



**Rancho Los Amigos**

*Post-Polio*

**Support Group**

**Newsletter - January 2007**

## **Current Research in Post-Polio Syndrome – May 2006**

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This report is based on Dr. Perlman's May 21, 2006 presentation to the Post-Polio Support Group of Orange County, California.

The cause of post-polio syndrome (PPS) is thought to have many components:

- partially an immune system malfunction
- aging
- cumulative injuries over the years can wear out tendons, ligaments, and joints
- overuse

Nobody currently believes that viral damage is occurring.

The underpinnings of post-polio, the beginning and the changes that appear thirty or forty years later, do affect a neurologic component of the body. The motor

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units, and sometimes the central connections are affected. Soft tissues, muscles, tendons, ligaments, and joint related structures can also be involved in post-polio syndrome.

This report includes information on post-polio research related to diagnosis, aging with a disability, immune treatments, current research studies, and proposed research studies. It concludes with what we already know. There is a little bad news but there is an increase in the amount of good news.

## **The Bad News**

The World Health Organization's (WHO) goal of eradicating polio by the end of 2005 was not met. Unfortunately, there is still active, natural, native polio in the world and it continues to spread as countries get lax in their vaccination policies.

The strain of African poliovirus that has spread in northern Nigeria due to a two-year boycott of the vaccine has now been carried to other African countries, to Saudi Arabia, and to Indonesia, which had been polio-free for ten years.

There is still an incidence of oral vaccine related polio. Stool or saliva from an infected person can transmit the virus. In vaccinating countries, 90% of new cases were vaccine-related, although most cases of acute flaccid paralysis were non-polio (e.g. West Nile virus, Coxsackie B, Echo, enterovirus 71).

West Nile virus might become an increasing concern as a mimic of acute poliomyelitis. This is one of our major public health concerns in Southern California.

Although use of the live polio virus vaccine stopped in the United States in 2000, polio remains a concern even in the United States. In October 2005 five children in an unvaccinated Amish community in central Minnesota tested positive for non-paralytic polio. These cases are the first known occurrence of polio in the United States in five years. The polio strain found in Minnesota's Amish community appears to be a mutated version of an oral live polio vaccine still used in some countries, according to the U.S. Centers for Disease Control and Prevention.

WHO has been trying to move from the modified oral live polio vaccine to a new injectable vaccine (used in the USA) that has been modified from the original Salk vaccine to be longer acting and not have the risk of the oral vaccine. However, the increased cost of this injectable vaccine is a concern in some countries.

Vaccination programs must continue even if active polio infection is not apparent. There is some thought that people who were vaccinated twenty or more years ago

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may need to be revaccinated. The polio vaccine we received may not last our entire lives. A study in Greece reported that levels of polio antibodies seemed to be going down in people who are in their late teens to early twenties.

## **The Good News**

- In the past twelve months there have been twenty-three new publications in the medical literature:
  - 9 dealing with acute polio and vaccination
  - 2 review articles of post-polio syndrome
  - 9 dealing with better diagnostic techniques
  - 2 dealing with respiratory issues
  - 1 dealing with immune treatment
- Four abstracts were presented at the Neurology meetings.
- One new National Institutes of Health (NIH) research study has been launched and one was completed.
- One new Post-Polio Health International (PHI) study will be announced later this year.

## **Taking the Pulse of New Research**

### **More Accurate Diagnosis**

Every new symptom a survivor has may not be related to a history of polio. It is important to have good diagnostic techniques to go beyond the physician's knowledge of new onset, atrophy, muscle weakness, fatigability, and pain. Better diagnosis will make it easier to say, "Yes, this is post-polio." or, "No, this is not post-polio."

**1. Development and factor analysis of an index of post-polio sequelae.** Kalpakjian CZ, Toussaint LL, Klipp DA, Forchheimer MB. *Disabil Rehabil.* 2005 Oct 30;27(20):1225-33.

This is the first validation of a standardized scale to assess the severity of post-polio sequelae. The researchers were able to extract six or seven symptoms that seemed to be very accurate measures of the severity of fatigue, muscle strength, etc. in a post-polio individual.

When more standardized scales are available it will be easier for physicians who

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are not PPS specialists to identify post-polio.

**2. Non-invasive assessment of respiratory muscle strength in patients with previous poliomyelitis.** Soliman MG, Higgins SE, El-Kabir DR, Davidson AC, Williams AJ, Howard RS. *Respir Med.* 2005 Oct;99(10):1217-22. Epub 2005 Apr 12.

