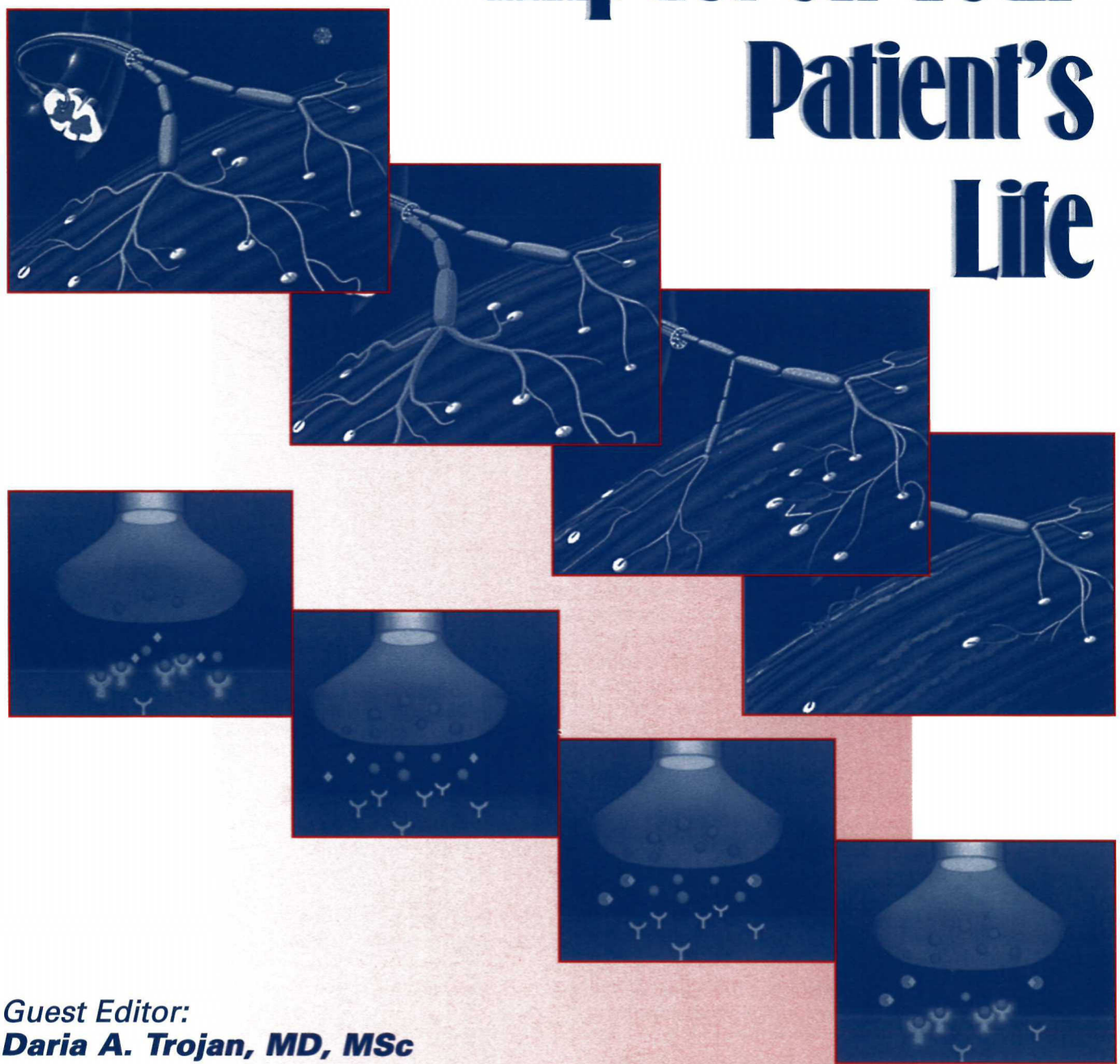
Post-Polio Syndrome (PPS): Making a Practical Impact on Your Patient's Life



Guest Editor:
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Post-Polio Syndrome Fact Sheet

The phenomenon

Individuals who have recovered from acute paralytic poliomyelitis (APP) can develop a cluster of new symptoms later on in life that are directly or indirectly related to the original motor neuron destruction by the poliovirus.

Definition criteria*

1) a prior episode of paralytic poliomyelitis with residual motor neuron loss (which can be confirmed through a typical patient history, a neurologic examination and, if needed, an electrodiagnostic exam;
2) a period of neurological recovery followed by an interval (usually 15 years or more) of neurologic and functional stability;
3) a gradual or abrupt onset of new weakness and/or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy and/or pain;
4) the exclusion of medical, orthopedic and/or neurologic conditions that may be causing the symptoms mentioned in (3).

