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\$100,000 Grant Announced at 11th International Conference

Joan L. Headley, PHI Executive Director, St. Louis, Missouri

Antonio Toniolo, MD, FAMH, University of Insurbia, Varese, Italy, accepted the Post-Polio Health International two-year grant award of \$100,000 (\$50,000 each year) at the organization's 11th International Conference on May 31, 2014. The announcement at the opening dinner of the conference by Research Committee Chair, Daniel J. Wilson, PhD, represents the eighth award year. PHI/IVUN has given nine awards between 2001-2014 totaling \$295,000. (Two awards were granted in 2011.)



Antonio Toniolo, MD, FAMH

Dr. Toniolo's proposal, "Poliovirus genome in patients with post-polio syndrome (PPS): Defining virus mutations by novel genome sequencing methods and investigating possible treatments with antiviral antibodies and drugs," was selected from 11 proposals reviewed by the expert Review Panel and approved by PHI/ IVUN's Board of Directors. Proposals were submitted from researchers representing seven different countries.

Dr. Toniolo also received PHI's \$25,000 award in 2009. He and team member Andreina Baj, also at

the University of Insurbia, conducted an observational study of post-polio syndrome in a cohort of polio survivors and consenting family who were attending Northern Italy Hospitals for neuromuscular problems over the last four years.

In humans, the only evidence for persisting poliovirus infection has been found in individuals with deficiencies in B lymphocytes and low or absent immunoglobulins. Results of virology studies (detection of poliovirus genome and virus activity) show that a persistent low-level infection is associated with post-polio syndrome (PPS). So far, however, the Italian group has been unable to demonstrate that the persisting virus does play a role in the development of post-polio syndrome, a progressive disorder.

The data

In the investigated cohort, 97/107 individuals have been shown to have developed PPS 15 or more years after the acute attack. Family members of PPS patients (n=45) were also studied, together with a control group represented by healthy blood donors and controls with neurologic disorder other than PPS (n=47). Specimens included: cerebrospinal fluid, peripheral blood leukocytes, live cells of duodenal mucosa, skeletal muscle and peripheral nerve.

Poliovirus genomes were detected in 82/97 patients with PPS (85%) and in 3/92 controls (3.3%). Type 1 poliovirus was the most prevalent (61% of cases), followed by type 2 and type 3 (12% and 9%, respectively). Some cases (18%) could not be typed. Based on clinical history, 22/107 poliomyelitis cases were associated with

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polio vaccination (18%). In vitro, leukocytes of poliovirus-positive PPS patients did produce enhanced levels of inflammatory mediators as compared to leukocytes of healthy donors. This is in line with a pathogenic hypothesis indicating that chronic inflammation is a hallmark of PPS.

Serum immunoglobulin levels were measured in PPS patients, their family member and controls. As compared to healthy blood donors, levels of IgG1, IgG2, IgG4 and IgA were significantly reduced both in PPS patients and their family members. IgM levels were not significantly different. This suggests that modest immunoglobulin deficiencies may be present in individuals who developed clinical manifestations after being hit by poliovirus as well as in their family members.

The group also measured titers of neutralizing antibodies to the three poliovirus types in sera of PPS patients, their family members, and healthy controls. No significant differences were found.

Conclusions to date

The results lend support to the idea that residual poliovirus activity does persist in PPS patients and that virus persistence could be of pathogenic significance.

Their data also show that poliovirus cannot be found in family members of PPS patients, i.e., that virus is not transmissible within families. This finding tells that PPS people are "not infectious" and has reassuring implications. (This point has been made epidemiologically but not definitely in virology.)

The Next Steps (2014-2016)

The document submitted to PHI explained in detail the questions the study proposes to answer and the methods it will use. Building on the research previously described in this article, the group aims to verify the persistence of poliovirus components in post-polio syndrome patients decades after the acute attack and to determine whether the persisting viruses are still pathologically active.

To date, a problem has been the low levels of virus found in PPS individuals. Consequently, the prior tests used where unable to determine the genetic mutations of the poliovirus strains found.

Toniolo has enlisted the assistance of Dr. Konstantin Chumakov, U.S. Food and Drug Administration, to help solve this problem. Chumakov and his collaborators are well-known worldwide for having set up novel sequencing methods specifically designed for characterizing poliovirus genomes of different strains isolated from human cases and the environment. The U.S.-based group will analyze the poliovirus isolates from the Italian participants from the 2009 study with the goal of defining the mutations and deletions in the genomes of the poliovirus in those individuals over the decades. The test will also be able to determine vaccine strains from wild-type strains based on genetic markers.

Chumakov and collaborators have also produced and characterized human monoclonal antibodies capable of neutralizing the three poliovirus types. Another aim of the study is to check whether these antibodies are able to neutralize the biologic activity associated with the poliovirus strains obtained from PPS patients. If so, a new possibility of immunotherapy could emerge stopping the development or progression in survivors deemed chronic poliovirus carriers.

The study also plans to test in vitro the most promising antiviral drugs that may be capable of blocking PPS progression.

Finding "stable" post-polio participants

During the review of the grant internally by PHI, concern was expressed that the study did not include samples from polio survivors who were not described as having post-polio syndrome. The research as planned tested PPS patients, family members and individuals with other neurological disorders. The researchers agreed to check whether poliovirus is detectable in a cohort of polio survivors who, in spite of age, failed to develop PPS.

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PHI will assist the team in finding nonsymptomatic polio survivors in Italy. An earlier study done in Arkansas, in 2007/ 08, had problems recruiting stable polio survivors. The reason was not analyzed fully, but it could have been due to lack of interest of "healthy" polio survivors in participating, inadequate recruiting or the dilemma of the expansion of the definition of post-polio syndrome to the point that anyone who had polio is assumed to have PPS particularly as they get older.

It takes a team

Dr. Toniolo is the face of this research but does not work alone and acknowledges the contribution of neurologists Giorgio Bono, Salvatore Monaco, Laura Bertolasi, Franco Molteni, Luisa Arrondini who provided samples of their PPS patients and the essential contribution of virologists Martina Colombo, Giuseppe Maccari, Merja Roivainen who dedicated their time and efforts to this noble task.

Lastly, he acknowledges Post-Polio Health International and Regione Lombardia, Milan, Italy, and expresses gratitude to Joan L. Headley, St. Louis, and Dr. Frans Nollet, Amsterdam, for their continuous encouragement and support.

More about the Fund

The Research Fund was started in 1995 with a bequest from the estate of Thomas Rogers, a quadriplegic polio survivor who spent about a year and a half in three hospitals. He had been successfully weaned from the iron lung to a rocking bed and with a "great proficiency in frog breathing." In later years, he used the portable Bantam Positive Pressure Respirator and the PLV-100. Rogers died in 1994 leaving a lasting legacy of supporting research for the ventilator user and post-polio communities.

Contributions to the fund may be made online at http://shop.post-polio.org or by check to 4207 Lindell Boulevard, #110, St. Louis, Missouri 63108.

Ask Dr. Maynard continued from page 9

In regard to treatment for your wife's pain, if it is a result of post-herpetic neuralgia that results from the shingles infection in one localized area of skin, Zostrix cream applied on the skin twice daily for several days is the best and safest way to gain relief. If her pain is very severe and more widespread, she would have to be fully evaluated by a specialist physician in management of post-herpetic neuralgia pain for other options. Encourage your wife to maintain a positive outlook because in the vast majority of cases, post-shingles pain does eventually improve and resolve.

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