unequal numbers of cases and controls, the number of cases (n) required changes by a factor of 1/c, and the number of controls by cn (52). Thus, if one has a 2/1 ratio of cases to controls, c = 0.5, and n is

208 (or 120 for OR = 2.5) as compared to previous requirement of 104 or 60, and the necessary number of controls is 54 (or 30 for OR = 2.5) (21). In this study, 127 cases and 39 controls were identified. Therefore, even with unequal numbers of patients in each group, large enough numbers of patients were available to detect an odds ratio between 2.0 to 2.5.

Ethical considerations.

This study involved a chart review of patients evaluated at the Montreal Neurological Institute post-polio clinic. As previously mentioned, permission to obtain old hospital charts was obtained from the individuals involved. No invasive studies were performed on the patients for the purposes of the study. The confidentiality of the patients involved was preserved during the study, and will be preserved in any publications arising from the work. The approval of the Montreal Neurological Institute ethics committee has been obtained for the study (see Appendix for form submitted to the committee along with the approval).

TABLE 1: SAMPLE CALCULATION FOR SEVERITY OF WEAKNESS SCORE 1

SITE	PATIENT ESTIMATE	100 - PATIENT ESTIMATE
Left arm	0	100
Right arm	100	0
Left leg	0	100
Right leg	30	70
Respiration	0 (ventilator)	100
Speech/swallowing	100 (normal)	0
Total		370
Final Score (Total/100)		3.7

TABLE 2: NUMBER OF MISSING VALUES FOR INDEPENDENT VARIABLES FOR 166 CASES AND CONTROLS

VARIABLE	NUMBER OF MISSING VALUES	PERCENT
Age	0	0
Latency	0	0
Age at polio	10	6
Weakness at Acute Polio 1A	40	24
Weakness at Acute Polio 1B	4	2
Weakness at Best After Polio 1	18	11
Current Weakness 1	34	20
Recovery 1A	49	29
Recovery 1B	21	13
Disability Index at Best After Polio	6	4
Current Disability	4	2
Physical Activity	9	5
Sex	0	0
Recent Weight Gain	8	5
Recent Trauma	4	2
Muscle Pain	1	1
Joint Pain	0	0
Muscle Pain with Exercise	26	16

Legend Weakness and Recovery Scores A are without imputed missing values, Weakness and Recovery Scores B are with imputed missing values

RESULTS

1 Reliability of case/control status and validity of some of risk factors.

Inter-rater reliability between the author and Dr. Neil Cashman, a recognized expert in the field, of case/control status on a random sample of 10% of cases and controls (n=16) was found to be 94% Coefficient K (which corrects the percent agreement score for chance agreement) was found to be 87.5%. The second rater did not agree with the inclusion of one of the 16 patients in the study. He thought that despite the fact that the patient complained of new weakness and fatigue (and was thus considered to be a case by the author), the patients' habits of extreme overexercising and dieting were the most likely cause of the new symptoms, and that consequently she should not be included in the study

Correlation coefficients (concurrent criterion-oriented validity coefficients) of patient estimates of severity of weakness at acute polio, age at acute polio, and length of hospitalization at acute polio and data obtained from old hospital charts are presented in Table 3. A comparison of means of patient estimates with means of data obtained from old hospital charts for these 3 variables is presented in Table 4. Patients tended to overestimate their weakness at acute polio and length of hospitalization, however their assessment of the age at which they had acute polio was accurate.

The relationship between the effect of length of time since acute polio (latency) and age at acute polio, and recall inaccuracy was assessed Recall inaccurancy was measured as the difference in patient estimates of severity of weakness at acute polio with percent weakness score obtained from old hospital records. The correlation coefficients for both of these univariate regression models were low and negative ($r = -.2893$, $n = 19$ for latency, and $r = -.3518$, $n = 19$ for age). The estimated coefficients for the independent variables were also small and negative (-.0619 for latency and -.0465 for age) indicating

an inverse relationship between time and recall inaccuracy (i.e. a greater inaccurancy at a younger age and a lesser time interval since acute polio)

The concurrent criterion-oriented validity of current severity of weakness was estimated by computing correlation coefficients between patient estimates of current severity of weakness and motor strength scores (obtained at time of initial evaluation) for each extremity. The results are presented in Table 5

The construct validity of the severity of weakness at acute polio measure was evaluated in two ways by comparing mean severity of weakness at acute polio in those patients who were and were not hospitalized at acute polio, and by calculating a Pearson correlation coefficient for the two variables of severity of weakness at acute polio and length of hospitalization. The results are presented in Tables 6 and 7

2. Outlier analysis.

To check the data for data entry errors and for outliers, ranges of all continuous independent variables were calcuated, and leverage was calculated for all observations using two models, each with 8 possible risk factors. Evaluation of ranges revealed errors in data entry for 8 patients. These were corrected Leverage for each observation (n=191) was calculated using 2 models, each with 8 risk factors which were not collinear with each other. The same seven observations with significant leverage values ($> .146$ for $\alpha=.05$ and n=191 (55)) were identified for both models The data for these seven observations was checked, and an additional error in data entry for one observation was found. This was corrected. However, this patient also had a very high age for acute polio (39 years). Because all 7 outliers were found to have relatively extreme values for at least one possible risk factor, some logistic regression analyses were computed both with and without these seven observations to assess their impact on the results The

results are presented in Table 8. On comparison of Table 8 with Tables 17 and 18 (with outliers), it is evident that the outliers produced only small changes (in either direction) in the computed univariate and multivariate odds ratios and their associated confidence intervals. For example, the odds ratio for acute polio (per year) without outliers was 1.06 and 1.062 with outliers. For the variable muscle pain with exercise, the odds ratio without outliers was 4.042, whereas with outliers this was 3.86.

3. Information on missing values.

Appropriate logistic regression analyses were calculated both with and without imputed missing values to evaluate their impact on the results. However, the primary analysis is considered to be that which incorporates imputed values. Missing values were ascribed only for the weakness severity score at acute polio, and thus for the recovery score, and were based on information provided by the patients as discussed above. The results are presented in Table 9. The results indicate that the addition of the imputed missing values produced only a small increase in the odds ratios for weakness at acute polio in both the univariate and multivariate models. However, in the univariate models, the addition of imputed missing values improved the statistical significance of the odds ratio for weakness at acute polio. In the multivariate models, the imputed missing values did not change the statistical significance of the corresponding odds ratios.

4. Preliminary statistical analysis.

Plots of frequency histograms for all continuous risk factors were made. The variables current age, latency, weakness at acute polio, disability index at best after acute polio, and current disability were all near normal in distribution. However, age at acute

polio showed a deviation to the left (toward the younger age groups). Descriptive statistics for the entire population of cases and controls are presented in Tables 10 and 11. Descriptive statistics, along with t-tests, X^2 tests, differences (with confidence intervals) in means and proportions between cases and controls are presented in Tables 12 and 13. Cases were significantly different ($p<0.05$) from controls with respect to an older age, longer latency (time since acute polio to initial evaluation), greater weakness at acute polio, greater current weakness, and greater current disability. In addition, cases were significantly more likely to have experienced a recent weight gain, recent trauma, muscle pain, joint pain, and muscle pain with exercise than controls. Descriptive statistics (including means, proportions, standard deviations), t-tests, and X^2 tests were calculated for cases, borderline cases, and controls. These results are presented in Tables 14 and 15. Borderline cases were found to be significantly ($p<0.05$) older at time of acute polio, and to have a greater disability index at best after acute polio than controls. Trends ($p<0.10$) between borderline cases and controls were observed in terms of a greater current age and a greater current disability in borderline cases.

5. Collinearity analysis.

A correlation coefficient matrix was computed for all continous variables. The highest correlation coefficients were observed between age and latency ($r=0.844$, $n=166$, $p<0.0001$) and severity of weakness at best after acute polio and current severity of weakness ($r=0.76$, $n=130$, $p<0.001$). However, these correlation coefficients were not so high as to prevent the entry of both variables into the same analysis (i.e. they were not greater than $r=0.9$) (55). Of interest is that there was no correlation between current disability and physical activity ($r=-0.304$, $n=154$) and disability at best after acute polio

and physical activity (r=-0.224, n=152) To further evaluate the variables for presence of collinearity, eigenvalue and condition index analysis was performed with several models Significant collinearity was observed between the variables current age, latency, and age at polio, and the variables severity of weakness at acute polio, severity of weakness at best after acute polio, and recovery. The reason for collinearity between these two sets of three variables is that each set is a linear combination of each other (i.e. latency = current age - age at polio, and recovery = weakness at acute polio - weakness at best after polio) When any one variable from these two sets was removed, no collinearity was detected. Thus, all three variables from each of these two sets of variables were not entered into the same multivariate logistic regression models.

6. Linearity of continuous variables.

The linearity of all continuous risk factors in the logistic regression model was evaluated by plotting logit (p) for each quartile of each variable versus the midpoint of each quartile for each variable. Logit (p) was calculated as ln (number of cases/number of controls) for each quartile of a continuous variable The plots for each variable are presented in the Figures Based on the results of these plots, the variables were entered either as continuous or categorical variables into subsequent logistic regression models. Current age, latency, weakness at acute polio (A and B), and current weakness were entered as continuous variables. The remaining variables were entered as categorical variables. The categorization of these variables is presented in Table 16.

7. Univariate logistic regression models

Univariate logistic regression models were calculated for each independent variable.

Odds ratios and their 95% confidence intervals were computed for each variable. The results are presented in Table 17. The variables which were found to have significant odds ratios were current age, latency, severity of weakness at acute polio, current severity of weakness, current disability, recent weight gain, muscle pain, joint pain, and muscle pain with exercise. It was mathematically impossible to calculate a meaningful odds ratio for recent trauma because no controls experienced recent trauma. To provide an estimate of the odds ratio for recent trauma, 0.5 was assigned as the number of controls with recent trauma. With this change, and odds ratio of 11.5 (95% confidence interval of 623 to 212) was obtained. The risk for PPS was found to increase by 1.8 for each decade of life, and was also found to increase by 1.6 for each decade after acute polio. The odds ratio for PPS was 1.5 and 7 for each increment of 1 on the weakness at acute polio measure and the current weakness measure, respectively. Patients with a recent weight gain (in the last 5 years) were 3.8 times as likely to have PPS, while 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.

8. Multivariate logistic regression models.

Multivariate logistic regression models were calculated via a stepwise approach. The statistically significant and biologically plausible models are presented in Table 18. Interaction terms were also added to these models, but were found not to significantly improve the model. The results from computation of a multivariate logistic regression models with interaction of weakness at acute polio and latency are presented in Table 19. Five multivariate models with the five interaction terms were computed. None of the interaction terms proved to be statistically significant.

