Muscle Dystrophy

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A LONG-TERM FOLLOW-UP STUDY OF PATIENTS WITH POST-POLIOMYELITIS NEUROMUSCULAR SYMPTOMS

MARINOS C. DALAKAS, GREGORY ELDER, MARK HALLETT, JOHN RAVITS, MICHAEL BAKER, NICHOLAS PAPADOPOULOS, PAUL ALBRECHT, AND JOHN SEVER

Abstract A "post-polio" syndrome characterized by new neuromuscular symptoms, including muscle weakness, may develop years after recovery from acute paralytic poliomyelitis. We studied 27 patients (mean age, 50.6 years) in whom new muscle weakness developed a mean of 28.8 years after recovery from acute polio. We reevaluated these patients during a mean follow-up period of 8.2 years (range, 4.5 to 20) after they were originally studied at the National Institutes of Health. The total mean follow-up period after the onset of new weakness was 12.2 years (range, 6 to 29). The patients were assessed with quantitative muscle testing, muscle biopsy, electromyography, and virologic and immunologic examination of the cerebrospinal fluid.

Muscle strength had declined in all patients. The rate of decline averaged 1 percent per year. The decrease was irregular, with subjective plateau periods that ranged from 1 to 10 years. None of the patients had amyotrophic lateral sclerosis. Oligoclonal bands (IgG) were found in the cerebrospinal fluid of 7 of 13 patients studied, but no specific elevation of antibodies to poliovirus was observed in the cerebrospinal fluid. The newly affected muscles that were evaluated longitudinally with follow-up muscle biopsies and electromyography showed signs of chronic and new denervation. Groups of atrophic muscle fibers (group atrophy) and "neurogenic jitter" were not present.

New post-polio muscle weakness is not a life-threatening form of motor-neuron deterioration. It appears that this weakness is not due to a loss of whole motor neurons, as in amyotrophic lateral sclerosis, but that it is due to a dysfunction of the surviving motor neurons that causes a slow disintegration of the terminals of individual nerve axons. (N Engl J Med 1986; 314:959-63.)

MUCH anxiety has arisen among the estimated 300,000 survivors of polio in the United States because of recent reports about a new muscular weakness, often called the "post-polio syndrome," that develops in some of these persons.[1] It is known that some people may experience new neuromuscular symptoms many years after their recovery from acute paralytic poliomyelitis.[2-8] These symptoms vary from simple nonprogressive deterioration of function, with joint pain, fatigue, and subsequent stabilization,[4-6] to atypical forms of spinal muscular atrophy[2,3] or to what appears to be a forme fruste of amyotrophic lateral sclerosis (ALS).[2,9,10] The new, slowly progressive muscle weakness, which we have termed "progressive post-poliomyelitis muscular atrophy (PPMA),"[4-7] may occur in muscles that were previously affected by polio and recovered or in muscles that were clinically unaffected by the acute illness. The cause and rate of progression of PPMA, the future anticipated disability, and the risk of ALS (which has been reported in small series)[9,10] among patients with the disorder are unknown.

In an attempt to answer some of these questions, we reevaluated 27 patients who had recovered from polio and who were initially admitted to the National Institutes of Health in 1960 to 1981 because of PPMA that was diagnosed by complete neurologic and electrophysiologic examinations and studied by means of muscle biopsies and analyses of the spinal fluid. In this article, we report our findings in the same group of patients after a mean follow-up period of 8.2 years (range, 4.5 to 20). The patients were evaluated with a follow-up series of neurologic, electrophysiologic, single-fiber electromyographic, and muscle-biopsy studies. Virologic and immunologic investigations of the serum and cerebrospinal fluid were also conducted.

From the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Md. Address reprint requests to Dr. Dalakas at Bldg. 36, Rm. 5D06, NIH, NINCDS, Bethesda, MD 20892.