Symptoms

- Fatigue (general and/or muscular)
- New weakness
- Pain (muscle or joint)

Less common symptoms

- New muscular atrophy
- Respiratory insufficiency from progressive muscular weakness
- Dysarthria
- Dysphagia
- Muscle cramps
- Cold intolerance
- Fasciculations
- New or progressive joint deformities

Epidemiology

Frequency of PPS: 20%-40% of patients with previous APP

Time of onset

Most commonly 30 to 40 years after the initial illness.

Predictive factors

- Greater severity of initial APP
- Greater functional recovery after APP
- More advanced age at APP
- Greater length of time since APP
- Lower disability level at presentation to clinic
- Presence of a permanent impairment after recovery from APP
- Increased recent physical activity
- Greater age at time of presentation to clinic
- Recent weight gain, muscle pain (especially with exercise), and joint pain.

Prognosis

Symptoms slowly increase with time, but status quo or improvement is possible

Pathophysiology

Peripheral disintegration of enlarged motor units

Differential diagnosis

- Hypothyroidism, respiratory dysfunction (including sleep apnea), rheumatoid arthritis, cardiac, hematologic or endocrine conditions, cancer, chronic, or systemic infections
- Osteoarthritis, tendinitis, bursitis, repetitive injury syndromes, and failure of previous orthopedic surgical procedures.
- Adult spinal muscular atrophy, multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, diabetic amyotrophy, and heavy metal toxicity.
- Lumbar spinal stenosis, cervical spondylosis, disc herniation with root entrapment, entrapment neuropathies, and cauda equina syndrome
- Amyotrophic lateral sclerosis
- Fibromyalgia syndrome frequently mimics some of the symptoms of PPS, primarily pain and fatigue, and occurs in 11% of patients presenting to a post-polio clinic.

Management of weakness

- Judicious exercise
  - Isometric exercise
  - Isotonic or isokinetic exercise
  - Aerobic exercise (e.g., walking, swimming)
- Stretching of contractures
- Avoidance of muscular overuse
- Bracing
- Use of assistive devices

Management of fatigue

- Improvement of sleep
- Energy conservation techniques
- Lifestyle changes
- Pacing (rest periods during activity) and regular rest periods or naps
- Possibly pyridostigmine

Management of pain

- Reduction of activity, pacing (rest periods during activity), use of moist heat and stretching for cramps, use of assistive devices and lifestyle modifications.
- Fibromyalgia: Amitriptyline, cyclobenzaprine, fluoxetine, aerobic exercise and other measures.
- Modification of extremity use, physiotherapy, use of physical modalities, strengthening, orthoses, assistive devices, NSAIDs, acetaminophen, steroid injections or rarely, surgery.

* These criteria represent a consensus statement of the Post-Polio Task Force. The sensitivity, specificity and reliability of these criteria have not yet been tested in a prospective manner

Post-Polio Syndrome (PPS): Making a Practical Impact on Your Patient's Life

INDIVIDUALS who have recovered from acute paralytic poliomyelitis (APP) may develop difficulties later on in life that are directly or indirectly related to the original motor neuron destruction by the poliovirus. The late onset of new weakness, fatigue and atrophy in APP survivors was first reported in 1875, but the greatest advances in our understanding of PPS have only occurred in the last two decades.

Definition

PPS is a neurological disorder characterized by a cluster of symptoms in individuals who had paralytic polio years earlier. Typically, these symptoms occur after a period of functional stability of at least 15 years following APP and include new weakness, fatigue and pain (of muscles and/or joints). Less commonly, these symptoms include muscle atrophy, breathing and swallowing difficulties and cold intolerance.[1]

The new weakness, abnormal muscle fatigability (decreased endurance) and atrophy are most likely caused by a slowly progressive deterioration of motor units. Muscle and joint pain are most likely caused by chronic new weakness and/or chronic musculoskeletal wear and tear.

Recently, specific criteria for PPS have been proposed.[1] They include:

1) a prior episode of paralytic poliomyelitis with residual motor neuron loss (which can be confirmed through a typical patient history, a neurologic examination and, if needed, an electrodiagnostic exam;
2) a period of neurological recovery followed by an interval (usually 15 years or more) of neurologic and functional stability;
3) a gradual or abrupt onset of new weakness and/or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy and/or pain;
4) the exclusion of medical, orthopedic and/or neurologic conditions that may be causing the symptoms mentioned in (3).