9 Subanalyses.

a. Comparison of proportions of lower extremities with upper extremites currently exhibiting increased weakness

To indirectly assess the effect of physical activity in the development of increased weakness, the proportions of previously involved lower extremities currently exhibiting increased weakness were compared with the proportions of previously involved upper extremities currently exhibiting increased weakness in ambulatory PPS cases. The same analysis was carried out in PPS patients who were using a wheelchair for mobility. The results are presented in Table 20. In ambulatory PPS cases, increased weakness occurred much more frequently in the lower extremites than the upper extremites ($p<.001$), whereas in wheelchair-dependent PPS cases, no difference was found in the proportions of upper extremities and lower extremities exhibiting increased weakness

b Comparison of proportions of previously involved and uninvolved extremities currently exhibiting increased weakness

To provide descriptive information on PPS, the proportions of previously involved and uninvolved extremities currently exhibiting increased weakness were compared. The results are presented in Table 21 Increased weakness was found to occur much more frequently in previously involved than uninvolved extremities ($p<.001$).

c Evaluation of effect of time on development of new symptoms in PPS.

An analysis was performed to determine the importance of time after polio, current age, and weakness at acute polio on the development of different symptoms, all considered to be part of PPS. Post-polio patients were divided into four groups:

Group 1: post-polio controls (no new symptoms, referrant group)

Group 2: post-polio patients with new fatigue (borderline cases)

Group 3: post-polio patients with new weakness and fatigue (cases)

Group 4: post-polio patients with new fatigue, weakness, and atrophy

The results are presented in Table 22

An ANOVA was performed to determine if a significant difference in latency was present between patient groups A significant difference was found between Groups 1 and 4, and Groups 2 and 4. Of note is that during the chart review, only 5 borderline cases with only new weakness were found, all other cases also complained of fatigue In addition, all patients with atrophy had additional symptoms of weakness and fatigue with the exception of one who had an additional symptom of weakness only

d. Evaluation of the three weakness severity measures.

Means, standard deviations, two sample t-tests were calculated for cases and controls using the three different weakness severity measures (as described in the METHODS section) at the three different time periods used in the study The results are presented in Table 23. Similar results were obtained using all three measures A significant difference between cases and controls was found with all three measures at time of acute polio and currently However, a disparity in the results was observed with the three measures at best point after polio Weakness severity score 1 revealed a trend between cases and controls (p=.0848), weakness severity score 2 revealed no significant difference (p=.1560), and weakness severity score 3 revealed a significant difference between cases and controls (p=.0029). Univariate logistic regression models were also computed for the three weakness severity scores. Because weakness severity score 1 was the only measure which could easily be entered into the models as a continuous variable, it had the greatest

chance of producing a significant result. Weakness severity score 3 had to be entered as a categorical variable with 6 categories, greatly reducing the likelihood of having a statistically significant result with the numbers of patients that were available for the study. Thus, for the purposes of logistic regression modeling, weakness severity score 1 is probably the most efficient.

TABLE 3: CORRELATION OF PATIENT ESTIMATES OF VARIABLES AT TIME OF ACUTE POLIO WITH DATA OBTAINED FROM OLD HOSPITAL CHARTS

VARIABLE	R	N
Weakness Severity Measure 1	4130	19
Weakness Severity Measure 2	3678	19
Weakness Severity Measure 3	4283	19
Age at Acute Polio	9882	28
Length of Hospitalization at Acute Polio	7801	23

Legend Please refer to text for computation of weakness severity measures, R = correlation coefficient

TABLE 4: COMPARISON OF PATIENT ESTIMATES WITH DATA OBTAINED FROM OLD HOSPITAL CHARTS FOR 3 INDEPENDENT VARIABLES

VARIABLE	MEAN±SD		N	P-VALUE
	Patient Estimates	Data from old Hospital Charts		
Weakness Severity Measure (at acute polio)	2 976±1 488	2 108±1 155	19	0521
Age at Acute Polio (yrs)	8 72±9 46	8 71±9 23	28	9968
Length of Hospitalization at Acute Polio (mos)	4 28±2 79	3 78±2 79	23	5465

Legend SD = standard deviation, yrs = years, mos = months, p-value = p-value for unpaired t-statistic

TABLE 5: CORRELATION OF CURRENT SEVERITY OF WEAKNESS WITH MOTOR STRENGTH SCORES IN EACH EXTREMITY

EXTREMITY	R	N
Left upper extremity	6738	184
Right upper extremity	7509	183
Left lower extremity	8119	163
Right lower extremity	7865	167

Legend R = correlation coefficient

TABLE 6: SEVERITY OF WEAKNESS AT ACUTE POLIO IN PATIENTS WHO WERE AND WERE NOT HOSPITALIZED

WEAKNESS SEVERITY SCORE	MEAN ± SD Hospitalized	Not Hospitalized	T-VALUE	P-VALUE
1A	2.77±1.44 (n=108)	2.11±1.33 (n=24)	2.04	.043
1B	2.58±1.43 (n=128)	1.79±1.15 (n=42)	3.25	.0014
2A	2.72±1.17 (n=94)	2.10±1.03 (n=22)	2.25	.0262
2B	2.63±1.64 (n=106)	1.97±0.88 (n=38)	3.21	.0016
3	2.98±1.51 (n=128)	2.17±1.34 (n=42)	3.09	.0023

Legend Weakness severity scores A are without imputed missing values, Weakness severity scores B are with imputed missing values, SD = standard deviation, p-value = two-tailed p-value for unpaired t-statistic for difference between hospitalized and not hospitalized patients, please refer to text for computation of weakness severity scores

TABLE 7: CORRELATION OF LENGTH OF HOSPITALIZATION WITH SEVERITY OF WEAKNESS AT ACUTE POLIO

WEAKNESS SEVERITY SCORE:	R	N
1A	2812	92
1B	1983	108
2A	2548	93
2B	2005	87
3	1669	108

Legend Weakness severity scores A are without imputed missing values, Weakness severity scores B are with imputed missing values, please refer to text for computation of weakness severity scores

TABLE 8. EFFECT OF OUTLIERS ON LOGISTIC REGRESSION MODELING

VARIABLE	β	SE	-LOG-LIKELIHOOD	P-VALUE	ODDS RATIO	95% CI
Univariate Analyses						
Age (yrs)	0586	0177	83 221	0013	1 060	1 02-1 1
Latency (yrs)	0466	0178	85 598	0110	1 048	1 01-1.08
Age at Polio (yrs)	1323	4511	89 369	7701	1 142	43-1 02
Weakness at Acute Polio	3904	1611	81 396	0172	1 478	1 08-2 02
Weakness at Best after Polio	5447	4258	71 498	2060	1 724	75-3 97
Current Weakness	1 916	4782	54 29	0003	6 795	2 66-17 35
Recovery (1)	7357	5937	67 73	5235	2.087	65-6 68
(2)	5170	5751			1 677	54-5 18
(3)	8196	6238			2 27	67-7 71
Disability at (1)	6245	4184	82 85	5117	1 867	82-4 24
Best after (2)	1 5433	1 108			4 68	53-41 06
Polio (3)	4447	1 204			1 56	15-16 52
(4)	9 5489	94 84			14030	?
Current (1)	1 813	5338	75 76	0014	6 129	2 15-17 45
Disability (2)	2 612	7737			13 62	2 99-62 05
(3)	3 452	1 13			31 57	3 43-289
(4)	2 698	1 16			14 86	1 52-143
Physical (1)	- 0734	3898	86 49	6905	9288	43-1 99
Activity (2)	- 5931	6826			5526	15-2 11
Sex	3989	3747	88 852	2916	1 49	7-3 1
Recent Weight Gain	1 3355	4588	79 944	0044	3 802	1 55-9 34
Muscle Pain	1 0127	3818	79 944	0092	2 753	1 3-5 82
Joint Pain	9443	4084	86 829	0229	2 57	1 15-5 72
Muscle Pain with Exercise	1 4016	4658	73 619	0033	4 062	1 63-10 12

TABLE 8. EFFECT OF OUTLIERS ON LOGISTIC REGRESSION MODELING (cont.)

VARIABLE	β	SE	-LOG-LIKELIHOOD	P-VALUE	ODDS RATIO	95% CI
Multivariate Analysis						
Age (yrs)	1066	0317	39 46	0004	1 11	1 05-1 18
Weakness at Acute Polio	3174	2369		1425	1 374	86-2 19
Muscle Pain with Exercise	1 782	6942		0056	5 941	1 52-3 9
Recent Weight Gain	2 209	7094		0009	9 105	2 27-36 57
Constant	-5 639	1 709		0004	0036	

Legend: β = the estimated slope coefficient, SE = the estimated standard error of the estimated slope coefficient, 95% C I = the 95% confidence interval of the odds ratio, yrs = years

TABLE 9. EFFECT OF MISSING VALUES ON LOGISTIC REGRESSION MODELING

VARIABLE	β	SE	-LOG-LIKELIHOOD	P-VALUE	ODDS RATIO	95% CI
Univariate models						
Weakness at Acute Polio 1A	323	1705	62 163	0614	1 382	99-1 93
Weakness at Acute Polio 1B	4009	1595	82 127	0134	1 493	1.09-2 04
Recovery 1A(1)	6366	6557	54 993	4305	1 89	52-6 83
(2)	0953	6174			1 100	33-3 69
(3)	1 1097	7514			3 033	69-13 23
Recovery 1B(1)	6932	5922	68 51	5068	2 0	63-6 38
(2)	4745	5736			1 61	52-4 94
(3)	8755	6197			2 4	71-8 08
Multivariate models						
Weakness at Acute Polio 1A	4585	2311	38 529	0256	1 582	1 01-2 49
Latency	0954	0323		0011	1 100	1 03-1 17
Muscle Pain with Exercise	1 2987	6657		0281	3.665	99-13 4
Recent Weight Gain	1 5540	6729		0097	4 730	1 26-17 1
Constant	-4 3921	1 493		0011	0124	
Weakness at Acute Polio 1B	5519	2135	54 111	0043	1 737	1 14-2 64
Latency	0536	02115		0052	1.055	1 01-1 09
Muscle Pain with Exercise	1 521	5629		0029	4 577	1 52-13 78
Recent Weight Gain	1 8628	,5760		0004	6 442	2 08-19 86
Constant	-3 2754	1 125		0014	0378	

Legend Weakness and Recovery Scores A are those without imputed missing values, Weakness and Recovery Scores B are those with imputed missing values, β = the estimated slope coefficient, SE = the estimated standard error of the estimated slope coefficient, 95% C I = the 95% confidence interval of the odds ratio

TABLE 10. DESCRIPTIVE STATISTICS ON INDEPENDENT VARIABLES IN ENTIRE POPULATION OF POST-POLIO PATIENTS (continuous variables)