METHODS

Patient Selection

All patients, who were studied after giving informed consent, had a history of acute paralytic poliomyelitis in childhood or adolescence. This was established by a careful review of records to document as well as possible the clinical occurrence of an acute febrile illness followed by paralysis. We checked the neighborhood or school epidemics, and we selected patients who were affected in the United States, particularly during the later epidemics, when the diagnosis of poliomyelitis was probably made with more accuracy. All patients were referred to the National Institute of Neurological and Communicative Disorders and Stroke by their private physicians because they had begun to experience new muscle weakness. The patients enrolled in the study fulfilled the following criteria: they had partial recovery of motor function after polio and functional stability or recovery for at least 15 years; they had residual muscle atrophy, weakness, and areflexia in at least one limb but with normal sensation; and they had new muscle weakness and neuromuscular symptoms that were unrelated to any other neurologic or medical disorder. Patients with symptoms due to injury, compression neuropathy from the use of crutches or wheelchairs, or radiculopathies during the initial evaluation or the follow-up visits were excluded. Patients were also excluded if they had diabetes, polyneuropathy, collagen vascular disease, exposure to toxic agents, other major viral illnesses, or a family history of neuromuscular disease. Only patients who were less than 60 years old at the initial visit (mean age, 42.7; range, 24 to 59) were entered in the study. This was done to exclude patients who were subject to a loss of motor neurons due to normal aging. Ultimately, 15 men and 12 women were included in the investigation.

Neuromuscular Evaluation and Laboratory Studies

All patients were given neurologic examinations by several neurologists from the Institutes; specific attention was paid to neuromuscular function and quantitation of the patients' muscle strength in relation to the scale developed by the Medical Research Council.[11] Evaluations performed during both the initial and follow-up admissions to the National Institutes of Health included a complete

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blood count, blood chemistry and cerebrospinal fluid analyses, assessment of serum muscle enzymes, creatine kinase, aspartate aminotransferase, and alanine aminotransferase, electromyography, nerve-conduction studies, and open-muscle biopsy of a specimen from one of the currently affected muscles.

The muscle biopsy specimens were processed for histochemical analyses of muscle enzymes.[12] During the follow-up admission, six patients were also tested with single-fiber electromyography that used standard techniques.[13] These data were analyzed for fiber density, which is the average number of muscle fibers recorded by the needle during a single placement; jitter, which is the mean consecutive difference in the intervals between the activation of two muscle fibers in the same motor unit; blocking, the failure of a muscle fiber to activate when its motor unit is activated; and neurogenic jitter, a synchronous variation of at least two muscle fibers with respect to a third that must be due to an abnormality of the nerve rather than the neuromuscular junction. In the follow-up visits, serum and cerebrospinal fluid from 13 patients were tested for oligoclonal bands with immunofixation, as previously described,[14,15] and for viral antibodies to measles and to poliomyelitis virus type 1 (Maloney strain), type 2 (mouse-embryo fibroblast strains), and type 3 (Sankett strain), with a neutralizing antibody assay and with an enzyme-linked immunosorbent assay[16] (and Dalakas MC: unpublished data). The extent of production of poliovirus antibody inside the blood–brain barrier was determined by making a correction for the permeability of the blood–brain barrier by use of the ratio between the cerebrospinal fluid and the serum albumin level.[17]

Neuromuscular Quantitation of Strength

The patients' own descriptions of the functional decline in their muscle strength were recorded. We also used an objective quantitative assessment of the newly developed muscle weakness in order to establish the degree of progression of that weakness. Because the initial quantitative muscle testing of patients with PPMA was based on the Medical Research Council rating,[11] we used the same Medical Research Council scale during our follow-up evaluation to estimate the degree of decline in the strength of the affected muscles. Since almost all the patients had a residual asymmetric weakness from the attack of polio years earlier and PPMA is predominantly a focal condition involving the muscle groups of one or two extremities,[4-7] we needed a formula that would allow quantitative determination of the changes in the function of all four extremities, based on the Medical Research Council rating for each muscle group in each limb. For this reason, we considered the total normal strength of the four limbs as 100 points of neuromuscular function and assigned 25 of those points to each of the four extremities. These 25 points were equally distributed among five major muscle groups (e.g., in the leg, 5 points each were assigned to the foot extensors, foot flexors, knee extensors, knee flexors, and hip flexors and extensors). Five points of neuromuscular function of each of the major muscle groups corresponded to a "5" (normal) rating on the Medical Research Council scale.[11] Weaker muscle groups that rated 4, 3, 2, 1, and 0 on the scale received 4, 3, 2, 1, and 0 points, respectively. These calculations provided an automatic estimate of the cumulative total strength of every limb. The points for the total strength that remained at the initial and subsequent follow-up visits were plotted against the age of the patient at those visits, as shown in Figure 1 for the 12 patients with the longest follow-up period (average, 11.6 years).