EMG studies can be reserved for patients with an unclear history of APP, no obvious signs of previous APP on standard examination, or possible superimposed neurologic disease.

Symptoms

Fatigue, new weakness and pain are the three most common symptoms of PPS, but a wide variety of other symptoms may occur.[2,3]

Exhaustive fatigue is probably the major symptom (up to 90% of patients) and perhaps the most disabling. Fatigue can be general or muscular or —as is often the case— both.[2,3]

Generalized fatigue is usually described as a generalized exhaustion similar to that which accompanies influenza. Typically, patients feel well rested in the morning but experience a progressive fatigue during the day which worsens with physical activity. Manifestations include increased sleep requirement, naps or rest periods during the day and decreased concentration.

Muscular fatigue is defined as increased weakness, with activity that improves with rest. It may be perceived as decreased endurance.

New weakness can affect any muscle, but is more frequent in muscles involved at the time of APP. It may be described as permanent or transient. Permanent new weakness is usually insidious, although it may also start suddenly, and is usually slowly progressive. Transient weakness is most likely muscular fatigue or decreased endurance.

Pain usually occurs in muscles or joints and is generally described as an aching or sore feeling that occurs after light physical activity and frequently improves with rest. Joint pains may be transient or chronic and also are usually aggravated by physical activity.

Less common symptoms include new muscular atrophy, respiratory insufficiency from progressive muscular weakness, dysarthria, dysphagia, muscle cramps, cold intolerance, fasciculations and new or progressive joint deformities.

Epidemiology

APP is uncommon in the U.S. and Canada, and is rapidly declining worldwide. However, a large group of polio survivors is still present. In 1987, a nationwide survey esti-

mated there were approximately 640,000 survivors of APP in the U.S.[4]

The studies completed thus far note a relatively high frequency of new difficulties (up to 64%) in survivors of APP. However, the frequency of PPS (defined as new weakness many years after acute APP) is probably between 20% and 40%.

Time of onset

APP is usually followed by a period of neurologic and functional recovery over several months to years and, subsequently, a period of functional stability lasting several decades. PPS most commonly occurs 30 to 40 years after the initial illness.

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Predictive factors

Several studies have identified predictive factors for PPS.[5,6] They are listed on the Fact Sheet on page 2 of this document.

Knowledge of predictive factors can help identify patients potentially at risk for acquiring PPS and, in the case of modifiable factors, can be used to help prevent the development of PPS.

Prognosis

PPS is a slowly progressive neuromuscular disease, which is rarely fatal, but can produce significant problems in work productivity and general level of functioning. PPS most commonly produces difficulty with mobility and in instrumental activities of daily living; less frequently, it affects basic activities of daily living.

PPS is potentially dangerous in individuals with respiratory muscle weakness as a result of APP and/or PPS because any further deterioration may result in respiratory failure. Similarly, severe dysphagia could also be life-threatening.

The impact of PPS on life span has not been studied.

Clinical experience suggests that symptoms slowly increase with time, but that improvement is possible if patients learn how to manage their new difficulties.

Pathophysiology

The most widely accepted model of new weakness in PPS is that of peripheral disintegration of massively enlarged motor units. Immediately following APP, brain stem and spinal cord motor neurons that persist are capable of elaborating new branches called axonal sprouts (Figure 1.3). Motor axonal sprouts are capable of reinnervating muscle fibers that have lost their motor innervation due to APP, producing motor units that can be seven to eight times the normal size.

However, it has been postulated that compensatory enlargement of motor units after APP is not indefinitely stable, and that terminal axonal sprouts may degenerate over time (Figure 1.4).[7] According to this model, distal degeneration of enlarged motor units with denervation of muscle fibers is the most likely cause of PPS.

As our understanding of PPS evolves, however, it may be fruitful to consider the symptoms of PPS to be due to two types of lesions of the motor unit: A progressive lesion and a fluctuating lesion.

A progressive lesion is degeneration of terminal axons resulting in slow progressive new weakness that is irreversible.

A fluctuating lesion in PPS might give rise to the symptoms of muscle fatigability and generalized fatigue. These symptoms may change over the course of minutes to days, and are more consistent with a dysfunction of terminal axons. Defective synthesis and release of acetylcholine into the neuromuscular junction (NMJ) may participate in the NMJ transmission defects underlying these symptoms (Figure 2). Thus, agents that support NMJ transmission may provide novel therapies for PPS.

