Rancho Los Amigos Post-Polio Support Group

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Post-Polio: Now and the Future

A neurologic update for polio survivors

Presented at the Orange County, CA. PPSG meeting, May 15, 2009

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Once again Dr. Perlman generously shared her time and energy with local polio survivors. The focus of her presentation, based upon current research, related to the neuromuscular problems of polio survivors and those with post-polio syndrome (PPS). This report on her talk includes what we already know, the role of the immune system, old polio virus, biomarker research, treating autoimmune disorders, conclusions from other studies, and standard guidelines for managing PPS. There is also information about an online registry of polio survivors to promote research on the late effects of polio and post-polio syndrome.

What We Already Know

New symptoms are PPS only about one-third of the time but still need to be

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identified and treated. They may be due to another medical or neurological illness, orthopedic problems, or to medications which have been prescribed.

It is known that pain is increased in people who have less muscle activity, and the occurrence of limb swelling relates to muscle activity. For instance, joint pain that accompanies the flu may be felt more. There might be more sensitivity to the effects of surgery. Plan on a longer recovery, but just don't lay back, work with it. Similarly, polio survivors are more sensitive to chemotherapy, to cholesterol lowering medications, and to the side effects of other drugs. If a drug has a side effect of fatigue – and many do – they may be felt more.

Those with symptoms of PPS require good self- observation and need to modify their lifestyles in these ways:

- Avoid overuse.
- Use appropriate assistive devices and bracing.
- Control weight gain, sleep problems, stress, and pain.
- Engage in non-fatiguing exercise for strength and conditioning.

Many studies have shown that success in controlling these areas, or a portion of these areas, can halt progression of PPS symptoms and may even promote improvement of 1-2% per year. It doesn’t have to be a downhill slide. If a person is sliding downhill, everything in his medical and life history needs to be examined to see what needs to be changed.

Immune system – Trials and Funding

At the April 2009 meetings of the American Academy of Neurology there were no new posters or presentations from the platform dealing with post-polio but that is not so unusual. The most positive thing taken from that meeting was discussion with peers about President Obama's new stimulus grants which include new money for research. One thing that has been holding back post-polio research and specifically clinical trials is the lack of money. Every neurologist Dr. Perlman met who is involved in clinical research had submitted at least two or three grant requests for this available funding.

From year to year it appears that the data supporting the role of the immune

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system in PPS is steadily increasing. The immune system plays a role in causing symptoms of post-polio and there may be effective treatments to slow or stop the progression of symptoms, beyond what it is already being done by lifestyle modifications. There is evidence to support doing an organized clinical trial in the United States to validate what researchers in Sweden and Norway have learned. Dr. Dalakas, at the U. S. National Institutes of Health, has been at the forefront of trying to get a clinical treatment trial for Intravenous Immunoglobulin (IvIg), which is gamma globulin, infused into a vein.

The reason it has taken so long to gather preliminary data and design a trial that will be acceptable to regulatory agencies that approve treatments is that symptoms of PPS and the underlying physical signs change very slowly. It is very difficult to measure slow improvement in those circumstances unless you're willing to run a clinical trial that goes on for 10 years. Most drug companies and most funding agencies are not going to have the funds for a 10-year clinical trial.

After some kind of shorter trial that can show benefits (biomarkers perhaps) people with PPS can then start getting treated and followed on that treatment, providing additional data over 10 years. This would be similar to research on the immune component in multiple sclerosis and the benefits of certain drugs discovered during five or ten years of use and continual monitoring. The same thing could happen with PPS.

Dr. Perlman said, ***"Indeed, there should be benefits sooner than 10 years and there will probably be symptomatic benefits from the immune modifications that will happen pretty quickly with any immune treatment, IvIg specifically. Cumulative benefits, potentially reversing some of the weakness and fatigability that has built up, could take one or two years to really turn the corner and come back up again."***

Dr. Perlman is hoping there will be a design and funding for a multi-center clinical trial of IvIg in the United States this year. There are a number of large centers that are well prepared to do that from their own polio clinics, including Dr. Perlman at UCLA.