Results

Clinical Evaluation

All patients had PPMA, as previously defined,[4-7] with new muscle weakness and atrophy involving either the muscles that had been previously affected and had fully or partly recovered or muscles that were clinically unaffected by the original disease. In all patients, the new weakness was asymmetrical and was often associated with increasing muscular atrophy. Some patients experienced myalgias. Occasional fasciculations were noted in all patients, even in muscles that did not appear to have become weaker.

At the reexaminations at the end of the follow-up period (average, 8.2 years; range, 4.5 to 20), the mean age of the patients was 50.5 years (range, 36 to 69); the mean age at which their new symptoms began was 39.6 (range, 25 to 56); and the mean number of years after acute polio when those symptoms began was 28.8 (range, 15 to 54).

All patients were weaker and had a much lower level of function. The pace of worsening during the period between the first and latest neurologic examination was very slow and varied from patient to patient and within individual patients. Some patients had a stepwise progression of weakness, with subsequent relative stability, whereas others had a slow, continuous decline in strength. Figure 1 depicts the progression of weakness in the 12 patients who had the longest mean follow-up times in the study (11.6 years; range, 6 to 20). In four of these patients (No. 5, 6, 8, and 9), the new muscle weakness had increased but remained almost completely confined to the same muscles that had appeared to be weaker during the initial examination; in three others (No. 1, 2, and 12), new weakness had appeared in additional muscle groups. Three patients (No. 7, 10, and 11) who had a more severe residual disability in one or more groups of muscles from the original disease had increased weakness in all the other muscle groups, and although the new decline in strength was mild within each muscle group, the cumulative effect on the patients' overall neuromuscular function was considerable, and they had become severely disabled. In fact, all three were using electric wheelchairs, whereas 10 years earlier, they had required only crutches. The remaining two patients (No. 3 and 4), who were followed for 13 and 11 years, respectively, felt a very slight new generalized weakness, which did not substantially alter their life styles or interfere with their everyday activities.

The mean total estimated loss of neuromuscular function for the 12 patients with the longest follow-up was 11.8 points (range, 7.5 to 17.5); for the other 15 patients (mean follow-up, 4.7 years) the mean loss was 4.1 points (range, 2.2 to 6.5). However, the mean calculated total yearly loss was identical in both groups — i.e., 1.05 points of muscle strength (range, 0.7 to 2.5). Generally, the new weakness was so mild that it often could not be appreciated on a year-to-year basis; the patients experienced it over a longer period (mean, 3 years; range, 1 to 10).

None of the 27 patients had ALS, which is defined as new, rapidly progressive, generalized muscle weakness and wasting and the presence of upper motor-neuron signs, bulbar signs, or respiratory difficulties. The age of onset of new symptoms, the sex of the patient, and the degree and type of physical activities of each patient before the manifestation of the new weakness were not factors in the progression of the weakness. All patients had remained active, with rea-