Differential diagnosis

The diagnosis of PPS is based on clinical findings. Many medical, neurological and musculoskeletal conditions must be considered in a patient with previous APP presenting with new difficulties.

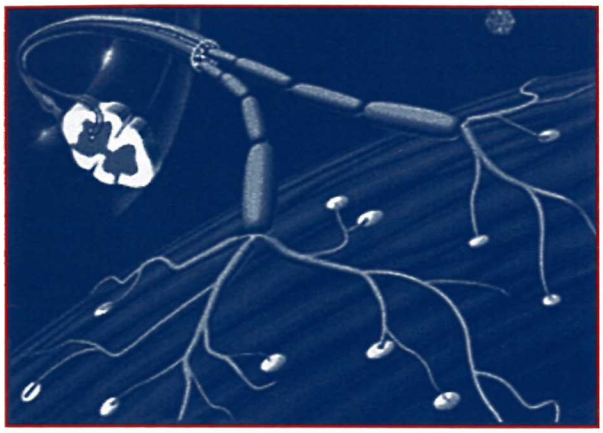
Pain, weakness and fatigue may be a manifestation of hypothyroidism or rheumatoid arthritis. Medical diseases (eg., cardiac, hematologic or endocrine conditions, cancer, chronic or systemic infections) must also be considered. Respiratory dysfunction (including sleep apnea) can also occur.

Other syndromes may be precipitated or accelerated by APP, but do not constitute true PPS. Chronically abnormal gait or weight-bearing may give rise to tendinitis and bursitis. Other musculoskeletal syndromes to consider are osteoarthritis, biomechanical deficits in gait, repetitive injury syndromes, and failure of previous orthopedic surgical procedures.

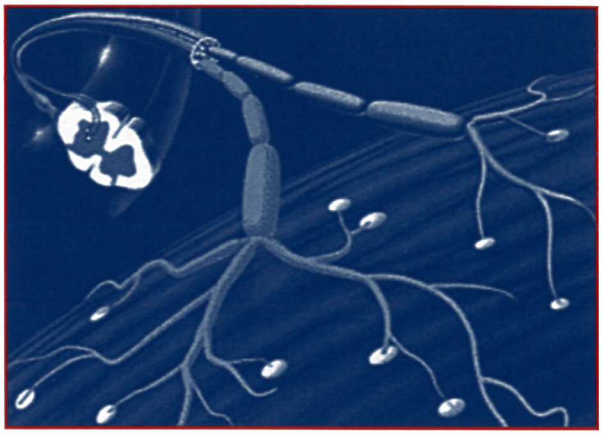
Neurologic syndromes that may be mistaken for PPS include diseases of the lower motor neurons or peripheral

Fatigue is probably the major symptom (up to 90% of patients) and perhaps the most disabling. Fatigue can be general or muscular or — as is often the case — both.

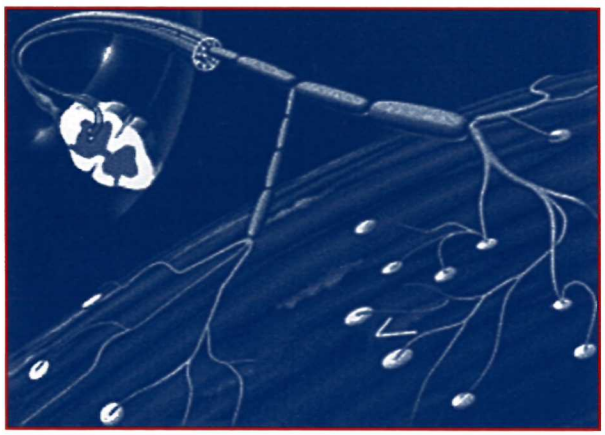
Figure 1.
PATHOPHYSIOLOGY OF PPS



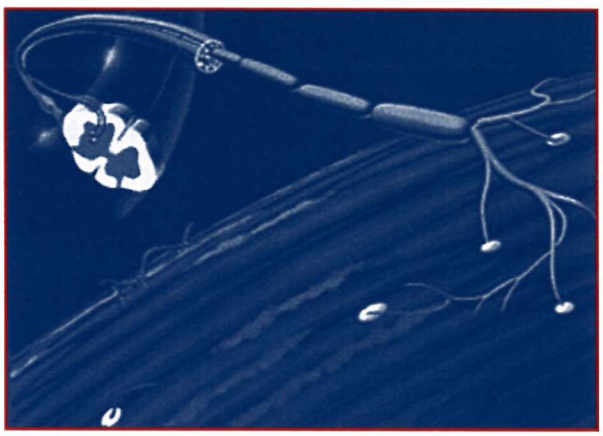
1) Normal motor units innervating muscle fibers.