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Virus Detection

"We've known for 10 or 15 years, mainly from the work of Dr. Dalakas, that in the spinal fluid of polio survivors they had been able to identify small fragments of the old polio virus, little bits of protein debris that were left behind and may possibly be the trigger that gets the immune system going and causes this smoldering immune reaction which seems to be one of the causes of PPS.

"There are still these underlying questions. Is there still polio virus in the nervous system of polio survivors and are those viral particles infectious? We know that the debris could trigger the immune system, but could that viral debris have some type of activity where it is still behaving like an infectious particle, triggering other parts of the immune system that only fire off when there is an infection as opposed to an inflammation?"

The Post-Polio Health International (PHI) fifth research award team will investigate that question to see which parts of the virus remain and compare them to the wild type polio virus from which they were degraded, to see if there might be a role for antiviral treatment as well as anti-immune treatment in PPS. This $25,000 award went to the team from University of Insubria, Varese, Italy, led by Antonio Toniolo, MD, PhD, Professor of Medical Microbiology and Virology, to study "Persisting Noninfectious Fragments of Poliovirus in PPS Patients: Virus Detection and Susceptibility to Antiviral Drugs."

The results of the Post-Polio Health fourth research grant on biomarkers had not been published at the time of this report.

Biomarkers

Biomarkers are distinctive biological indicators of a condition or disease. It is very common for polio survivors to have a mild elevation of the biomarker CPK (creatine phosphokinase), indicating that muscle membranes are under some stress and leaking CPK. If the nerve connections back to the muscles could be improved (the goal of many of the treatment strategies for PPS), theoretically the CPK levels would come down. A treatment has not yet been found that will reconnect the nerve endings to the muscle but there is ongoing research.

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1. A Swedish publication reported research by the Gonzalez group which looked for novel proteins that might help in the diagnosis of PPS and might help understand what is going on in nerves or muscles. They also searched for specific markers that would indicate immune system involvement.

In the spinal fluid of 15 people with PPS they found five distinct, sensitive proteins, seen elevated only in polio survivors. These could serve as very good biomarkers for a treatment aimed at reducing inflammation and dealing with those viral particles, or a variety of future treatment possibilities that may be suggested. This group recommended evaluating these five proteins as candidate biomarkers for the diagnosis and development of new therapies.

2. Dr. Trojan's group in Canada studied serum inflammatory markers in PPS. They had 51 PPS patients and 26 normal control people and looked at disease duration, muscle strength, fatigue, and pain. In polio patients they found that the well known serum inflammatory markers TNF alpha, IL-6 and leptin were significantly increased compared to the controls. The elevated TNFalpha levels in PPS were associated with increased muscle pain. There were no correlations between inflammatory markers in PPS and joint pain, muscle strength, fatigue, or disease duration.

These may be good biomarkers for treatment; if a treatment is found that reduces that inflammation and normalizes the immune system, these inflammatory markers should go down.

"It could happen that some survivors will have all the symptoms of post-polio but do not have elevations in these biomarkers. Will there be two types of post-polio syndrome? More people with PPS need to be studied before any conclusions can be made. For years there has been some discussion about the possibility of two types of post-polio: one with more pain and fatigability and the other with more focal atrophy and weakness. Perhaps previous studies of various treatments such as Mestinon and Provigil, didn't seem to show consistently significant benefits, because there may be several subsets of PPS. Certain treatments might work for some people but not for others. We will need better ways to determine the type of PPS a person has, so that the proper treatment can be tried."

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Treating Autoimmune Disorders

Dr. Dalakas reviewed the current status and future prospects for using IvIg to treat autoimmune disorders, where “bad antibodies” are thought to be attacking nerves, muscle, etc. If there is an immune system reaction that is directing antibodies to attack viral protein particles that are left over in polio survivors, those antibodies may cross-react with other broken-down pieces of protein that could be from the polio survivor’s own nerve and muscle. The immune system could end up attacking old debris from polio virus and also attacking relatively healthy nerves and muscles, leading to symptoms of post polio.