VARIABLE	N	MEAN ± SD	RANGE
Age (yrs)	166	49 4 ± 12 08	18 9-79 6
Latency (yrs)	166	43 4 ± 12 1	15 8-77 6
Age at Polio (yrs)	156	5 98 ± 6 8	05-39
Weakness at Acute Polio	162	2 37 ± 1 43	5-6
Weakness at Best after Polio	148	82 ± 66	0-3 05
Current Weakness	132	1 33 ± 92	0-4 4
Recovery	145	1 65 ± 1 25	0-5
Disability Index at at Best after Polio	160	93 ± 75	0-4
Current Disability	162	1 44 ± 1 05	0-4
Physical Activity	157	1 59 ± 62	1-3

Legend N = number, Latency = difference between current age and age at polio, SD = standard deviation, yrs = years, please refer to text for description of computation of weakness and recovery scores

TABLE 11. DESCRIPTIVE STATISTICS ON INDEPENDENT VARIABLES IN ENTIRE POPULATION OF POST-POLIO PATIENTS (categorical variables)

VARIABLE	PROPORTIONS (%)
Sex (female)	104/166 (63)
Recent Weight Gain	64/158 (41)
Recent Trauma	15/162 (9)
Muscle Pain	89/165 (54)
Joint Pain	128/166 (77)
Muscle Pain with Exercise	57/140 (41)

TABLE 12. COMPARISON OF MEANS OF INDEPENDENT VARIABLES IN CASES AND CONTROLS (continuous variables)

VARIABLE	MEAN ± SD		P-VALUE	DIFF	95% CI
	CASES	CONTROLS			
Age (yrs)	51 26±11 68 (n=127)	43 31±11 45 (n=39)	0003	7 95	3 82-12 07
Latency (yrs)	44 83±11 94 (n=127)	38 82±11 70 (n=39)	0064	6 01	1 8-10 22
Age at Polio (yrs)	6 44±7 37 (n=127)	4 49±3 9 (n=39)	0819	1 95	18-3 72
Weakness at Acute Polio	2 53±1 46 (n=126)	1 83±1 18 (n=36)	0093	7	24-1 16
Weakness at Best after Polio	87± 67 (n=119)	63± 58 (n=29)	0848	24	-005- 485
Current Weakness	1 52± 90 (n=103)	63± 58 (n=29)	< 0001	89	62-1 16
Recovery	1 71±1 26 (n=118)	1 40±1 22 (n=27)	2595	31	-09- 85
Disability Index at Best after Polio	99± 77 (n=123)	73± 65 (n=37)	0633	26	0052- 51
Current Disability	1 61±1 03 (n=124)	87± 88 (n=38)	0001	74	41-1 07
Physical Activity	1 57± 61 (n=118)	1 64± 67 (n=39)	5247	07	16- 31

Legend P-value = two-tailed p-value for unpaired t-statistic for cases and controls, Latency = difference between current age and age at polio, SD = standard deviation, yrs = years, DIFF = difference between means for cases and controls, 95% CI = 95% confidence interval of difference in means between cases and controls, please refer to text for description of computation of weakness and recovery scores

TABLE 13. COMPARISON OF PROPORTIONS OF INDEPENDENT VARIABLES IN CASES AND CONTROLS (categorical variables)

VARIABLE	PROPORTIONS (%) CASES	CONTROLS	X^2 P-VALUE	DIFF.	95% CI
Sex (female)	82/127 (65)	22/39 (56)	357	9	-9-17
Recent Weight Gain	57/121 (47)	7/37 (19)	.0002	28	14-42
Recent Trauma	15/123 (12)	0/39 (0)	022	12	6 1-17 9
Muscle Pain	75/126 (60)	14/39 (36)	010	30	14 3-45 7
Joint Pain	103/127 (81)	25/39 (64)	027	17	1 3-33
Muscle Pain with Exercise	50/104 (48)	7/36 (19)	003	29	13 3-44 7

Legend DIFF = difference between proportions of cases and controls (measured in percent), 95% CI = 95% confidence interval of difference in proportions between cases and controls (measured in percent), X^2 p-value presented is not continuity unadjusted

TABLE 14. COMPARISON OF MEANS OF INDEPENDENT VARIABLES IN GROUPS OF POST-POLIO PATIENTS (continuous variables)

VARIABLE	MEAN ± SD			P - VALUE	
	CASES	BORDERLINE CASES	CONTROLS	1	2
Age (yrs)	51.26±11.68 (n=127)	48.37±10.51 (n=25)	43.31±11.45 (n=39)	.0003	.0803
Latency (yrs)	44.83±11.94 (n=127)	39.74±8.79 (n=25)	38.82±11.70 (n=39)	.0064	.7373
Age at Polio (yrs)	6.44±7.37 (n=127)	8.63±10.48 (n=25)	4.49±3.9 (n=39)	.1169	.0286
Weakness at Acute Polio	2.53±1.46 (n=126)	2.17±1.36 (n=25)	1.83±1.18 (n=36)	.0093	.2998
Weakness at Best after Polio	.87± .67 (n=119)	.78± .79 (n=23)	.63± .58 (n=29)	.0848	.4316
Current Weakness	1.52± .90 (n=103)	.85± .77 (n=23)	.63± .58 (n=29)	< .0001	.2427
Recovery	1.71±1.26 (n=118)	1.33±1.066 (n=23)	1.40±1.22 (n=27)	.2595	.8242
Disability Index at Best after Polio	.99± .77 (n=123)	1.13±1.01 (n=24)	.73± .65 (n=37)	.0633	.0448
Current Disability	1.61±1.03 (n=124)	1.33±1.01 (n=24)	.87± .88 (n=38)	.0001	.0594
Physical Activity	1.57± .61 (n=118)	1.56± .58 (n=25)	1.64± .67 (n=39)	.5247	.6212

Legend Borderline cases had either weakness (n=5) or fatigue (n=20), P-value 1 = two-tailed p value for unpaired t-statistic for difference between cases and controls, P-value 2 = two-tailed p-value for unpaired t-statistic for difference between borderline cases and controls, Latency = difference between current age and age at polio, SD = standard deviation, yrs = years, please refer to text for description of computation of weakness and recovery scores

TABLE 15. COMPARISON OF PROPORTIONS OF INDEPENDENT VARIABLES IN GROUPS OF POST-POLIO PATIENTS (categorical variables)

VARIABLE	PROPORTIONS (%)			X^2 P-VALUE	
	CASES	BORDERLINE CASES	CONTROLS	1	2
Sex (female)	82/127 (65)	18/25(72)	22/39 (56)	357	209
Recent Weight Gain	57/121 (47)	8/24 (33)	7/37 (19)	0002	202
Recent Trauma	15/123 (12)	1/25 (4)	0/39 (0)	022	208
Muscle Pain	75/126 (60)	10/24 (42)	14/39 (36)	010	647
Joint Pain	103/127 (81)	16/25 (64)	25/39 (64)	027	993
Muscle Pain with Exercise	50/104 (48)	8/23 (35)	7/36 (19)	003	187

Legend X^2 p-value 1 = p-value for X^2 test for difference in proportions between cases and controls (p-value presented is not continuity unadjusted), X^2 p-value 2 = p-value for X^2 test for difference in proportions between borderline cases and controls (p-value presented is not continuity unadjusted), borderline cases are post-polio patients with either new weakness (n=5) or fatigue (n=20)

TABLE 16: CATEGORICAL BREAKDOWN OF CONTINUOUS VARIABLES

VARIABLE	CATEGORIES
Age at Polio (yrs)	0 - 7.0
	7.1 - 40
Weakness at Best after Polio	0 - 0.6
	0.7 - 3.05
Recovery A	0 - 0.6
	0.7 - 1.6
	1.7 - 2.6
	2.7 - 5
Recovery B	0 - 0.5
	0.6 - 1.45
	1.46 - 2.45
	2.46 - 5.0

TABLE 17. UNIVARIATE LOGISTIC REGRESSION MODELS

VARIABLE	β	SE	β/SE	-LOG-LIKELIHOOD	P-VALUE	ODDS RATIO	95% CI
Age (per year)	0606	0176	3 45	83 659	008	1 062	1 026-1 099
(per decade)	606	176				1 833	1 3-2 59
Latency (year)	0464	0176	2 645	86 541	0098	1 048	1 012-1.084
(per decade)	464	176				1 59	1 13-2 25
Age at Polio	181	4482	4039	75 816	6886	1 198	5-2 88
Weakness at Acute Polio	4009	1595	1 896	82 127	0134	1 493	1 09-2 04
Weakness at Best after Polio	576	424	1 358	72 275	1794	1 78	77-4 08
Current Weakness	1 95	478	4 08	54 59	0003	7 03	2 75-17 94
Recovery (1)	6932	5922	1 170	68 51	5068	2 0	63-6 38
(2)	4745	5736	8272			1 61	52-4 94
(3)	8755	6197	1 413			2 4	71-8 08
Disability (1)	6739	4176	1 614	83 811	4650	1 96	86-4 45
Index at (2)	1 543	1 108	1 393			4 68	53-41
Best After(3)	4447	1 204	3693			1 56	15-16 5
Polio (4)	9 55	94 84	1007			14,030	?
Current (1)	1 857	5332	3 484	76 656	0011	6 407	2 25-18 21
Disability (2)	2 6115	7737	3 375			13 62	2 9-62
Index (3)	3 452	1 131	3 053			31 57	3 44-289
(4)	2 816	1 154	2 441			16 71	1 74-161
Sex (female)	342	3724	9189	90 081	3624	1 408	68-2 92
Recent Weight Gain	1 3395	4576	2 927	80 958	0042	3 817	1 56-9 36
Muscle Pain	9655	3800	2 541	86 871	0125	2 626	1 25-5 53
Joint Pain	877	4035	2 173	88 219	0322	2 403	1 09-5 3
Muscle Pain with Exercise	1 344	4646	2 894	74 938	0047	3 836	1 54-9 54

Legend β = the estimated slope coefficient, SE = the standard error of the estimated slope coefficient, 95% CI = 95% confidence interval of the odds ratio, Latency = time between current age and age at polio