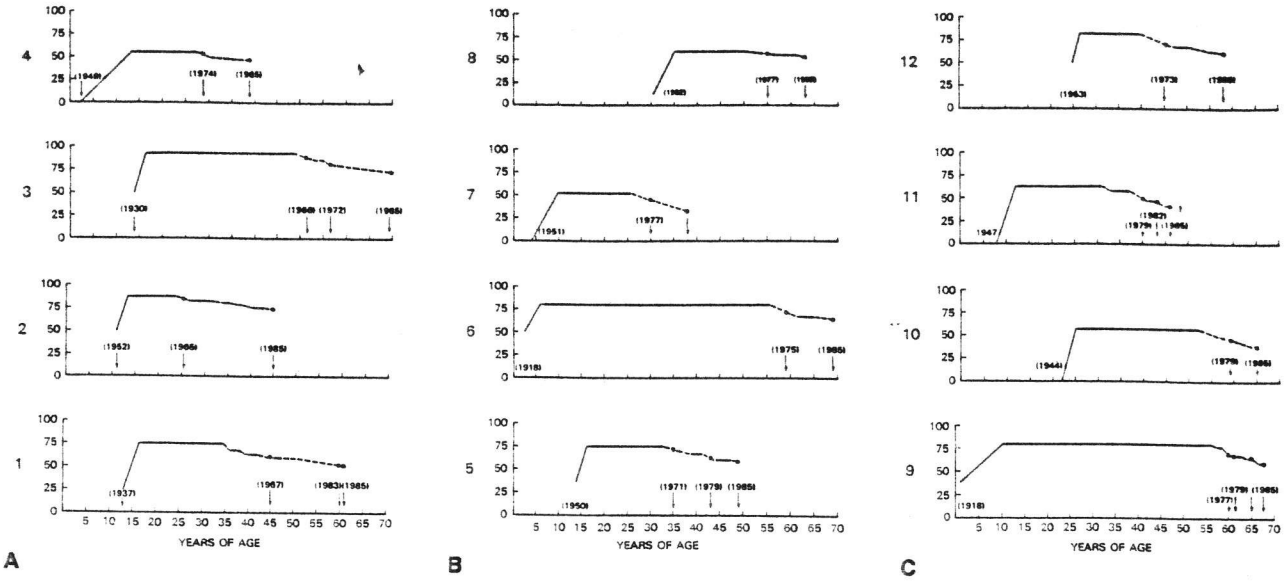

Figure 1. Progression of Muscle Weakness in 12 Patients with Post-Poliomyelitis Muscular Atrophy, Expressed as Total Points of Estimated Neuromuscular Function at Various Years of Age.

Numbers on the left refer to individual patients. Points of muscular function (100 points is the normal strength in all four limbs) are on the ordinate. The continuous line represents the patients' course after the attack of acute polio and their progressive partial recovery with subsequent long stabilization, as determined from information provided by the patient or early records. The interrupted line represents the course of new muscle weakness from onset until the latest follow-up evaluation. Arrows with the year in parentheses represent the time of the acute polio attack (first arrow), the time of the first examination after the manifestation of new weakness (second arrow), and subsequent examinations (third or fourth arrow). The sharp angulations in many of the curves are due to the subjective data on neuromuscular function provided by the patient. A decline in muscular strength that was either continuous or that occurred in a stepwise fashion took place in all 12 patients between the first and last evaluations (mean follow-up period, 11.6 years).

sonable use of their unaffected muscles. No overexertion or inactivity was reported.

Laboratory, Electromyography, and Muscle Biopsy Findings

The results of blood chemistry evaluations and complete blood counts were normal in all the patients. Four patients had levels of creatine kinase that were up to three times the normal value. Electroneurographic studies during the initial and follow-up visits revealed normal motor and sensory conduction velocities and action-potential amplitudes. Repetitive-stimulation studies of the ulnar nerve and (occasionally) of the axillary nerve in six patients showed no pathological decrement at 4 Hz and no pathological increment at 50 Hz. Electromyographic studies showed widespread chronic denervation with large-amplitude voluntary motor units (up to 25 mV) in almost all muscles studied. Chronic denervation was observed even in muscles that were apparently not involved in the original attack of polio. Fibrillation and positive sharp waves were seen in sparse to moderate amounts in many muscles, but the presence of these findings did not correlate in an obvious fashion with the recent deterioration. Fasciculations were seen in many of the patients, but the discharge frequency was very low (less than one per minute). The single-fiber electromyographic studies carried out in six patients during their follow-up visits showed an increase in fiber density and many fiber clusters (groups of three or more fibers with small time differences that made formal jitter analysis impossible). Increased jitter and blocking were seen in most muscles, and the amount of jitter and blocking appeared to correlate with the degree of recent deterioration. Neurogenic jitter was not observed.

