Research

FINAL REPORT:

Persisting Noninfectious Genome Fragments of Poliovirus in PPS Patients

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Dr. Toniolo's team submitted an interim report that is posted online at www.post-polio.org/res/.

UPDATE on PHI's Research Fund:

The money invested in the fund is on the rebound with a current value of $550,000.

PHI received six Phase 1 applications for its next award to be given in late 2010. The submissions, from Brazil, Israel, United States and Sweden, will be reviewed by an expert panel, which includes polio survivors, to determine which applicants will be asked to submit Phase 2 requirements.

Purpose of the grant: The funds our team received from The Research Fund of Post-Polio Health International helped us continue our ongoing research of identifying poliovirus (PV) genome fragments in the survivors of polio. Our goal also is to clarify whether the presence of fragments is related to the symptoms of post-polio syndrome (PPS).

Recent findings: Using molecular tests and cell lines expressing poliovirus receptors, PV genome fragments and low-level infectivity have been detected in CSF (cerebral spinal fluid) and peripheral blood leukocytes of 52 out of 63 patients (82 percent) diagnosed with PPS (median age, 58 yrs; range 46 to 81 yrs; median time from acute paralytic poliomyelitis, 55 yrs).

Using these same methods, PV genome fragments could be detected in only one of 58 control subjects (blood donors, n=26; family members of PPS patients, n=21; adult pathologic controls with neurologic conditions other than PPS, n=11).

In a few PPS patients undergoing surgical procedures, PV genome fragments have been detected also in primary cultures of skeletal muscle, peripheral nerve and duodenal mucosa cells.

The amounts of PV genome fragments were extremely low in all patients. This made the detailed analysis of these fragments extremely difficult. When dealing with other viral infections, it is common to "sequence" the genome of the virus isolated from the patient (i.e., to express the composition of its genome as a sequence of nucleotides). The sequence of the viral isolate is then compared to genome sequences of reference strains of the same species in order to identify potential unique properties of the isolate. In the case of PPS, sequences of genomic PV fragments must be compared to those of the three wild-type PVs.

So far, we have only been able to obtain partial sequences of some genomic fragments (the so-called 5'UTR, VP1, and $3D^{pol}$ regions). However, the limited data obtained have been sufficient to indicate that the majority of patients (70 percent) were carrying genome fragments belonging to PV type-1, 16 percent to PV-2, and 4 percent to PV-3 (some fragments remain to be identified). Partial sequences also showed that the genome fragments detected in PPS patients contained extensive mutations as compared to wild-type PVs. Tests in cultured cells exposed to PV genome fragments showed that these fragments contained some residual biological activity, such as low production of PV capsid proteins and induction of some pro-inflammatory cytokines.

Conclusions: The data indicate that low-level PV activity can persist for decades in most polio survivors. The results, however, *do not* provide a pathogenetic link of PV persistence with the development of PPS. Through collaboration with other virology laboratories, we now hope to characterize in detail the mutated PV strains obtained from PPS patients in order to understand their possible contribution to pathogenetic events.

Subsequently, we will use *in vitro* assays to test the activity of novel antiviral compounds against the mutated and persisting PV strains. The hope is to find drugs capable of eradicating viral genome fragments from the body of PPS patients. ▲