TABLE 18. MULTIVARIATE LOGISTIC REGRESSION MODELS

VARIABLE	β	SE	β/SE	-LOG-LIKELIHOOD	P-VALUE	ODDS RATIO	95% CI
Model 1							
Age (per year)	054	0226	2 362	51 773	0106	1 055	1 01 1 1
(per decade)	54	226				1 7	1 09 2 6
Weakness at Acute Polio	4886	2216	2 205		0168	1 63	1 06 2 52
Muscle Pain with Exercise	1 6027	58573	2 736		0032	4 967	1 6 15 6
Weight Gain	1 8571	5883	3 157		0007	6 405	2 02-20 3
Joint Pain	8461	5654	1 496		1026	2 33	77-7 06
Constant	-4 0783	1 246	-3 273		0005	0169	
Model 2							
Latency(per year)	0529	0237	2 230	48 976	0176	1 054	1 006 1 1
(per decade)	529	237				1 69	1 07 2 7
Weakness at Acute Polio	6416	2261	2 837		0026	1 899	1 22 2 96
Muscle Pain with Exercise	2 5704	8614	2 984		0016	13 07	2 4-70 7
Weight Gain	1 9651	6004	3 273		0005	7 135	2 2-23
Muscle Pain	-1 216	7473	-1 627		0800	2965	07-1 3
Joint Pain	8451	5757	1 468		1138	2 328	75 7 2
Constant	-3 9249	1 244	-3 155		0008	0197	
Model 3							
Latency (per year)	0536	02115	2 532	54 111	0052	1 055	1 01-1 09
(per decade)	536	2115				1 71	1 13 2 6
Weakness at Acu Polio	5519	2135	2 586		0043	1 737	1 14 2 64
Muscle Pain with Exercise	1 521	5629	2 702		0029	4 577	1 52 13 78
Weight Gain	1 863	5760	3 234		0004	6 442	2 08 19 86
Constant	-3 2754	1 125	-2 911		0014	0378	
Model 4							
Age (per year)	0632	02215	2 852	52 878	0019	1 065	1 02 1 11
(per decade)	632	2215				1 88	1 2 2 9
Weakness at Acute Polio	4364	2140	2 039		0248	1 547	1 02 2 35
Muscle Pain with Exercise	1 6601	5844	2 841		0020	5 26	1 67 16 53
Weight Gain	1 9646	5906	3 327		0003	7 132	2 24 22 6

Legend β = the estimated slope coefficient, SE = the standard error of the estimated slope coefficient, 95% CI = 95% confidence interval of the odds ratio, Latency = time between current age and age at polio

TABLE 19. MULTIVARIATE LOGISTIC REGRESSION MODEL WITH INTERACTION

VARIABLE	β	SE	β/SE	-LOG-LIKELIHOOD	P-VALUE	ODDS RATIO	95% CI
Latency (per year)	0536	02115	2 532	54 111	0052	1 055	1 01-1 09
(per decade)	536	2115				1 71	1 13-2 6
Weakness at Acute Polio	5519	2135	2 586		0043	1 737	1 14-2 64
Muscle Pain with Exercise	1 521	5629	2 702		0029	4 577	1 52-13 78
Weight Gain	1 863	5760	3 234		0004	6 442	2 08-19 86
Weakness x Latency					7338		
Constant	-3 2754	1 125	-2 911		0014	0378	

Legend: β = the estimated slope coefficient, SE = the standard error of the estimated slope coefficient, 95% CI = 95% confidence interval of the odds ratio, Latency = time between current age and age at polio

TABLE 20: COMPARISON OF PROPORTIONS OF PREVIOUSLY AFFECTED EXTREMITIES (ARMS VS LEGS) CURRENTLY EXHIBITING INCREASED WEAKNESS

PATIENT GROUP	PROPORTIONS OF EXTREMITIES WITH INCREASED WEAKNESS (%)		X^2 P-value
	ARMS	LEGS	
Ambulatory (current disability index <3)	54/198 (27)	114/179 (64)	<.0001
Using wheelchair (current disability index >2)	27/44 (61)	30/44 (68)	.503

Legend X^2 p-value = p-vaule for X^2 test for difference in proportions between previoulsy involved arms with new weakness and previously involved legs with new weakness

TABLE 21: COMPARISON OF PROPORTIONS OF PREVIOUSLY AFFECTED AND UNAFFECTED EXTREMITIES CURRENTLY EXHIBITING INCREASED WEAKNESS

EXTREMITY	PROPORTIONS WITH INCREASED WEAKNESS (%)		X^2 P-value
	PREVIOUSLY UNINVOLVED	PREVIOUSLY INVOLVED	
Left Arm	15/71 (21)	27/55 (49)	.001
Right Arm	17/74 (23)	25/50 (50)	.002
Left Leg	7/24 (29)	66/90 (73)	<.001
Right Leg	7/24 (29)	68/89 (76)	<.001
All	46/193 (24)	186/284 (65)	<.001

Legend X^2 p-value = p-value for X^2 test for difference in proportions between previously uninvolved extremities with new weakness and previously involved extremities with new weakness

TABLE 22: EFFECT OF TIME ON DEVELOPMENT OF NEW SYMPTOMS IN PPS

VARIABLE	MEAN ± SD			
	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Latency	38.82±11.70 (n=39)	38.39±7.68 (n=20)	43.79±11.75 (n=85)	47.47±12.31 (n=39)
Age	43.31±11.45 (n=39)	46.89±10.79 (n=20)	50.42±11.77 (n=85)	52.66±11.58 (n=39)
Weakness at Acute Polio	1.83±1.18 (n=36)	2.24±1.41 (n=20)	2.56±1.42 (n=85)	2.35±1.59 (n=38)

Legend: SD = standard deviation, Group 1 = post-polio controls (no new symptoms), Group 2 = post-polio patients with new fatigue (borderline cases), Group 3 = post-polio patients with new weakness and fatigue (cases), Group 4 = post-polio patients with new weakness, fatigue, and atrophy

TABLE 23. COMPARISON OF MEANS OF WEAKNESS SEVERITY MEASURES IN CASES AND CONTROLS

VARIABLE	MEAN ± SD		T-TEST P-VALUE
	CASES	CONTROLS	
Weakness at Acute Polio 1	2.53±1.46 (n=126)	1.83±1.18 (n=36)	.0093
Weakness at Best after Polio 1	.87±.67 (n=119)	.63±.58 (n=29)	.0848
Current Weakness 1	1.52±.90 (103)	.63±.58 (n=29)	<.0001
Weakness at Acute Polio 2	2.53±1.17 (n=125)	1.99±.94 (n=36)	.0117
Weakness at Best after Polio 2	1.18±.61 (n=119)	1.01±.5 (n=29)	.1560
Current Weakness 2	1.72±.81 (n=101)	1.01±.50 (n=29)	<.0001
Weakness at Acute Polio 3	2.89±1.59 (n=126)	2.14±1.27 (n=36)	.01
Weakness at Best after Polio 3	1.92±1.16 (n=126)	1.31±.89 (n=39)	.0029
Current Weakness 3	2.85±1.43 (n=127)	1.33±.96 (n=39)	<.0001

Legend: Calculation of weakness measures is described in Methods Section, SD = standard deviation, t-test p-value = p-value for unpaired t-statistic for difference in means between cases and controls

DISCUSSION

This study has shown that 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 risk factors shown to be important in univariate analyses are a longer time since acute polio, muscle pain, and possibly recent trauma. Age at acute polio, recovery after polio, weakness at best point after polio, physical activity, and sex were not contributing factors. Our study confirms the findings of previous investigations which have shown that severity of acute polio is important in determining who will develop PPS (4,6,18,19). Even though degree of recovery after polio (19), age at acute polio (18), and physical activity (19) have been shown to be significantly greater in PPS patients than in controls in previous studies, and were greater in cases than controls in our study, these differences did not reach statistical significance. To our knowledge, the variables of weakness at best point after polio, recent weight gain, recent trauma, muscle pain, muscle pain with exercise, and joint pain have not been previously studied.

A case-control design was used primarily because it allowed efficient use of data already available through the Montreal Neurological Institute post-polio clinic, and the study of many potential risk factors concurrently. The main difficulties in this type of design are bias in the identification of cases and controls, and in the assessment of potential risk factors (usually assessed by recall). However, these sources of bias are not all unique to case-control studies. Cohort studies are also susceptible to many of the same errors. An attempt was made to assess the reliability of case/control selection, and the validity of some of the potential risk factors. The results of these analyses with their possible impact on the results obtained are discussed below.

The establishment of case and control groups can be biased through improper

ascertainment, diagnosis, or selection of study subjects (52) Surveillance bias can occur in diseases which are asymptomatic or have mild symptoms Patients who are seen more often by medical personnel (for a variety of reasons) would be more likely to be diagnosed and to be included in a study However, for a disease which is progressive and requires medical attention, little or no surveillance bias would be present because the patient would tend to seek medical attention Patients with PPS do develop symptoms which affect their ability to do everyday activities, therefore they would tend to seek medical attention for their problems For this reason, surveillance bias is probably not important in this situation Survival bias is also not an important issue in this study because PPS is rarely fatal Bias in diagnosis can occur when the person performing the diagnostic test is aware of the patient's exposure status There are no well established criteria and no specific diagnostic test for PPS (1,7,14). The diagnosis is made based on the clinical symptoms of the patient and the exclusion of other possible causes for the symptoms. In this study, the person assigning case/control status was aware of the patients' exposure status because both were determined through a clinic chart review Thus, bias in diagnosis could have been present, however case/control status was determined as objectively as possible Because of these difficulties, inter rater reliability of case/control status was assessed and was found to be acceptable at 94% Selection bias can occur through a variety of ways The most important source of selection bias in this study could have occurred because of the clinic chosen from which to identify cases and controls. A hospital-based specialty clinic was used as a source for the study population Hospital-based clinics generally attract more severely involved patients However, because both cases and controls were identified from the same clinic population, this bias should have cancelled out Another difficulty in using a metropolitan, hospital based clinic as a study population source is that some exposures could have been over or under

represented Again, if cases and controls come from the same population, this effect should cancel out However, certain exposures (such as increased physical activity) could be under represented in a metropolitan study population with a consequent difficulty in identifying a significant odds ratio The power of a case-control study decreases with a reduction in the exposure rate in controls (52) Thus, numerous sources for bias in case/control selection can occur, however the most important one for this study was probably error in diagnosis This was at least partially evaluated as discussed above.