2) During polio infection, invasion of motor neurons by polio virus produces denervation of the affected neuron with resultant denervation of associated muscle fibers. In this diagram, one of the neurons has been infected by the polio virus while its neighbor has not.



3) Immediately following paralytic polio, surviving motor neurons in the brain stem and spinal cord are capable of extending new branches called axonal sprouts to reinnervate muscle fibers that have lost their motor nerve supply.



4) These new axonal sprouts are not indefinitely stable but rather deteriorate over time due to an overexhaustion phenomenon resulting once again in denervation of muscle fibers.

nerves, such as adult spinal muscular atrophy, chronic inflammatory demyelinating polyneuropathy, diabetic amyotrophy, and heavy metal toxicity. Other disorders include lumbar spinal stenosis, disc herniation with root entrapment, entrapment neuropathies, and cauda equina syndrome. Amyotrophic lateral sclerosis, multiple sclerosis and myasthenia gravis must also be considered.

Finally, fibromyalgia syndrome frequently can mimic some of the symptoms of PPS, primarily pain and fatigue, and occurs in 11% of patients presenting to a post-polio clinic.

Management

Although there is currently no specific treatment for PPS, patients can benefit from appropriate management. This document presents general guidelines for the management of the main symptoms of PPS—new weakness, fatigue and pain.

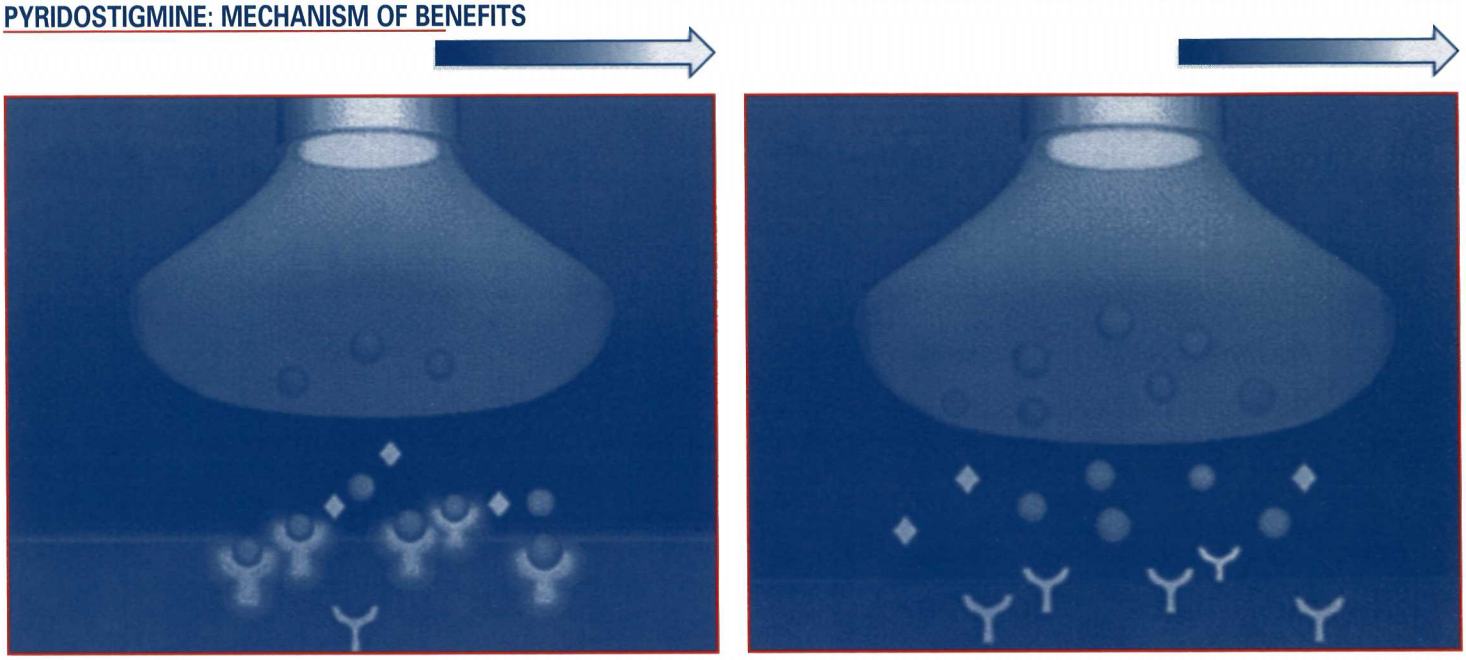
Management of weakness

Strengthening exercise, stretching of contractures, avoidance of muscular overuse, bracing, use of assistive devices and weight loss may be of benefit in the treatment of weakness.