Muscle biopsy studies of previously recovered and newly affected muscles (performed twice in eight patients, during the initial and follow-up visits) confirmed the presence of reinnervation, which was indicated by the formation of large groups that contained both type I and type II fibers.[10] In addition, all the biopsy specimens showed several isolated, atrophic, angulated fibers compressed in the interstices between large fibers (Fig. 2). These small fibers, which stained darkly with an enzymatic reaction, are characteristic of new active denervation.[12] The fibers remained isolated and scattered randomly throughout the follow-up period. No clusters of atrophic fibers (group atrophy) were observed, even in the muscles subjected to two biopsy evaluations. This is in contrast to the findings in the weakening muscles of patients with ALS, in which the atrophic fibers always form groups (group atrophy), and the number of atrophic fibers in the groups increases rapidly until the whole fascicle is atrophied, thereby reflecting the death of whole neurons.[12]

In 12 of 27 biopsy specimens (including those from muscles that had two assessments), occasional small perimysial or perivascular lymphocytic infiltrates were observed, as in earlier studies.[7,9] In two

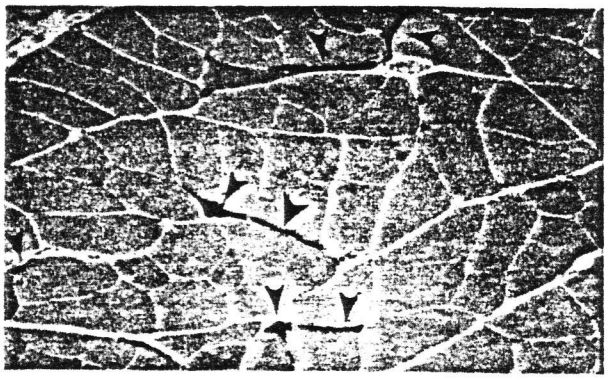

Figure 2. Transverse Frozen Section of a Muscle Biopsy Specimen from Patient No. 2.

Note the scattered small, angulated fibers with the dark stain (arrowheads). There are no groups of atrophic fibers (indicative of loss of the whole motor unit). The same type of change, but in a milder degree, was noted in the same muscle of the same patient during a biopsy examination 12 years earlier, when the muscle was slightly stronger. Staining was with a nonspecific esterase histochemical reaction (×125).

patients (No. 5 and 7),[7] the degree of lymphocytic response was more prominent, prompting a therapeutic trial with 100 mg of prednisone; however, the therapy was unsuccessful.

Spinal Fluid Studies

In confirmation of the earlier findings in a smaller series of patients with PPMA,[4,5] 7 of the 13 patients in our study whose cerebrospinal fluid was examined had two to four oligoclonal bands in that fluid. An immunofixation assay showed that the bands were IgG. The total IgG, the IgG index, and the IgG synthesis[15] in the cerebrospinal fluid were normal. No bands were found in the serum. The calculated ratios of cerebrospinal fluid to serum antibody titers to poliomyelitis and measles virus (for control) were normal,[17] indicating that there was no in situ antibody production to poliovirus.

Discussion

A reevaluation of 27 patients with PPMA after a mean follow-up period of 8.2 years from the time they were first seen at the National Institutes of Health showed that their muscular weakness had progressed. However, the degree of decline of their neuromuscular function was slow, predominantly focal, and minimal (about 1 point of the total 100 points of muscle strength per year), and it was not life-threatening. Progression varied from patient to patient and within individual patients, who often had long periods of subjective stability. New weakness was not objectively appreciable on a year-to-year basis. The overall progression, although minimal, had a substantial effect on neuromuscular function in patients in whom polio had caused severe disability and limited muscle reserves — i.e., patients who at best were functioning at or below 50 percent of their total strength. Contrary to previous reports that ALS or an ALS–like disorder occurs more frequently in persons who have had polio,[9,10] none of the 27 patients in our study, who were followed for a mean of 8.2 years (range, 4.5 to 20) from the time they were originally examined and up to 12.2 years (range, 6 to 29) from the onset of their new weakness, were found to have ALS, as indicated by generalized muscle weakness and wasting and respiratory, bulbar, or upper-motor-neuron signs. Similarly, none of a recent group of 11 persons who had recovered from polio and who had been referred to the National Institutes of Health because of new weakness had ALS (Dalakas MC: unpublished data).