Measurement error in determining past exposures in case/control studies can occur from imperfect records, faulty recall, prevarication, or improper interviewing techniques (52) The most important source of error in this study was probably recall bias in determination of some of the risk factors Cases may overestimate exposure or may be more careful in assessing it In addition, the length of time since exposure and the age at which the exposure occurred may have been important sources of error for some of the variables in this study Patients were asked to recall an event that had occurred several decades ago and at an early age For these reasons, an evaluation of recall inaccuracy was carried out for some of the risk factors To evaluate the recall accuracy of age at acute polio, length of hospitalization at acute polio, and weakness at acute polio, patient estimates of these measures were correlated with data obtained from old charts on a proportion of cases and controls The correlation coefficients for age at acute polio and length of hospitalization were good [0 98 (n=29), and 0 78 (n=23], respectively). Thus, the potential risk factors of age at acute polio and latency (length of time since acute polio) were well measured by patient recall However, the correlation coefficient for weakness at acute polio was low at 0.41 (n=19). This may be indicative both of inaccuracy in patient recall and in the data available in hospital charts Many of the charts had no accurate motor examination, and when a description was present, frequently

there was only one. Because the development of weakness during acute polio can occur over a period of 2 to even greater than 7 days (20), it was difficult to know whether the one examination recorded described the patient at the worst point of the illness. Our data show that patients tended to overestimate the degree of their weakness at acute polio as compared to data available from old hospital charts. We also found no significant relationship between degree of recall inaccuracy with both age at acute polio and length of time since acute polio. Unfortunately, the effect of case/control status on recall inaccuracy of weakness at acute polio was impossible to evaluate because old hospital records were available on only one control. To measure the construct validity of weakness at acute polio, mean severity of weakness at acute polio was compared in those patients who were and were not hospitalized, and found to be significantly different. The concurrent-criterion oriented validity of current severity of weakness was assessed by correlating patient estimates of current severity of weakness in each extremity with motor strength scores (based on physical examination) for each extremity, and was found to be acceptable (range was r=0.67 to 0.81 for the four extremities). Thus, patient recall of age at acute polio, latency, and length of hospitalization was accurate, however the accuracy of patient estimates of severity of weakness at acute polio will need further study. Despite this difficulty, patient estimates of weakness severity at acute polio and at present correlated fairly well with other measures of weakness severity. The possible inaccuracy in patient recall of weakness at acute polio may have reduced the statistical significance of some of our results with this variable, however this measure did appear to assess degree of weakness from polio at least to a moderate degree.

Other sources of measurement error of exposures are interviewer bias and prevarication. Interviewers may probe cases more deeply on exposure than controls, and interviewers may themselves overestimate certain exposures because of their own

hypotheses. In addition, interviewers can express pleasure or displeasure about certain responses directly or indirectly through "body language." To avoid such sources of bias, trained interviewers should be used (52). Interviewer bias could have been a source for error in this study. Trained interviewers were not used and no attempt was made to assess this possible source for error. However, a standardized form was used for gathering data on most risk factors considered in this study, therefore all cases and controls were asked to assess most variables. For a few variables such as obesity and trauma, the data were not always available since these variables were not listed on the form. Rather, the data for them were obtained from the past medical history in the letters prepared for each patient (to the referring physician). Thus, a bias could have arisen with these variables since cases would be more likely to be questioned about certain variables than controls. Bias arising from prevarication can be a problem in cases who may receive disability pay or some other form of compensation if they overestimate an exposure. Conversely, if a particular exposure means loss of a job, the patient may underestimate it. No bias would arise if the same phenomenon occurs in both groups. This may have been a relatively small source for error in our study (based on clinical experience) with variables such as physical activity, trauma, muscle pain, and joint pain. No attempt was made to assess this possible source for error in this study.

Another limitation in this study may be the number of cases and controls identified for the study, and the consequent limitations in the power of the study, and in the size of the odds ratio which the study was able to detect. As discussed previously in the Methods section, this study should have been able to detect an odds ratio of 2.5 for a control exposure rate of $p = 0.4$. The relatively small number of controls (39) identified in this study produces a larger confidence interval of the estimated odds ratios, and thus reduces the accuracy and the statistical significance of the results. Because of this, a

larger multi-center study may be indicated in the future to assess the importance of possible risk factors which were measured by imprecise methods in this study (such as physical activity, and obesity), or which revealed specific trends, rather than statistically significant odds ratios (such as recovery)

Alternative study designs were a prospective cohort study, a retrospective cohort study, and a prospective-retrospective cohort study A prospective cohort study of individuals with acute paralytic polio that followed individuals for a sufficiently long period of time so that a certain proportion would develop PPS would be impossible in North America because acute polio is virtually non-existant This type of study design may still be possible in the third world where acute polio continues to be common However, the long time period of follow-up necessary (several decades) would make it very difficult A retrospective cohort study was another possibility, but may have still presented difficulties with assessment of risk factors (done in a retrospective fashion), and in identification of cases. Because not all patients from the initial cohort identified could have been traced, those found may be selected in a biased manner The patients traced might have been those more severely involved (with less mobility) In addition, the initial cohort identified would probably have been from a registry of patients hospitalized for acute polio at a particular hospital, and may thus have represented the more severe cases of acute polio A retrospective cohort study was performed by Codd et al with data available at the Mayo Clinic (2) The purpose of this study was not to assess risk factors for PPS, but to provide information on the proportion of patients who have had acute polio who will develop PPS, and to provide descriptive information on these patients Even in the ideal circumstances present in the Olmstead County, Minnesota database (i e detailed and standardized medical records, a relatively immobile population), 23 out of 173 (13%) of patients initially identified remained untraced Therefore, the long time

period necessary for development of PPS, even in the most ideal circumstances, still makes this type of study difficult. A third cohort design alternative was a study which combines both retrospective and prospective features. For this type of study, a cohort of patients with a history of paralytic polio without PPS could have been identified, certain potential risk factors such as physical activity and obesity measured, and then the group could have been followed for a period of 5 to 10 years to development of PPS. This type of study design would have allowed accurate assessment of certain risk factors, but would have necessitated the utilization of multiple centers, a long follow-up period, and considerable expense. Thus, a case-control study design was used, and some of the possible sources for error were assessed.

Despite all the possible sources of error in our study, our findings on the important risk factors for PPS are consistent with previously proposed hypotheses for PPS. The severity of the original motor neuron poliovirus invasion as estimated by the severity of weakness at acute polio has been proposed to be important for the development of PPS (4,6,8,9,18,19). This was confirmed by our study. 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) (8,9), the degree of motor unit enlargement as measured by the degree of muscular recovery after polio may also be a risk factor for PPS (19). Although we found a greater recovery in cases than controls, this difference did not reach statistical significance (p-value 0.26, Table 12), and did not result in a significant odds ratio. Rather, our study showed that the superimposition of later phenomenon such as overuse, development of pain, and ageing over initial severity are of greater importance than recovery.

Time since acute polio and age have also been proposed as possible contributors to PPS (6-9). Time since acute polio may be a measure of overuse of enlarged motor units,

and current age may be a measure of the normal ageing process. The normal progressive dropout of motor neurons and the decrease in growth hormone and somatomedin C levels (with loss of their supportive effects on muscle fiber hypertrophy and motor neuron sprouting) with greater age can be a precipitating factor for PPS (7,39-47). These variables are correlated with each other, and we found both to be important in predicting PPS in univariate and multivariate analyses, however current age was found to be a more important factor statistically than length of time since acute polio.

Chronic overuse has also been proposed as a contributing factor to PPS (1,10). Thus, variables such as physical activity, weight gain, muscle pain with exercise, and recent trauma may a[illegible]e possible risk factors. Our study showed that recent weight gain, muscle pain with exercise, and possibly recent trauma are important factors in determining who would develop PPS, thus confirming this hypothesis. Physical activity (measured by an imprecise scale) was found not to be important. This may be due to measurement error or to insufficient power. However, muscle pain with exercise which may be a clinical measure of overuse and damage to muscle was a significant risk factor (48,49). This finding is consistent with a previous report of increased CPK levels (an enzyme which is known to be released by injured muscle) in PPS patients and not in post-polio controls (6). In addition, our finding that increased weakness occurs much more frequently in the lower extremities than the upper extremities in ambulatory PPS patients gives credence to the notion that physical activity may indeed be important for the development of increased weakness. Lower extremities are presumably used much more than upper extremities in ambulatory patients. An explanation for our contradictory findings is that the amount of physical activity is not as important as the intensity to which the activity is carried out. Frequent periods of activity, if interspersed with rest periods and the avoidance of muscle pain with activity may be safe in post polio patients.

These findings will need further study.

Joint pain and muscle pain were also shown to be significant factors in univariate analyses. This finding may simply be a reflection of the fact that pain is the third component of PPS, or it may be another measure of overuse or even disuse. Joint and muscle pain can be related to exercise, and thus be indirect measures of overuse (7,50,51). Pain, especially joint pain may be more likely to occur in weaker or newly weakened limbs because of the lack of muscular support to joints in the involved extremites (50,51). Pain can also lead to decreased use of certain muscles with the development of disuse atrophy and weakness (51). Thus, pain can precede or follow the development of increased weakness. For all these reasons, it is very difficult to establish the exact role of pain in PPS.

Of note is that some of the variables which we have referred to as risk factors may not be true "risk factors." Rather, they may be factors which are associated with the disease. This may be true for the variables recent trauma, recent weight gain, muscular pain with exercise, muscle pain, and joint pain. From the data available in clinic charts, it was impossible to determine for all patients whether these factors actually occurred before the onset of PPS, or concurrently with PPS. Thus, the importance of these variables as true risk factors, appearing before the onset of the disease will need further study.

In the subanalyses, we evaluated the proportions of previously involved and uninvolved extremities currently exhibiting increased weakness, and the effect of time on development of new symptoms in PPS. We confirmed the findings of previous investigators who showed that new weakness can occur in extremities previously clinically unaffected by paralytic polio, but that increased weakness tends to occur much more frequently (χ^2 p-value < 0.001) in previously affected than unaffected extremities

(7). The finding of new weakness in previously "unaffected" extremities can be explained by subclinical involvement of motor neurons during acute polio (7,17,24). We also evaluated the time interval since acute polio in groups of post polio patients with various symptoms typical of PPS. We found evidence for progression of symptoms in PPS, beginning with fatigue (mean 38.4 years after polio), followed by weakness (mean 43.8 years after polio), and then by atrophy (mean 47.5 years after polio). The differences in latencies between the group with atrophy (and new fatigue and weakness), and the groups with only fatigue and with no symptoms reached statistical significance ($p < 0.05$). A similar progression was seen with current age, but not with weakness at acute polio. The notion that PPS is a progressive phenomenon was proposed by Cashman et al (32), however their data did not strongly support this hypothesis. They found no difference in latency and current age between patients with new atrophy and all others seen in their clinic, but did find a small (2 year) not statistically significant difference in time of new symptoms between these two patient groups. Our results provide evidence for the hypothesis that fatigue is an early symptom of PPS, which is followed by weakness, and then by atrophy.