The immune system can be suppressed by giving chemotherapy but there are a lot of side effects and concerns. It definitely reduces the bad antibodies but it reduces good antibodies too. Chemotherapy drugs including steroids have been tried in PPS but the risk of suppressing the entire immune system made their use risky. Two things can be done to selectively dilute out the bad antibodies which are only a small proportion of all the antibodies that a person’s body makes.

1. Plasmapheresis can be done by filtering off blood and pulling off antibodies, returning the remaining blood to the patient. The body will then make new antibodies, to keep the total immunoglobulins at a certain level, hopefully making more good ones than bad ones.
2. An infusion of IvIg which dilutes out the bad antibodies can be given. If there were five-percent bad antibodies before infusion, that decreases to about one-tenth of one percent after IvIg infusion. Then there is less chance of the bad antibodies attacking nerves and muscles.

IvIg seems to be more direct: the system is flooded with random, normal antibodies and the percentage of bad antibodies goes down. Many insurance companies will not pay for IvIg unless it is an approved use. PPS is not yet on the approved list.

Dr. Dalakas believes there should be more IvIg studies looking at the proper dosing, the proper timing, and the number of treatments that are needed. Hopefully he will soon get funding for multiple sites to begin a study of IvIg for PPS.

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Conclusions from Other Studies

Exercise: A small study in Turkey on the short-term effects of aerobic exercise in home and hospital exercise groups concluded that fatigue and quality of life were both improved. A regular non-fatiguing exercise program is beneficial to patients with post-polio syndrome.

Coenzyme Q10: In Sweden a study of 14 patients with PPS concluded there was no effect of coenzyme Q10 supplementation during resistance training on post-polio syndrome symptoms. Thus, supplementation with coenzyme Q10 has no beneficial effect on muscle function in patients with post-polio syndrome.

Rehabilitation: A pilot study in London, UK concluded that prolonged benefits from comprehensive rehabilitation were found for physical, psychological and functional outcomes in PPS.

Restless Legs Syndrome (RLS): Another group in London, UK alerted clinicians to be aware of the possibility of associated RLS in PPS.

Standard Guidelines for People with PPS

Dr. Perlman believes that these standard guidelines for people with PPS are still valid:

- Make sure the symptoms are polio related and not due to other neurologic, orthopedic, or medical/medicine issues. Every symptom that a polio survivor has will not necessarily be PPS. They are not immune to other conditions.
- Use Rehab to develop a program of appropriate non-fatiguing exercise and reconditioning, assistive devices, pacing, and finding your limit. You have to choose the right device for you, pace yourself, and find your limit.
- Do <u>not</u> push past the limit of pain and fatigue, find the limit. Don't just sit back and say, "I'm going to conserve"-- find what can be done, and then pace it out without causing further injury.

Everyone needs:

- a good general doctor (a Primary Care MD)

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- a knowledgeable Physical Therapist (PT) who understands the limitations of people with PPS, if physical therapy is being prescribed
- attention to good general health (weight control, exercise, assistive devices, relaxation training, sleep hygiene, emotional health).

One of the problems some people face is, "How do you find a PT who is knowledgeable about post-polio within your individual health plan?" Dr. Perlman suggested there may be a need for continuing education in post-polio for physical therapists.

Future Research

Thousands of polio survivors need to be identified in order to do really good research. Having a large number that can be presented to the National Institutes of Health or a funding agency, saying we have this many polio survivors who are interested in being involved in clinical trials, will be a strong push to get the funding that is needed for trials.

In 2008 the John P. Murtha Neuroscience and Pain Institute, Johnstown, Pennsylvania, launched an online registry of polio survivors to promote research on the late effects of polio and post-polio syndrome. There are 5-10 minutes of on-line questions and your identity is kept confidential. If you have not yet registered, please consider it.
https://www.conemaugh.org/apps/postpolio/

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