SNIP (sniff nasal inspiratory pressure) is more sensitive to post-polio respiratory muscle weakness than other non-invasive tests. It can measure pressure when a patient quickly breathes in through his nose, it is brief, and less fatiguing. Thus measurement of SNIP is a valuable tool for monitoring the progression of respiratory muscle weakness due to previous poliomyelitis.

Pulmonary function tests can be very stressful for some survivors. Forced Vital Capacity (FVC) measures volume - how deeply a person can inhale and exhale. Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) measure how much air pressure a person can generate when breathing in and breathing out. They all require effort and depend upon the muscles.

## **Differential Diagnosis**

Diagnostic criteria for Post-Polio Syndrome include the exclusion of all other neurological conditions. In about one-third of the PPS cases which are referred to Dr. Perlman, the problems are related to spine disease, pinched nerves, or a neuropathy from another cause. Electrical studies, imaging studies, and appropriate lab tests can help identify suspected new neurologic or medical problems of post-polio patients.

These four reports indicate conditions that can mimic PPS symptoms:

**1. Myasthenia gravis masquerading as post-poliomyelitis syndrome.** Singh R, Pentland B., *J Rehabil Med.* 2006 Mar;38(2):136-7.

This article reports on a polio survivor having increased swallowing problems. After a long period of time he developed facial muscle weakness and fatigue. These new symptoms were due to myasthenia gravis and not post-polio.

**2. Respiratory failure in a patient with antecedent poliomyelitis: Amyotrophic lateral sclerosis or post-polio syndrome?** Terao SI, Miura N, Noda A, Yoshida M, Hashizume Y, Ikeda H, Sobue G. *Clin Neurol Neurosurg.* 2005 Sep 13; [Epub ahead of print]

This post-polio patient had a rapid loss of respiratory function over months and

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was ultimately diagnosed with amyotrophic lateral sclerosis.

When changes are happening over a period of weeks or up to 6 months, something besides post-polio must be considered. In PPS, a patient would show losses in muscle strength, endurance, and fatigability over a period of two to five years. Rapid changes in performance may not be due to PPS.

**3. A case of cervical spondylotic amyotrophy resembling post-polio syndrome.** Isobe T, Yaguchi H, Matsui K, Inoue K.A., *Rinsho Shinkeigaku*. 2006 Jan;46(1):59-61. Japanese.

This case reports a PPS patient with cervical spondylotic amyotrophy (changes in the disks in the cervical spine and overgrowth of bone spurs) causing atrophy and weakness in the arms. In this case the weakness and atrophy in his arms was not being caused by PPS but by the neck disease.

**4. Muscle hypertrophy with complex repetitive discharges in C-6 radiculopathy.** Rousseff RT, Tzvetanov P. *Clin Neurol Neurosurg*. 2005 Aug;107(5):425-7

This person's shoulder muscle did not show atrophy but the muscle got bulkier as it was becoming painful and weaker. An electrical study revealed that a pinched nerve was causing the pain and weakness.

## **Aging with a Disability**

**Prevalence and risk factors of post-polio syndrome in a cohort of polio survivors.** Ragonese P, Fierro B, Salemi G, Randisi G, Buffa D, D'Amelio M, Aloisio A, Savettieri G. *J Neurol Sci*. 2005 Sep 15;236(1-2):31-5.

This observational study in Italy suggests that the stress of other illnesses might be perceived by the body in a way that would weaken motor units and contribute to the symptoms of post-polio. This interpretation shows the close linking between general health and neuromuscular health.

These researchers observed that chronic physical stress, which may be caused by other illnesses, seemed to have a negative effect on weakened motor units. If you are a polio survivor doing reasonably well, the stress of your body dealing with another medical illness could stress the polio motor units and cause them to become weaker.

A reverse interpretation was reflected in a previous study done at Rancho Los Amigos which concluded that polio survivors were more likely to develop other

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medical conditions because of having had polio. If a polio survivor is less mobile and less active, he will gain weight, his joints will suffer, he might develop diabetes which might lead to heart problems, etc.

## **Immune Treatments - Effect of intravenous immunoglobulin (IVIG) in patients with PPS**

In May 2005 Dr. Perlman reported on Scandinavian groups who have explored the role of the immune system in PPS for five years. They found old viral debris activating the immune system to make anti-motor neuron inflammatory chemicals that cause motor nerve dysfunction and central fatigue.