Strengthening exercise. Judicious exercise has been shown to be beneficial in PPS patients, even in muscles where new weakness has been reported. The exact exercise prescription is dependent on a number of factors. Isometric exercise is most useful in muscles with less than grade 3 strength (Medical Research Council [MRC] scale) or in muscles over a painful joint. An isotonic or isokinetic

Figure 2.

PYRIDOSTIGMINE: MECHANISM OF BENEFITS



Normal motor neurons. In normal NMJs, the enzyme cholinesterase breaks down acetylcholine to prevent its accumulation in the NMJ.

In PPS patients, there are defects in acetylcholine release by dysfunctional motor nerve terminals.

exercise program is most useful in muscles with grade 3 or better strength and without a painful joint. Isokinetic exercise can be used when special equipment is available.

An aerobic exercise program such as using a bicycle ergometer, walking or swimming may also be useful, but should be an activity that the patient enjoys in order to increase compliance. A warm-up and cool-down period with stretching exercises should also be included.

For the first few weeks, it is best for the patient to be monitored carefully (a few times weekly) to ensure that the exercise prescription is being followed correctly and that overuse of muscles and joints does not occur. Once the patient understands the exercise program well and demonstrates the ability to self-monitor, regular follow-up every few months is reasonable.

Stretching of contractures. Some patients may also benefit from stretching of contractures (if no contraindication exists), such as knee flexion contractures and ankle plantarflexion contractures to improve gait and stability. However, some contractures can be beneficial and should not be stretched.

Avoidance of muscular overuse. Even though several different types of exercise have been shown to be beneficial in the late post-polio patient, exercise should always be used judiciously and should be avoided completely in some patients.

Bracing. Joint instability due to weakness and muscle groups that are being overused may benefit from rest or supportive devices such as braces.

Use of assistive devices. Various assistive devices may be useful for post-polio patients to improve mobility and safety, including orthoses, canes, crutches, wheelchairs and motorized scooters.

Weight loss. Excessive weight can contribute to overuse of muscles and joints.

Management of fatigue

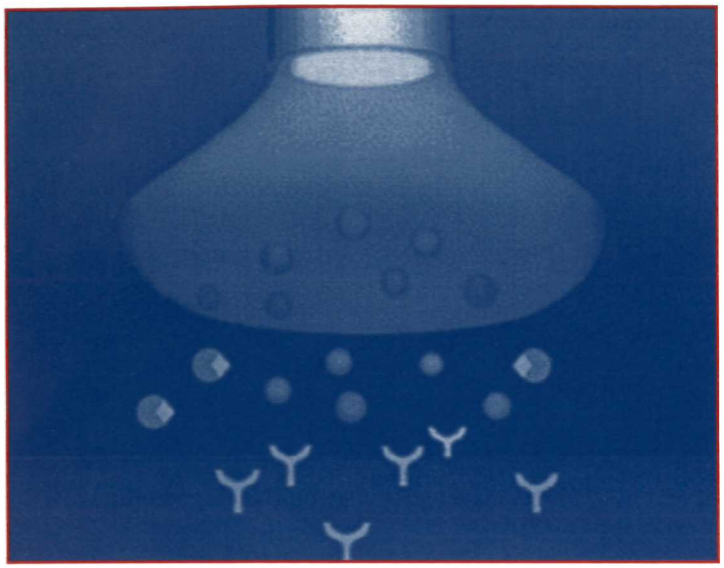
Excessive fatigue in PPS patients may be managed with the use of energy conservation techniques, lifestyle changes, pacing and regular rest periods or naps. Pharmacologic agents may also play a role.

Energy conservation techniques may include discontinuing unnecessary energy-consuming activities (eg., making the bed), using a "handicapped" license plate, sitting instead of standing, moving the location of certain items and supplies to make them more easily accessible, and using an electric scooter for longer distances.