Although PPMA appears to be a disorder of the motor neuron, its pathophysiologic aspects differ in a number of ways from those of ALS, the archetypal disorder of motor neurons. Clinically, PPMA is predominantly focal and always progresses slowly, without producing upper-motor-neuron signs or involvement of bulbar muscles. In biopsy specimens of newly weakened muscles of patients with PPMA, the denervation is characterized by a few single scattered, angulated fibers (Fig. 2) and by fiber-type grouping, rather than by the atrophic muscle fibers that form in groups (group atrophy) because of the death of the whole motor neuron that are typically seen in the weakened muscles of patients with ALS.[12] This observation on the type of denervation was reinforced by follow-up muscle biopsies in eight of our patients, which indicated that even though the patients had a mild but progressive weakness for a mean of 11.6 years, the weak muscles did not show group atrophy. ALS is caused by the death of anterior horn cells. In contrast, it would be reasonable to assume that PPMA is caused by the death of individual nerve terminals in the motor units that remain after polio, rather than the death of the whole unit. This would explain most of the clinical, physiologic, and histochemical features of the syndrome. As each terminal dies, the weakness progresses slowly. Regeneration proceeds muscle fiber by muscle fiber, and there is no opportunity to form new groups of fibers. This theory is supported by the presence of single scattered, angulated fibers in the muscle biopsy specimens (without group atrophy) (Fig. 2) and the observation by means of single-fiber electromyography that there is no "neurogenic jitter." In single-fiber electromyography, increased jitter can be due to instability at the neuromuscular junction or at the branch points of axons. Newly regenerated axons may show instability at the points of the axon branches during active reinnervation. Neurogenic jitter, which is characterized by groups of action potentials that jitter together, can be seen in patients with ALS. Its absence in our patients with PPMA supports the observation that there is a lack of reinnervation of groups.[13]

Deterioration of individual nerve terminals in PPMA might be an outcome of the process of recovery from an acute attack of polio. After such an attack, the surviving motor neurons sprout to reinnervate more muscle fibers than normal. This process produces

large motor units that may stress the cell body. After a number of years, these hyperfunctioning motor neurons (with their excessive sprouting) may not be able to maintain the metabolic demands of all their sprouts, and a slow deterioration of the individual terminals may result, as previously speculated.[18] Some individual fibers may be able to be reinnervated a second time, but eventually enough nerve terminals are destroyed and enough reserves are diminished for weakness to appear. This would be consistent with the focal nature of PPMA and its very slow, stepwise, unpredictable progression. Normal aging alone cannot be responsible for this process, since neuronal loss does not occur in persons younger than 60,[19] and muscle biopsy specimens from normal persons who are younger than 70 rarely show small scattered, angulated fibers[20] (and Dalakas MC, Cutler NA: unpublished data). For these reasons, our study included only patients who were younger than 60 at the time of their first symptoms of PPMA (mean age, 39.6 years; range, 25 to 56). Furthermore, with the Medical Research Council scale we employed,[11] the muscle strength was standardized so that the grades of weakness did not change with normal aging.[11] At this time, the frequency and the possible risk factors of PPMA among polio survivors are unknown.

The roles of virologic or immunologic mechanisms in the development of PPMA are unclear. The lymphocytic response in the biopsy specimens (a response that had previously been observed[4-7]) and the presence of oligoclonal bands in the cerebrospinal fluid may suggest immunopathologic mechanisms. Treatment with prednisone in two patients (No. 5 and 7) and with interferon in another (No. 9)[21] failed to improve muscle strength or change the progression of muscular weakness. Although poliovirus can cause persistent infection in animals[22] and in neural tissues,[23] searches for poliovirus antibodies in the cerebrospinal fluid with a neutralizing plaque assay and enzyme-linked immunosorbent assays (Dalakas MC, Albrecht P: unpublished observations) have yielded negative results, indicating that possible reactivation of the poliovirus in patients with PPMA cannot be substantiated with the methods used. The nature of the IgG oligoclonal bands in the cerebrospinal fluid is not clear. The possibility that they represent an antibody response — perhaps directed against viral or neuronal proteins — should be studied further. It is especially interesting, however, that no oligoclonal bands were found in the cerebrospinal fluid of six asymptomatic persons who were examined 3 to 20 years after an initial attack of polio (Dalakas MC, et al.: unpublished data).

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