The level of some inflammatory chemicals found in spinal fluid of polio survivors has been as high as the levels seen in someone with multiple sclerosis, which is an immune mediated inflammatory disease of the central nervous system.

The first trial of intravenous immunoglobulin (IVIG), which was reported on previously, determined that more research was needed.

**1. Treatment with IVIG reduced the levels of some of the inflammatory chemicals (IFN-gamma, TNF-alpha) present in PPS.** Gonzalez H et al. 2004; *J Neuroimmunol. 150:139-44.*

Further trials are needed to assess relief of symptoms.

**Case report:** Farbu E et al. 2004; *Tidsskr Nor Laegeforen 124:2357*

This case report of a woman with PPS treated with IVIG showed improved strength and reduced fatigue.

An infusion of large amounts of IVIG can neutralize antibodies so the body area that is being attacked (liver, kidneys, nerves, muscles) can temporarily recover.

**2. Effect of intravenous immunoglobulin in patients with post-polio syndrome** Kaponides G, Gonzalez H, Olsson T, Borg K. *J Rehabil Med. 2006 Mar;38(2):138-40.*

In this uncontrolled pilot study:

- The 14 subjects in this first study were aware that everyone was getting IVIG.
- The goals were to look for changes in muscle strength, physical performance, and quality of life during treatment.

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- Each person received 30 grams of IVIG daily for three days (one round).
- Quality of life (weakness and fatigue) was statistically improved for all but one item. The most improved quality was vitality (energy levels).
- There was no significant increase in muscle strength or physical performance.

This pilot study suggests that IVIG could have clinical relevant effects by improving quality of life and energy levels, possibly because these neutral antibodies (IVIG) were damping down the inflammatory process (bad antibodies in the central nervous system). Possibly there was a placebo effect but the response was dramatic enough to be more than could be expected by a placebo. They felt that a randomized controlled study was needed.

**3. Intravenous immunoglobulin for the post-polio syndrome: a randomized controlled trial.** Gonzalez H, Stibrant-Sunnerhagen K, Sjoberg I, Kaponides G, Olsson T, Borg K *Lancet Neurology* 2006; 5:493-500

In this randomized controlled trial, half the subjects received intravenous immunoglobulin and the others received a placebo.

- This double-blind, placebo-controlled study analyzed changes in muscle strength during IVIG treatment in 135 PPS patients (seven others were withdrawn) with increased cytokine levels in spinal fluid.
- Each person received 90 g IVIG (30 g daily for 3 days). Two rounds were given, three months apart. Final assessment was three months later.

From baseline, the treatment group improved only 2.3%, but adding the decline of the placebo group of 6.3%, gives a total improvement of 8.6%.

Prior studies have revealed about 1%-2% per year decline of strength in untreated polio survivors. However, many other studies have shown that people with PPS can halt progression of PPS symptoms and promote improvement of 1-2% per year if they take care to modify lifestyle: avoid overuse; use assistive devices and bracing if appropriate; control weight gain, sleep problems, stress, and pain; and engage in non-fatiguing exercise for strength and conditioning.

**Interpretation:** This study indicates that IVIG may have a clinically relevant effect, with an improvement in muscle strength and perhaps other measures that were not mentioned. The effect may be due to a decrease in an inflammatory process in the central nervous system. The inflammatory process has been suspected and reported by researchers for many years. The placebo effect was ruled out.

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If this IVIG treatment were to become part of the PPS neurological “war”, spinal taps would be needed to measure cytokines. Cytokines are not available for routine laboratory testing; they are only available in research labs. To use IVIG as a clinical treatment (that would be accepted and paid for by insurance companies) might entail having a spinal tap, unless an effective way to measure cytokines in blood (through regular clinical labs) can be discovered.

### **Side Effects of IVIG**

- **During infusions** – A person can feel quite sick while getting IVIG infusions: headache, fatigue, nausea, low-grade fever, itching, joint pain, muscle pain, and backache. These symptoms typically resolve within a few days after the treatment.
- **Serious Risks** – Rare, serious, and potentially fatal side effects include severe allergic reactions, meningitis, acute renal failure, stroke, myocardial infarction, and other thrombotic complications.

Thirty grams of IVIG for 3 days can make the blood thicker and contribute to blood clots, strokes, and heart attacks. Many of these side effects have occurred in patients who had significant, underlying risk.