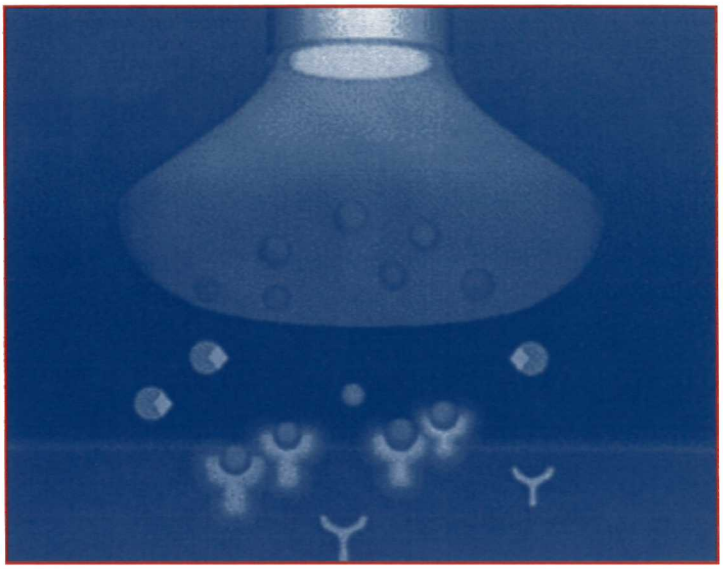
Lifestyle changes may include discontinuing certain activities such as volunteer work, changing to a more sedentary employment or working part-time.

Pacing and regular rest periods or naps. Regular rest periods during the day or naps, especially in the early after-

Several potential pharmacologic treatments have been evaluated in PPS, and thus far, pyridostigmine appears to be the most promising.



Pyridostigmine inhibits the breakdown of acetylcholine by cholinesterase.



Benefit. This property prolongs the survival of acetylcholine and its effect in the NMJ.

noon, are helpful in the management of general fatigue and should be encouraged.

Pharmacologic agents. Anecdotal reports exist on the use of tricyclic antidepressants, which may be helpful by improving sleep or possibly by other effects on central neurotransmission. The anticholinesterase pyridostigmine may also be useful (see below).

Management of pain

Pain in PPS patients may occur from a number of causes and management is dependent upon etiology. Pain may be caused by muscle, joint and soft tissue abnormalities and other superimposed neurologic abnormalities. Overuse is the most likely cause of many of the pain syndromes.

Common muscular causes for pain include post-polio muscular pain, muscle overuse, muscle cramps, fasciculations and fibromyalgia. Post-polio muscular pain may occur in muscles previously affected by APP and is usually described as an aching sensation similar to that experienced at the time of APP. It typically occurs at the end of the day and is aggravated by activity.

Patients can also experience muscle pain with activity. Painful muscle cramps can occur either with activity or at the end of the day. Muscle cramps and muscle pain with activity are most likely due to overuse; these types of pain should be avoided. Management can include reduction of activity, pacing (rest periods during activity), use of moist heat and stretching, use of assistive devices and lifestyle modifications.

Fasciculations are a sign of previous motor neuron damage, and are reported by APP patients. Fibromyalgia occurs commonly in patients presenting to a post-polio clinic and can be treated with amitriptyline, cyclobenzaprine, fluoxetine, aerobic exercise and other measures.

Joint and soft tissue abnormalities include osteoarthritis, tendinitis, bursitis, ligamentous strain, joint deformities and failing joint fusions. Because of weakness from APP, post-polio individuals may use certain joints and extremities in abnormal ways, which may predispose them to injury of joints, tendons, bursae and ligaments. In addition, abnormal forces around joints may produce joint deformities such as genu recurvatum and genu valgum. Treatments may include modification of extremity use, physiotherapy, use of physical modalities, strengthening, orthoses to control joint deformities and failing joint fusions, assistive devices, non-steroidal anti-inflammatory medications, acetaminophen and, rarely, steroids or surgery.

Superimposed neurologic disorders that can cause pain include peripheral neuropathies, radiculopathies and spinal stenosis. Use of assistive devices is a major risk factor for carpal tunnel syndrome in PPS. Treatments for carpal tunnel syndrome can include splinting, use of pads on canes or crutches, or use of a special grip for canes or crutches. For lumbosacral radiculopathies or low back pain, use of corsets, shoe lifts, back supports or pelvic supports may be useful. Spinal stenosis may be treated with exercise, use of a cane, TENS and a lumbosacral orthosis.

Pharmacotherapy

Pyridostigmine. Several small clinical trials of pharmacologic treatments have been completed in PPS patients. Pyridostigmine 180 mg/day has been evaluated by this author in an open trial using an objective measure of NMJ transmission (stimulation single-fibre electromyography [SFEMG]) in 17 patients.[8] A significant relation between

subjective fatigue response to pyridostigmine and improvement in NMJ transmission with edrophonium (a short-acting anticholinesterase similar to pyridostigmine) was found.