The results from this study can be applied to the clinical management of post polio patients. Even though patients have no control over their severity of weakness at acute polio, they do have control over some other possible risk factors for PPS. Patients can be advised that they should avoid gaining weight and exercising to the point of muscle pain as these variables have been found to be strongly associated with PPS. The exact role of physical activity will still need further study because of our contradictory results, however the usual recommendations of low level aerobic exercise with avoidance of muscle pain and fatigue are valid. Patients can be advised that new weakness occurs much more frequently in previously involved extremities, but that it can occur, although

much less frequently in previously uninvolved extremities. In addition, if symptoms do develop, PPS can be described as a slowly progressive disease with fatigue being an early symptom, followed by weakness, and finally by atrophy as a late phenomenon, if it occurs at all. In these ways, despite the numerous possible sources for error, this study provides descriptive information on PPS, and can provide the basis for physiologically reasonable and practical advice to post-polio patients who wish to avoid PPS

CONCLUSIONS

We conclude that in the unadjusted analyses, the most important risk factors for PPS are a greater current age, a longer time since acute polio, a greater weakness at acute polio, a recent weight gain, muscle pain with exercise, muscle pain, joint pain, and possibly recent trauma. The multivariate model which could best predict who would develop PPS was one containing the variables current age, weakness at acute polio, muscle pain with exercise, recent weight gain, and joint pain. A similar multivariate model containing length of time since acute polio rather than current age was slightly less effective in predicting PPS. Age at acute polio, degree of recovery after polio, weakness at best point after polio, physical activity, and sex were not contributing factors. Although physical activity with our crude measure was not a significant risk factor, in another analysis we found that increased weakness occurs much more frequently in lower extremities than upper extremities in ambulatory patients. Thus, the exact role of physical activity will need further evaluation. Some of the variables such as recent weight gain, recent trauma, muscle pain with exercise, muscle pain, and joint pain may not be true "risk factors," but rather may be associated factors because it was impossible to determine whether they occurred before or concurrently with PPS from the data available for all patients. Therefore, they will need further study.

Reliability and validity studies revealed that inter-rater reliability of case/control status was good at 94%, and that patient recall of age at acute polio and thus length of time since acute polio was accurate. However, patient recall of severity of acute polio did not correlate well (r=0.41) with weakness severity based on old hospital charts. This may have been due to both inaccuracy in patient recall and inaccuracy in the old charts themselves. Despite this, our weakness severity measure correlated well with other weakness measures. Mean severity of weakness at acute polio was found to be

significantly higher in hospitalized as compared to unhospitalized patients (p 0.0014), and current severity of weakness correlated well (r=0.67 to 0.81) with motor strength scores in each extremity. Thus, our weakness at acute polio measure did assess this construct, however there was discrepancy between measures based on patient recall and measures based on old hospital charts.

In our subanalyses, we confirmed the findings of previous investigators by showing that new weakness can occur in previously uninvolved extremities, but that it occurs significantly more frequently in previously involved extremities (24% versus 65%, X^2 p value < 0.001). We also found evidence for the hypothesis that PPS is a progressive disease, beginning with fatigue, followed by weakness, and finally by atrophy. Latency increased by a mean of 4 to 6 years in patient groups with these symptoms.

REFERENCES

1. Halstead LS. Post-polio syndrome: definition of an elusive concept. In: Munsat TL, ed. Post-Polio Syndrome. Boston: Butterworth-Heinemann 1991.

2. Codd MB, Mulder DW, Kurland LT, Beard CM, O'Fallon. Poliomyelitis in Rochester, Minnesota, 1935-1955: Epidemiology and long-term sequelae: A preliminary report. In: Halstead LS, Wiechers DO, eds. Late Effects of Poliomyelitis. Miami, FL: Symposia Foundation 1985;121-134.

3. Windebank AJ, Daube JR, Litchy WJ, Codd M, Chao EYS, Kurland LT, Iverson R. Late sequelae of paralytic poliomyelitis in Olmsted County, Minnesota. In: Halstead LS, Wiechers DO, eds. Research and Clinical Aspects of the Late Effects of Poliomyelitis. White Plains, NY: March of Dimes Birth Defects Foundation 1987;27-38.

4. Speier JL, Owen RR, Knapp M, Canine JK. Occurrence of post-polio sequelae in an epidemic population. In: Halstead LS, Wiechers DO, eds. Research and Clinical Aspects of the Late Effects of Poliomyelitis. White Plains, NY: March of Dimes Birth Defects Foundation 1987;39-48.

5. Halstead LS, Wiechers DO, Rossi CD. Late effects of poliomyelitis: A national survey. In: Halstead LS, Wiechers DO, eds. Late Effects of Poliomyelitis. Miami, FL: Symposia Foundation 1985;11-31.

6. Windebank AJ, Litchy WJ, Daube JR, Kurland LT, Codd MB, Iverson R. Late effects of paralytic poliomyelitis in Olmsted County, Minnesota. Neurology 1991;41:501-507.

7. Jubelt B, Cashman NR. Neurologic manifestations of the post-polio syndrome. Crit Rev Neurobiol 1987;3:199-220.

8. Wiechers DO, Hubbell SL. Late changes in the motor unit after acute

poliomyelitis. Muscle Nerve 1981;4:524-528.

9. Wiechers DO. New concepts of the reinnervated motor unit revealed by vaccine associated poliomyelitis. Muscle Nerve 1988;11:356-368.

10. Perry J, Barnes G, Gronley JK. The Postpolio Syndrome: An overuse phenomenon. Clin Orth Rel Res 1988;233:145-162.

11. Coers C, Woolf AL. The innervation of muscle; a biopsy study. Oxford, Blackwell Scientific, 1959.

12. Hodes R. Electromyographic study of defects of neuromuscular transmission in human poliomyelitis. Arch Neurol Psych 1948;60:457-473.

13. Dalakas MC, Elder G, Hallett M et al. A long-term follow-up study of patients with postpoliomyelitis neuromuscular symptoms. N Engl J Med 1986;314:959-963.8.

14. Cashman NR, Maselli R, Wollman RL, Roos R, Simon R, Antel JP. Late denervation in patients with antecedent paralytic poliomyelitis. N Engl J Med 1987;317:7-12.

15. Engel AG. Acquired autoimmune myasthenia gravis. In: Engel AG, Banker BQ, eds. Myology. New York: McGraw Hill Inc., 1986;1925-1954.

16. Trojan DA, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue. J Neurol Sci (in press).

17. Trojan DA, Gendron D, Cashman NR. Electrophysiology and electrodiagnosis of the post-polio motor unit. Orthopedics 1991;14:1353-1361.

18. Halstead LS, Rossi CD. Post-polio syndrome: Clinical experience with 132 consecutive outpatients. In: Halstead LS, Wiechers DO, eds. Research and Clinical Aspects of the Late Effects of Poliomyelitis. White Plains, NY: March

of Dimes Birth Defects Foundation 1987;27-38

19 Klingman J, Chui H, Corgiat M, Perry J Functional recovery: a major risk factor for the development of post-poliomyelitis muscular atrophy Arch Neurol 1988,45 645-647

20 Price RW, Plum F Poliomyelitis. In: Vinken DJ, Bruyn GW, eds. Handbook of Clinical Neurology (vol 34) Amsterdam North Holland Biomedical Press 1978,93 132

21 Wright PF, Kim-Farley RJ, Quadros CA, Robertson SE, Scott RM, Ward NA, Henderson RH Strategies for the global eradication of poliomyelitis by the year 2000 N Engl J Med 1991;325:1774-1779.

22 Adams RD, Victor M Principles of Neurology. New York: McGraw-Hill Book Company 1985,547-551

23. Young RR, Bradley WG, Adams RD Approach to clinical myology. In: Harrison's Principles of Internal Medicine New York: McGraw -Hill Book Company 1983,2169-2183

24. Bodian D Poliomyelitis Pathologic anatomy. In: Poliomyelitis: Papers and discussions presented at the first international poliomyelitis conference. Philadelphia Lippincott 1949,62

25 Halkelius L, Stalberg E Electromyographical studies of free autogeneous muscle transplants Scand Plast Reconstr Surg 1974;8:211-219.

26. Wiechers DO, Warmholts JR Anterior horn cell disorders. In: Johnson EW, ed. Practical Electromyography Baltimore, MD William and Wilkins 1980.135-154.

27. Wiechers DO Acute and latent effects of poliomyelitis on the motor unit as revealed by electromyography Orthopedics 1985,8:870-872.

28. Miller RG. The effects of nerve injury on the neuromuscular junction. In:

Brumback RA, Gerst J, eds The Neuromuscular Junction Mount Kisco, NY Futura Publishing Co 1984,203-255

29. Sharrard WJW Correlation between changes in the spinal cord and muscle paralysis in poliomyelitis Proc R Soc Med 1953;46 346-349

30. Borg K, Borg J, Edstrom L, Grimby L Effects of excessive use of remaining muscle fibers in prior polio and LV lesion Muscle Nerve 1988,11 1219-1230

31. Cornil, Lepine. Sur un cas de paralysie générale spinale, antérieure subaigue, suivi d'autopsie Gaz Med (Paris) 1875,4:127-129

32. Cashman NR, Maselli R, Wollmann R, Simon R, Herdkamp P, Antel JP New muscle atrophy as a late symptom of post-poliomyelitis syndrome Clinical Ecology 1987;5 11-13.

33. Finkelman R, Munsat T, Andries P, Thornell B, Brussock C Alterations of strength in post-polio syndrome In Munsat TL, ed Post Polio Syndrome Boston. Butterworth-Heinemann 1991,91-103

34. Mulder DW, Rosenbaum RA, Layton DO Late progression of poliomyelitis or forme fruste amyotrophic lateral sclerosis? Mayo Clin Proc 1972,47 756-761

35. Ravits J, Hallett M, Baker M, Nilsson J, Dalakas M Clinical and electromyographic studies of postpoliomyelitis muscular atrophy Muscle Nerve 1990;13,667-674

36. Dalakas M. Post-polio syndrome: Clues from muscle and spinal cord studies In: Munsat TL, ed Post-Polio Syndrome Boston, MA Butterworth Heinemann 1991;39-65

37. Lange DJ, Smith T, Lovelace RE. Postpolio muscular atrophy Diagnostic utility of macroelectromyography Arch Neurol 1989,46,502-506

38. Maselli RA, Cashman NR, Wollman RL, Salazar-Grueso EF, Roos R

Neuromuscular transmission as a function of motor unit size in patients with prior poliomyelitis Muscle Nerve 1992,15 648-655

39 McComas AJ, Upton HRM, Sica REP Motor neuron disease and aging. Lancet 1973,2 1477-1480.

40. Stalberg E, Thiele B Motor unit fiber density in the extensor digitorum communis muscle J Neurol Neurosurg Psychiatry 1975,38:874-880.

41. Tomlinson BE, Irving D The numbers of limb motor neurons in the human lumbosacral cord throughout life J Neurol Sci 1977;34 213-219

42 Shetty KR, Mattson DE, Rudman IW, Rudman D. Hyposomatomedinemia in men with postpoliomyelitis syndrome J Am Geriatr Soc 1991;39:185-191.

