units with normal aging does not become prominent until after the age of 60 years (see Ref. 23). In other mammals, terminal sprouting also becomes impaired with aging, and sprouting is no longer able to keep up with the normal loss of terminal fibers that occurs throughout life as part of the constant remodeling at the neuromuscular junction (23). The age at which this occurs in humans is unknown. Muscle biopsy studies do not reveal a significant increase in small angulated fibers until after age 70 years (105). More important than chronologic age is the interval from the acute polio to the onset of symptoms, an interval that averages 30 to 40 years (23). A discussion of more likely possibilities follows.

### Premature Exhaustion of New Sprouts Developing after Acute Poliomyelitis and of Their Motor Neurons due to Excessive Metabolic Demand

EMG and muscle biopsy studies have helped clarify this possible mechanism. Enlarged motor units that develop via sprouting after the acute polio may never fully stabilize (148). Findings from SFEMG studies reveal that the largest motor units are more likely to become unstable later in life (104,152), and with increasing time from the acute polio, neuromuscular transmission becomes more unstable, as increased jitter and blocking occur (146). Several studies have shown that spontaneous activity, jitter, and blocking occurred more frequently in symptomatic muscles (150,151). These findings are supported by muscle biopsy studies that describe an increasing number of angulated fibers accumulating over time with the eventual emergence of group atrophy (105). In fact, 30 to 40 years after the acute poliomyelitis, there is disintegration of the new terminal sprouts that form after the acute infection as demonstrated by the appearance of angulated fibers (156). A contributing factor in some is the reinnervation of fibers that may not result in effective synapses (150). This is followed by degeneration of axonal branches as shown by small group atrophy (104,157). It has been frequently hypothesized that the increased metabolic demand of an increased motor unit territory results in premature exhaustion and death of the motor neuron (23). Even though there are no definitive studies examining the cell soma to prove this, electrophysiologic and muscle biopsy data appear to be supportive. The overuse of muscles resulting in excessive muscular fatigue (158–160) may also contribute to the excessive metabolic demand on motor neurons, and premature exhaustion might also be enhanced by the prior poliovirus infection of motor neurons with residual damage (23).

### Chronic Persistent Poliovirus Infection

Poliovirus and other picornaviruses can persist in the CNS of animals and cause delayed or chronic disease (23,161). Poliovirus and other enteroviruses can also persist in the CNS and systemically in immunodeficient children (23). Studies in tissue culture have found that poliovirus mutants can persist without killing the host cell (162,163) and can also persist in neurons (164). Support for the persistent poliovirus hypothesis was enhanced by the findings of Sharief et al. (165), who demonstrated poliovirus antibodies and poliovirus-sensitized cells in the CSF of post-polio patients. My collaborators and I have been unable to find poliovirus antibodies in the CSF of post-polio patients using isoelectric focusing and ELISA techniques (166,167), similar to others (136,168,169). Conclusive viral isolation and histochmical or hybridization studies have not as yet been reported using spinal cord tissues. However, CSF specimens have been examined for the presence of poliovirus RNA by polymerase chain reaction, and most studies have been negative or inconclusive (169–172).

### An Immune-Mediated Disease

The strongest support for an inflammatory or immune-mediated mechanism for PPS stems from the study of Pezeshkpour and Dalakas (173) in which inflammation in the spinal cords of seven post-polio patients was found. It consisted of both perivascular and parenchymal lymphocytic infiltrates and neuronal degeneration and active gliosis. All changes were more prominent in the three patients with new weakness. Other findings that support this hypothesis are the finding oligoclonal bands in the CSF (136) and activated T cells in the peripheral blood (174). My collaborators and I have not found oligoclonal bands in these patients (104,166); however, other histologic studies suggest an immune-mediated or viral-induced pathogenesis or at least an inflammatory mechanism. Miller (175) examined the spinal cord from a post-polio patient and found perivascular intraparenchymal chronic inflammatory infiltrates primarily composed of B lymphocytes with rare macrophages and no T cells. Kaminiski et al. (176) found inflammation in the spinal cords of eight of nine PPS patients so studied.

### Management

The manifestations of PPS, such as fatigue, pain, and weakness, can be caused by other diseases; accordingly, the differential diagnosis and the exclusion of other diseases are important aspects in the evaluation of PPS patients, reviewed previously by Jubelt and Cashman (23).

### Symptomatic Treatment and Supportive Care

The management of PPS has been primarily symptomatic and supportive (23) and based primarily on empirical observations and subjective reports, not objective analyses (Table 5) (177,178). However, objective treat-
TABLE 5. Treatment of the post-polio syndrome

<table>
<thead>
<tr>
<th>Medical problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory insufficiency or failure: administer pneumovax and influenza vaccines, eliminate smoking, treat obstructive disease, assist ventilation</td>
</tr>
<tr>
<td>Treat secondary cardiac failure</td>
</tr>
<tr>
<td>Treat other complicating medical problems: anemia, thyroid disease, obesity, and others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excessive fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institute energy conservation measures</td>
</tr>
<tr>
<td>Provide pharmacologic treatment: amantadine, pyridostigmine, amitriptyline, pemoline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support respiratory insufficiency</td>
</tr>
<tr>
<td>Treat sleep apnea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal pain and joint instabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease mechanical stress on joints and muscles with lifestyle changes: weight loss, decrease activities causing overwork, return to using assistive devices (including orthoses, wheelchairs, adaptive equipment)</td>
</tr>
<tr>
<td>Prescribe anti-inflammatory medications, heat, massage Evaluate and, infrequently, surgically repair orthopedic problems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle weakness—stable or progressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid overwork of weakened muscle</td>
</tr>
<tr>
<td>Follow creatine kinase?</td>
</tr>
<tr>
<td>As per above, decrease stress on muscles and joints</td>
</tr>
<tr>
<td>Institute stretching exercises</td>
</tr>
<tr>
<td>Prescribe nonfatiguing (submaximal, short duration)</td>
</tr>
<tr>
<td>strengthening exercises</td>
</tr>
<tr>
<td>Institute cardiopulmonary conditioning</td>
</tr>
<tr>
<td>Supportive psychological care</td>
</tr>
<tr>
<td>Aid adjustment to second disability</td>
</tr>
<tr>
<td>Encourage adjustment to required lifestyle changes</td>
</tr>
</tbody>
</table>