In addition, other investigators have found improvements in some objective measures of strength and fatigue with pyridostigmine 180 mg/day in a double-blind, placebo controlled, crossover trial in 27 PPS patients.[9]

Other medications, including amantadine and high-dose prednisone have been tested with negative results. In small studies, human growth hormone showed little or no improvement in muscle strength, and bromocriptine produced an improvement in fatigue symptoms in some patients. Selegiline may warrant further study based on anecdotal reports of improvement in PPS symptoms. Insulin-like growth factor-1 (IGF-1) has been shown to improve recovery after exercise, but appeared to have no effect on strength or fatigability.

In summary, several potential pharmacologic treatments have been evaluated in PPS, and thus far, pyridostigmine appears to be the most promising.

Treatment of terminal axonal dysfunction

If PPS weakness, fatigue and fatiguability are due to degeneration and dysfunction of motor axonal sprouts, treatments that support the integrity and/or function of terminal axons may improve or delay PPS symptoms.

Pyridostigmine, an agent that has been widely used for the treatment of myasthenia gravis, is an anticholinesterase that inhibits the hydrolysis of acetylcholine, thereby prolonging its survival and effect in the NMJ and selected central synapses. In view of the NMJ transmission dysfunction observed in PPS, pyridostigmine has been suggested as a treatment for this disorder; in fact, pyridostigmine may have at least three beneficial effects on PPS motor units:

Acute improvement of fatigue and fatiguability by amelioration of NMJ transmission defects. Defects in NMJ transmission in PPS can be overcome partially with parenteral cholinesterase inhibitors such as neostigmine and edrophonium, and with oral pyridostigmine. Patients taking pyridostigmine report decreased muscle fatiguability and general fatigue, consistent with an immediate cholinergic effect on NMJ transmission.[8]

Acute improvement of strength by recruitment of blocked or defective NMJs. Subjects with prior APP show blocking with SFEMG, which can be reversed partially by oral pyridostigmine. Oral pyridostigmine may improve strength acutely, consistent with recruitment of dysfunctional NMJs. This acute mechanism of pyridostigmine may be responsible for some of the increased strength and endurance reported by subjects taking this agent.

Chronic improvement of muscle bulk and strength, and axonal sprout maintenance by trophic effects. The normal reduction of growth hormone (GH) and IGF-1 with aging may be a contributing factor to the onset of PPS. Because IGF-1 promotes synthesis of protein and nucleic acid in muscle cells and sprouting of peripheral motor axons, loss of IGF-1 may contribute to axonal degeneration and muscle weakness in PPS. Pyridostigmine increases GH secretion and subsequent circulating IGF-1 levels with growth hormone-releasing hormone (GHRH) infusion. Thus, the chronic effects of pyridostigmine may be due to cholinergic modulation of the GH-IGF-1 axis.

Other potential trophic effects of pyridostigmine include an acetylcholine effect on partially denervated PPS muscle and induction of calcitonin gene-related peptide secretion.

NAPPS: Rationale and result interpretation. In view of the preliminary efficacy data and the rationale detailed above, a multicentre, double-blind, placebo-controlled study involving 126 patients, the North American Postpoliomyelitis Syndrome Study (NAPPS), was organized to investigate the pyridostigmine dosage (60 mg three times daily) previously found to be effective in several small clinical trials. Measures used in the trial were health-related quality of life, subjective fatigue, isometric strength and IGF-1 levels.

While the final analysis has yet to be published and despite the fact that a trend to improved strength in weak muscles was found at month 6 with pyridostigmine, the results showed no statistically significant effect of pyridostigmine on the evaluated endpoints. These results did not reflect the investigators' clinical impression that there appeared to be a clear benefit with the medication in at least some patients. There may be several reasons to this discrepancy. This is the first multicentre trial of PPS and much remains to be learned about the disease and about the best medical outcome measures to be used in PPS trials. The outcome measures may not have been adequate to assess a difference with the medication. In addition, physical activity was not assessed. Investigators noted that some patients increased their level of physical activity during the study, but that fatigue levels remained stable. Further data analyses are still in progress.

Conclusion

PPS is a complex syndrome that does not lend itself to easy evaluation. Management also requires considerable attention and a good measure of persistence on the part of the physician. Effective rehabilitation must address general health, symptom reduction, functional enhancement and prevention of secondary disability. Finally, as pathophysiological mechanisms are better understood, new therapeutic avenues are emerging which may play an important role in optimizing the quality of life of PPS patients.

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