43 Florini JR, Prinz PN, Vitiello MV, Hintz RL Somatomedin-C levels in healthy young and old men relationship to peak and 24 hour integrated levels of growth hormone J Gerontol 1985,40 2-7

44 D'Ercole AJ, Stiles AD, Underwood LE Tissue concentrations of somatomedin C. Further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc Natl Acad Sci USA 1984;81:935-939

45 Zadik Z, Chalew SA, McCarter RJ Jr , et al The influence of age on the 24-hour integrated concentrations of growth hormone in normal individuals. J Clin Endocrinol Metab 1985,60 513-516

46 Rudman D, Kutner MH, Rogers CM, et al. Impaired growth hormone secretion in the adult population. Relation to age and adiposity J Clin Invest 1981,67 1361-1369.

47 Vermeulen A Nyctohemeral growth hormone profiles in young and aged men: Correlation with somatomedin C levels. J Clin Endocrinol Metab 1987;64:884-888

48. Nanji AA Serum creatinine kinase isoenzymes A review Muscle Nerve 1983,6:83-90

49 Waring WP, McLaurin TM Correlation of creatinine kinase and gait measurement in the post-polio population A corrected version Arch Phys Med Rehabil 1992,73:447-450

50. Liang MH, Fortin P Management of osteoarthritis of the hip and knee N Engl J Med 1991,325:125-127

51. Hicks JE, Gerber LH Rehabilitation of the patient with arthritis and connective tissue disease. In DeLisa JA, ed Rehabilitation Medicine Principles and Practice. Philadelphia J.B Lippincott 1988,765-794

52. Schlesselman JJ. Case-Control Studies: Design, Conduct, Analysis New York Oxford University Press 1982,124-143,144-170

53. Kaufert JM, Syrotuik J, Kaufert PL, Gilbert PK Epidemiological issues in follow-up studies of the impact of poliomyelitis In Halstead LS, Wiechers DO, eds, Late Effects of Poliomyelitis Miami, FL Symposia Foundation 1985;135-152.

54. Streiner DL, Norman GD Health Measurement Scales A Practical Guide to their Development and Use Oxford Medical Publications 1989,79-90

55. Kleinbaum DG, Kupper LL, Muller KE Applied Regression Analysis and Other Multivariable Methods Boston PWS-Kent Publishing Company 1988,181 227,662

FIGURES

Assessment of Linearity of Continuous Variables in Logistic Regression Model

Figure 1

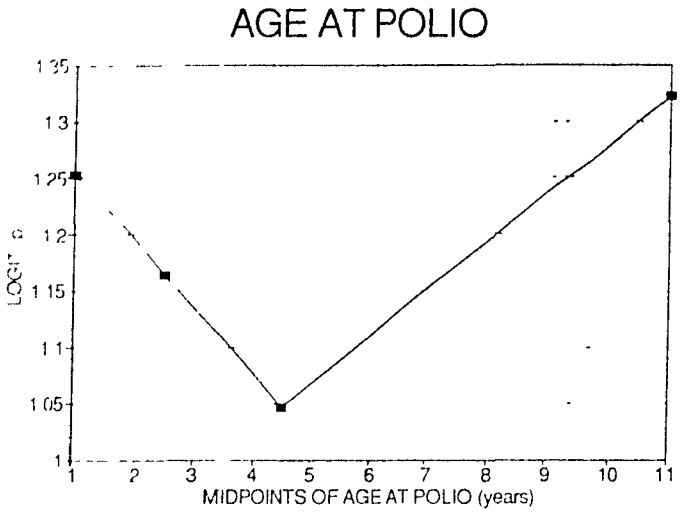


Figure 2

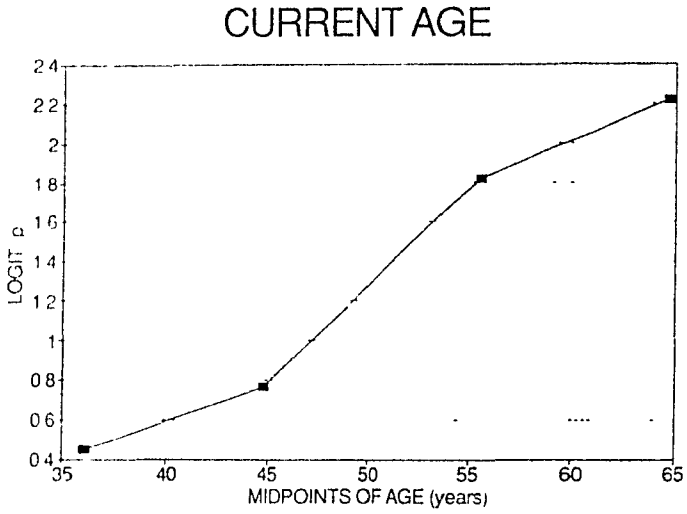


Figure 3

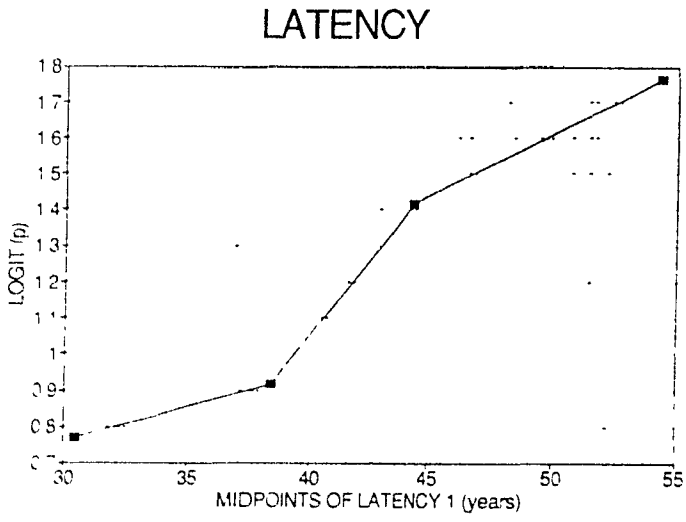


Figure 4

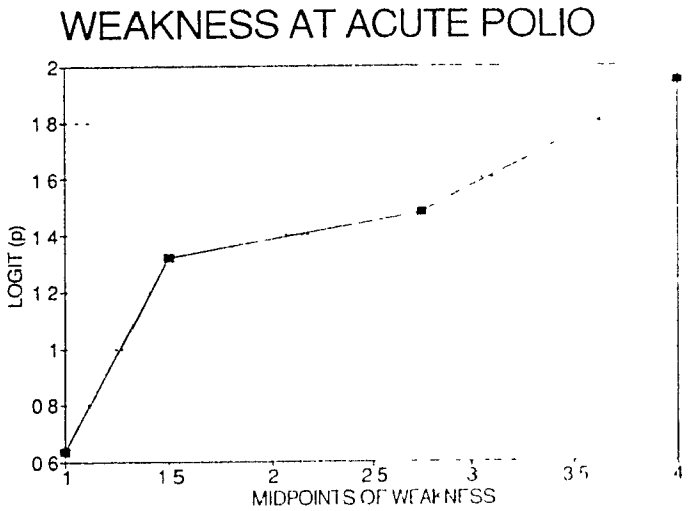


Figure 5

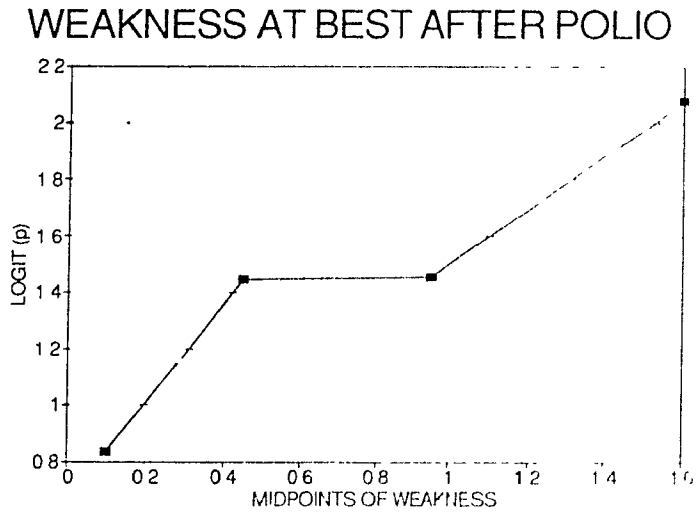


Figure 6

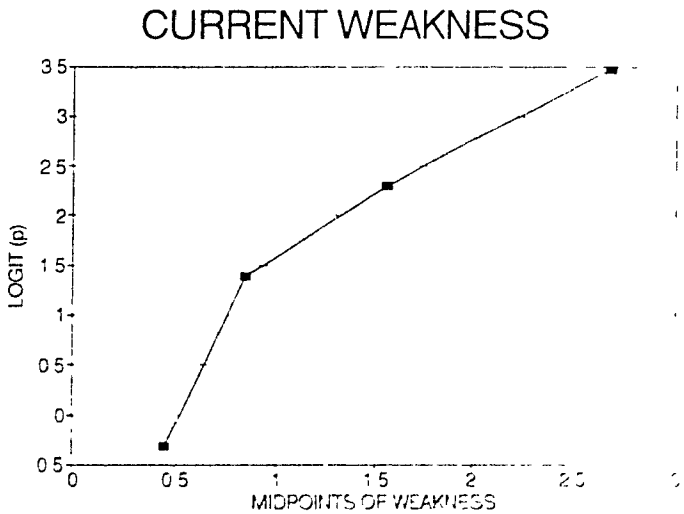
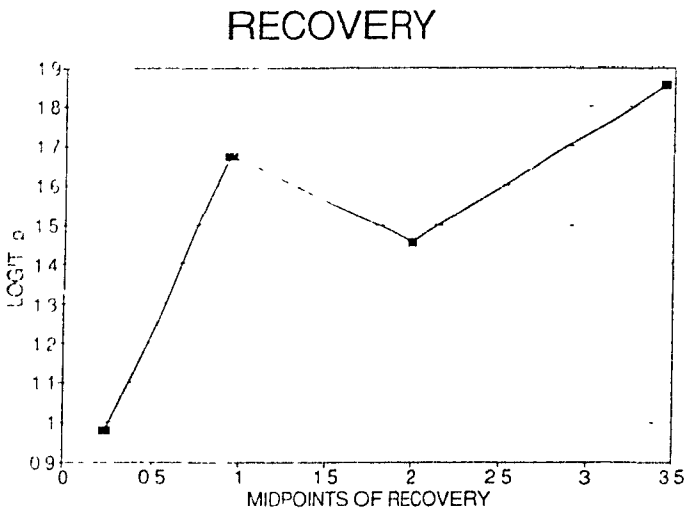