- **Financial** – The FDA has only approved IVIG treatment for certain immune deficiencies. But there is off-label use (as neutral antibodies to block bad antibodies) in other neurologic diseases caused by the immune system. However, insurance companies may only approve its use for certain immune-mediated neurologic conditions if the literature supports it. The cost of these treatments (\$10,000 - \$12,000) is a huge burden without insurance support.

### **Current Research Studies**

#### **Post-Polio Health International (PHI)/International Ventilator Users Network (IVUN)**

In 2005 Dr. Perlman reported on this newest research award to study the early use of noninvasive positive pressure ventilation (NIPPV) to prolong survival in patients with ALS and possibly other neuromuscular diseases (PPS).

Pilot studies of the use of NIPPV in chronic respiratory failure suggest that it prolongs survival. But it is not clear whether this was helping to strengthen the muscles or just helping with the symptoms. Results of this PHI/IVUN study are not yet published.

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If NIPPV begun at the time of diagnosis improves quality of life for ALS patients by as little as 13.5%, it would be a cost-effective treatment. (Gruis et al., 2005)

NIPPV does appear to improve quality of life and prolong survival reported by Mustafa et al., 2006.

**Interpretation:** While treating survivors of bulbar polio for many years, Dr. Perlman has learned that anything that can be done to rest and take pressure off the breathing muscles will keep them stronger for a longer period of time.

“The respiratory muscles are probably like any other muscles; if you protect them and prevent them from being overused, then they will last longer”, she said.

### **NIH Provigil Study**

In 2005 the NIH recruited for a study of Provigil (modafinil) to treat fatigue in Post-Polio Syndrome. Provigil is already approved for treatment of narcolepsy and other causes of excessive daytime sleepiness. It is also used off-label for fatigue in multiple sclerosis, supported by published research.

These results were published in a poster session at the Neurology meeting in San Diego, California, April 2006:

- Twenty-eight polio survivors were enrolled in a randomized, double-blind, placebo-controlled, crossover study of 400mg/d of modafinil vs. placebo. (In a crossover study, the drug and placebo subjects are switched over to the other halfway through, and nobody is aware of which they are taking.)
- Fatigue was measured using three different fatigue scales.
- Conclusion—modafinil was not superior to placebo in alleviating fatigue in patients with PPS. These results were similar to the pyridostigmine (Mestinon) study which showed that off-label use can suggest benefit but may not hold up under research conditions.

Dr. Perlman has patients who are taking modafinil and feeling better, so these thoughts occur:

- Were twenty-eight people enough to study?
- Did they study the wrong people?
- Is there a difference between central fatigue, brain fatigue, and peripheral-fatigue?

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- Perhaps they were looking at peripheral fatigue and modafinil only works for central fatigue. The full article has not yet been published.

## **Fatigue in Post-Polio Syndrome**

### **Is it different? Are we measuring the right things?**

This report is also from the Neurology meeting in San Diego, California, April 2006. Daria Trojan's group at the Montreal Neurological Institute presented a study of Fatigue in Multiple Sclerosis (MS) and Post-Polio Syndrome: Relationship with Disease-related, Behavioral, and Psychosocial Factors.

General fatigue, physical fatigue, and mental fatigue were examined separately for MS and PPS. The two groups did not respond in the same way.

#### **1. General fatigue**

In MS: general fatigue was associated with sleep problems, pain, and decreased independence.

In PPS: general fatigue was seen more in the male gender; more in situations where there was acknowledgement of stress or pain, with increased physical activity, and with greater post-polio duration.

The longer they had PPS the more likely they were to have general fatigue; the more active they were, the more likely they were to have general fatigue; if they had pain and stress and were of the male gender, the more likely they were to have general fatigue.

With at least one type of fatigue there is a difference between the MS group and the PPS group, suggesting that probably the fatigue they experience is not the same and isn't going to respond to the same treatment.

#### **2. Physical Fatigue**

In MS: physical (muscle) fatigue was associated with physical activity, body mass index, and decreased independence.

In PPS: people with decreased independence were more likely to have physical fatigue; people with increased physical activity or pain, were more likely to have physical fatigue.

There was a little more similarity in physical fatigue for these groups.

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### **3. Mental Fatigue**

In MS: mental fatigue was associated with stress and decreased independence.

In PPS: mental fatigue was only associated with stress.

Mental fatigue shared stress as an associated factor but not the decreased independence.