Modified from Ref. 91. See text for specific references.

...ment studies are beginning to emerge. Respiratory insufficiency is increasingly being managed with noninvasive respiratory support with intermittent positive pressure ventilation using nasal masks and mouthpieces (113,116). Excessive generalized fatigue has been treated with energy conservation measures. Agre and Rodriguez (96) demonstrated that pacing of physical activities with work–rest programs decreased local muscle fatigue, increased work capacity, and resulted in recovery of strength in symptomatic post-polio patients. Generalized fatigue has also been treated pharmacologically with amantadine, amitriptyline, pyridostigmine, and pemoline. Amantadine lacked benefit in a small controlled study but may be helpful in selected cases (179). Amitriptyline has not been studied in a controlled trial but may help fatigue in a small percentage of cases, possibly by controlling pain. Pyridostigmine was beneficial in an open trial (180) but not in a recently completed controlled trial (personal communication). Pemoline has not been evaluated in a controlled study.

Essential to the treatment of sleep disorders in PPS patients is to first determine whether the cause is central, obstructive, or mixed and if there is respiratory insufficiency (121,122). Dysphagia can be improved by learning swallowing techniques (178). Musculoskeletal pain, muscle pain, and joint instabilities can be treated by pacing activities, decreasing mechanical stress by bracing and wheelchairs, and by the judicious use of anti-inflammatory medications (23,181). In a controlled study, Jones et al. (182) demonstrated that aerobic exercise could be tailored to post-polio patients to obtain positive cardiorespiratory training without the untoward effects on limb function.

**Muscle-strengthening Exercises**

Many recent experimental treatment studies have addressed the role of exercise in altering the progression of the new weakness, and a number suggest that exhaustive strengthening exercises of partially denervated muscles can result in overwork and progressive weakness (23,91). Excessive exercise along with too few motor neurons may result in progressive weakness (183). These findings are supported by similar results in animal studies (23).

Others have demonstrated that a nonfatiguing exercise program improves strength in post-polio patients. Feldman and Soskoine (184) analyzed the effect of nonfatiguing exercises in six post-polio patients over a 3-month period: 14 muscles improved in strength, 17 were unchanged, and in 1 strength decreased. Emorsson and Grimby (185) and Emorsson (186) analyzed the effects of a 6-week, isometric-isokinetic, nonfatiguing strengthening program at 6 and 12 months after training in 12 post-polio patients. These patients had Medical Research Council grade 4 strength in quadriceps muscle that subsequently increased 29% isokinetically with exercise. Filleyaw et al. (187) studied the effect of nonfatiguing resistance exercises in 17 PPS patients for up to 2 years. Their strength increased significantly in exercised compared with contralateral unexercised muscles. Agre et al. (188) evaluated the effect of a low-intensity, alternate-day, 12-week quadriceps muscle-strengthening resistance exercise program. Strength significantly improved without changes in motor units by EMG or in serum creatine kinase levels. Spector et al. (189) evaluated changes in the dynamic and isometric strength in newly weakened quadriceps muscles and in asymptomatic triceps muscles of six PPS patients after 10 weeks of progressive resistance muscle training. They found that the training led to significant gains in dynamic strength in both symptomatic and asymptomatic muscles, without histologic or serologic evidence of muscular damage. These studies suggest that significant short-term improvement in muscle strength occurs with nonfatiguing submaximal strength, short duration, repetitious exercises. The effects of long-term continuous exercise remains to be determined.
SUMMARY

Polioymyelitis is now a rare occurrence in the United States although still a significant problem in underdeveloped areas of the world. The large epidemics of poliomyelitis in the 1940s and 1950s are now reflected by the large number of polio survivors who are developing new late manifestations, referred to as the post-polio syndrome, or PPS. It is now a well-recognized entity that occurs on average about 35 years after the acute poliomyelitis. Common manifestations include generalized fatigue, joint deteriorations with pain, cold intolerance, and prominent neurologic problems. Neurologic problems include new weakness, muscle fatigue, muscle pain, muscle atrophy, respiratory insufficiency, dysphagia, sleep apnea, and possibly generalized fatigue. It is estimated that there are 1.63 million polio survivors in the United States and that half will develop PPS. It is a very slowly progressive syndrome. Older age at the onset of the acute poliomyelitis, the severity of the poliomyelitis, the amount of recovery, and overexercise or overuse of muscles are risk factors for early development. The etiology is unclear, although premature exhaustion of the new sprouts that develop after acute poliomyelitis and of their motor neurons appear to be important factors. Other possible causative factors include persistent poliovirus infection and an underlying immune-mediated process. Treatment is primarily supportive; however, nonfatiguing strengthening exercises can clearly improve strength over the short term.

REFERENCES


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