Figure 7


RECOVERY
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MIDPOINTS OF RECOVERY

POST-POLIO HISTORY EVALUATION

Name: _____ Hosp. I.D.#: ___

Address: _____ Referring Dr.: _____

Telephone: _____ Date of Birth: _____

Age: _____ Sex: M or F (circle)

Age of polio: _____ Age onset new symptoms: _____

HISTORY OF WEAKNESS

Site	Worst	Best	Current
L arm			
R arm			
L leg			
R leg			
Speech & swallowing			
Respiration			

Symptoms	Yes	No
Increased fatigue		
Increased sleep requirement		
New muscle cramp		
New fasciculation		
New weakness		
New in formerly weak muscles		
New in formerly normal muscles		
New muscle pain		
New joint pain		
New muscle atrophy		
New or increased deformity		
Decreased mobility		
Increased need for ambulatory aids		
Increased difficulty dressing		
Increased need for personal assistance		
Change/cessation of occupation		
New respiratory problems		
New cold sensitivity		

Name: _____ Date: _____

Examination: _____

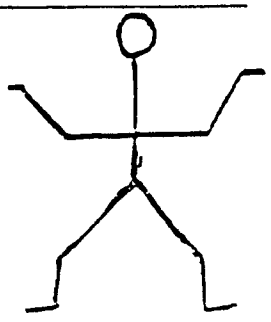
Bulbar

Motor

	Atrophy	Fasciculations	Strength
Deltoid R			
Deltoid L			
Biceps R			
Biceps L			
Triceps R			
Triceps L			
Wrist ext R			
Wrist ext L			
Intrinsic R			
Intrinsic L			
Hip flex R			
Hip flex L			
Quads R			
Quads L			
ham-strings R			
ham-strings L			
Dorsiflex R			
Dorsiflex L			
Plantar flex R			
Plantar flex L			

Sensory

Reflexes



Gait - orthoses + braces

Pulmonary function tests

Other labs

CRITERIA FOR INCLUSION IN STUDY AND FOR DETERMINATION OF CASE/CONTROL STATUS

Patient Name _____

I. Inclusion criteria into study (all should be yes)

____ 1. A credible history of past paralytic polio (an illness characterized by high fever, followed by muscular weakness) If this is uncertain, patient needs to have EMG documentation

____ 2. Partial or complete recovery of function after acute polio

____ 3. A history of at least 10 years of functional stability following recovery from acute polio

II. Exclusion criteria from study. (if any are "yes" patient is excluded)

____ 1. Presence of medical conditions which could produce weakness and fatigue

- cardiac disease (requiring medication)
- chronic obstructive pulmonary disease
- depresssion
- hypothyroidism
- diabetes mellitus
- anemia
- cancer
- cirrhosis
- connective tissue disease
- chronic infection
- chronic renal failure
- other _____

CRITERIA FOR INCLUSION IN STUDY AND FOR DETERMINATION OF CASE/CONTROL STATUS

(cont)

Patient name _____

____ 2. Presence of concurrent neurological disorders which could produce weakness and fatigue.

- peripheral neuropathy
- stroke
- Parkinson's disease
- radiculopathies
- spinal stenosis with myelopathy
- other _____

____ 3 Presence of severe pain which could make differentiation between pain and muscular weakness difficult. The presence of this difficulty would be mentioned in the impression as part of the initial evaluation

____ 4 Presence of new symptoms of fatigue (muscular or general) without increased or new weakness.

III. Determination of Case/Control Status. (Y = case, N = control)

____ 1 Presence of new symptoms of increased or new muscular weakness and fatigue (muscular or general) Muscular fatigue is defined as increasing muscular weakness on exertion, which improves with rest. Pain may or may not be present

IV. Final result. (please check)

1 Patient excluded from the study. ____

2 Patient is a case. ____

3 Patient is a control ____

DATA FORM

Patient name _____

Case/control status _____

Date of birth (MM/DD/YY) _____

Date of initial evaluation (MM/DD/YY) _____

Age at acute polio (years) _____

Time new symptoms present (years) _____

Patient estimates of weakness

Site/Function	Acute Polio	Best After Polio	Current
LUE			
RUE			
LLE			
RLE			
Speech/Swallowing			
Respiration			

Other measures of acute polio severity:

a Hospitalization at time of acute polio (yes/no) __

b. Length of hospitalization at time of acute polio (mos)

c. Respiratory involvement at time of acute polio (yes/no)

DATA FORM (cont)

Patient name _____

Other symptoms		yes/no
a	Any fatigue	_____
b	Muscle fatigue	_____
c	General fatigue	_____
d	Increased sleep requirement	_____
e	Any pain	_____
f	Muscle pain	_____
g	Joint pain	_____
h	Muscle pain with exercise	_____
i	New muscle atrophy	_____

Location of pain yes = +; no = -

	LUE	RUE	LLE	RLE	Back
Muscle pain					
Joint pain					

Disability Indices

a. At best after acute polio _____

b Present _____

Reported recent weight gain (within last 5 years) (yes/no) _____

Usual physical activity _____ (0, 1, or 2)

Motor strength scores.

a LUE _____ LLE _____

b RUE _____ RLE _____

Montreal Neurological Institute and Hospital

To Medical Ethics Committee

From Daria A Trojan, MD
Neil R Cashman, MD
Stanley Shapiro, PhD
John M Esdaile, MD, MPH

Date: February 5, 1992

Subject A case/control study of risk factors for post-poliomyelitis syndrome

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Post-poliomyelitis syndrome (PPS) is a clinical syndrome of new weakness, fatigue and pain in individuals who have experienced at least 10 years of neurological and functional stability after recovery from acute paralytic poliomyelitis. As many as 50% of individuals who have previously recovered from acute paralytic polio may develop PPS. Although a wide variety of symptoms are reported, this study will be concerned primarily with weakness and fatigue as these are most frequently reported and appear to be most disabling to the patients involved. Even though the cause of PPS is unknown, the most likely etiology attributes it to a distal degeneration of enlarged motor units which are present as a result of the recovery process after poliomyelitis. Two studies have identified several risk factors for PPS. These include greater severity of initial acute polio, a greater recovery after poliomyelitis, a higher age at acute polio, and possibly increased recent physical activity. Age at time of acute polio may actually be a measure of severity of polio since it is known that individuals who develop acute poliomyelitis at a later age usually have a more severe illness. In addition, severity of acute polio and recovery are obviously correlated. These clinical findings are in accord with the proposed etiology for PPS.

The primary objective of this study will be to identify risk factors for PPS in patients who have previously recovered from acute paralytic poliomyelitis. Previously defined and previously unstudied risk factors will be evaluated. A secondary objective will be to determine if increased weakness, in cases, occurs to a greater degree in the lower extremities than the upper extremities.

A case-control design will be used for this study primarily because it will allow efficient use of data already available through the clinic, and will allow the study of multiple potential risk factors for PPS. Cases and controls will be identified through a chart review of patients evaluated at the MNI post-polio clinic between 1986 and 1992. Approximately 350 patients have been seen during this time. Specific inclusion and exclusion criteria will be used for identification of cases and controls. In brief, all patients included in the study will have a credible history of past paralytic polio, followed by recovery, and at least 10 years of functional stability. Patients with any concurrent medical and neurological disorder which could be causing weakness and fatigue will be excluded. Cases will be those with new symptoms of increased or new muscular weakness and fatigue, and controls will not have these new symptoms. All patients included in the study may or may not have symptoms of pain. Because case ascertainment for PPS may be difficult in some cases (due to the lack of a definitive diagnostic test), a random sample of 10% of cases and controls will also be evaluated by another physician (Dr. Neil Cashman), and case/control status will be determined by him. In this way the inter rater reliability of case/control status will be assessed.

Data collection for the study will be performed through a chart review of all cases and controls. Information on many possible risk factors will be obtained. The primary risk factor will be severity of acute polio. Secondary

risk factors will be severity of weakness at point of greatest recovery after acute polio, present severity of weakness, recovery after polio, age at acute polio, age at time of examination, time since acute polio to development of new symptoms for cases (or to present for controls), disability index at best after acute polio, disability index at present, degree of usual physical activity prior to development of PPS (or to recent physical activity for controls), and presence of reported weight gain prior to development of PPS (or to recent weight gain in controls). Because in approximately 30% of cases and controls, the variables of severity of weakness at time of acute polio, severity of weakness at point of greatest recovery after acute polio, and consequently recovery have missing values, values will be assigned to these variables based on available information. Because inaccuracy in the recall or assessment of past and present risk factors may be present, the validity of some of the risk factors will be assessed. A random sample of 10% of cases and controls will be chosen, and old hospital charts (obtained from the time of hospitalization at acute polio). In addition, present severity of weakness (as reported by the patient in each extremity) will be correlated with a motor strength score in each extremity (obtained from patient examination at time of initial evaluation). Thus, the concurrent criterion-oriented validity of some of past risk factors (concerned with severity of acute polio) and present risk factors will be assessed.

Data analysis will include the following: (1) assessment of reliability of case/control status through computation of coefficient K and assessment of validity of some of risk factors through computation of Pearson correlation coefficients, (2) outlier analysis, (3) all subsequent analyses will be performed both with and without missing values, and with and without outliers to determine their impact on the results, (4) computation of simple descriptive statistics including frequency histograms for all continuous variables, means, standard deviations, proportions, ranges, two-sample t-tests, and X^2 tests, (5) collinearity analysis of continuous independent variables, (6) analysis of linearity of continuous independent variables in the logistic regression model, (7) univariate logistic regression analysis for each independent variable with computation of odds ratios with 95% confidence intervals, (8) multivariate logistic regression analysis with computation of adjusted odds ratios and their 95% confidence interval for significant models (those with improvement of $p = .10$ in loglikelihood when a variable is added to the model), (9) comparison of increased weakness in lower extremities with upper extremities in cases with X^2 test and analysis of covariance. Sample size calculations indicate that for $\alpha = 0.05$ (one-sided), $\beta = 0.10$, this study should be able to detect an odds ratio of 2.0 to 2.5 for initial severity. To detect an odds ratio of 2.5, 60 cases and controls would be needed, to detect an odds ratio of 2.0, 104 cases and controls will be needed.

This study does not involve any obvious risks to the patient. Patient confidentiality will be preserved both during the study and in any publications resulting from the study. Permission to obtain hospital records will be obtained from the individuals involved. No invasive studies will be performed on the patients for the purposes of this study.

There are no direct benefits to the patients involved, however, a better understanding of possible risk factors for PPS may shed further light on the pathophysiology of this disease and may provide some guidelines for the clinical care of patients with past paralytic polio.