There could be fully independent, reasonably functional polio survivors who had severe mental fatigue that seemed at least in part to be associated with stress.

**Interpretation:** This study suggests that if looking at MS to get ideas for drugs for polio fatigue, you may be comparing apples and oranges. If the two diseases do not have the same mechanisms, it may not be a worthwhile thing to explore.

However there are still polio survivors taking pyridostigmine (Mestinon) who do feel better; there are still people with PPS taking modafinil (Provigil) who do feel better. That effect cannot be minimized. This presents a shakier scientific position than the IVIG does. IVIG actually did show statistical significance.

### **NIH recruitment for two studies**

1. The NIH is still recruiting for a study of brain physiology in polio survivors. Transcranial magnetic stimulation will be used to check cortical networks and communication from the upper motor neuron cell bodies. Subclinical polio changes or compensatory alterations in cortical networks may predispose to the development of PPS.

2. The NIH is also recruiting for a natural history study of West Nile Virus (WNV), to determine how it affects the body.

What can we learn from this study? Some people infected with WNV have no symptoms. In others, symptoms may vary from fever and headache to a polio-like syndrome with paralysis, to coma and brain changes like those of a stroke. Many patients recover with no lasting effects, while a few can have long-lasting neurological damage or may die.

This study will collect clinical, laboratory, diagnostic, and radiographic information on people thought to have WNV to better understand the disease. It may also explain why some polio survivors develop PPS and others do not.

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To volunteer for NIH studies 1-800-411-1222

**Interpretation:** This looks like a little test tube study of what went on in the 1940s with people experiencing acute polio infection. But now we have better technology and better ways to measure what potentially occurred during acute polio infection and healing. Information learned from this study may be applied to polio survivors after learning what actually occurred in the brain and in the nerves.

### **Proposed Research Studies**

1. Riluzole, which works to protect motor neurons in ALS. Could it work in PPS? There has not yet been any published data.
2. DHEA or testosterone supplements for post-menopausal female polio survivors with low androgen levels and PPS: Can strength be improved without side-effects (virilization, liver damage)? There has not yet been any published data.
3. At the June 2005 PHI meeting Dr. B. Jubelt presented an update on his research with the mouse model of post-polio syndrome for growth factor therapy. Some of the early studies probably had difficulties due to the insulin-like growth factor doses being too low, in his opinion, and potentially they were not administered in a way they could get to the nerves. Prior studies of injections under skin or into muscle were not beneficial.

Dr. Jubelt is currently working with the mouse investigating the two growth factors that seem to have the most promise: GDNF (motor neuron cell body) and IGF-1 (motor neuron sprouts) attached to a neutralized virus, to carry the growth factors across the blood brain barrier and into the lower and upper motor neurons. The information from the mouse research may lead to ways growth factors can be studied in people.

### **What We Already Know**

- New symptoms in a polio survivor are post-polio only about 1/3 of the time.
- New symptoms may be due to another medical or neurological illness or to orthopedic issues 2/3 of the time. These must be identified and treated.

People do need to be seen by a neurologist. Any good neurologist can diagnose myasthenia gravis. Any good neurologist or orthopedist can rule out all the other possibilities. With post-polio syndrome, everything else needs to be ruled out to make a PPS diagnosis.

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Treatment of other illnesses in a polio survivor must be monitored relative to the sensitivities of PPS (e.g. surgery, chemotherapy, use of cholesterol lowering medication).

Polio survivors with symptoms of PPS must take care to modify lifestyle: avoid overuse; use assistive devices and bracing if appropriate; control weight gain, sleep problems, stress, and pain; engage in non-fatiguing exercise for strength and conditioning. Many studies have shown that success in these areas can halt progression of PPS symptoms and promote improvement of 1-2% per year.

## **Conclusion**

There are many articles in rehab literature that show that without drugs and without some of the new things that are being looked at now, people with PPS can stabilize and even improve. Information is already available on ways to prevent decline and avoid overlooking other disorders. Any good doctor should be able to listen to this, understand what the patient is telling him, understand the literature that is passed on to him, and be able to jumpstart the patient towards stabilization and preventing or slowing further decline.

We shouldn't ignore what is already known as the search continues to find something that will regenerate nerves.

## **Resources**

[www.post-polio.org](http://www.post-polio.org) (PHI)

[www.ncbi.nlm.nih.gov/entrez](http://www.ncbi.nlm.nih.gov/entrez) (PubMed articles)

[www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NIH source)

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