CurePSP’s 2021 International Research Symposium highlights advancements in neurodegeneration investigation

Proceedings cover recent advancements in biomarkers, brain imaging, computer modeling, therapeutic antibodies, brain organoids, and genetics.

CurePSP’s International Research Symposium Neuro2021, was held Feb. 4-5, 2021, using the foundation’s advanced online platform. At the New York City anchor desk were moderators and organizers Kristophe Diaz, PhD, CurePSP’s vice president – scientific affairs, and Jaclyn Zendrian, HMCC, CurePSP’s vice president – events.

The meeting was attended by 250 professionals from 15 countries who heard leaders in academia, industry, and philanthropy address pressing questions related to progressive supranuclear palsy (PSP) and related neurodegenerative diseases. Attendees represented 43 universities, 29 biotech and pharmaceutical companies, 14 NGOs, and 10 research hospitals.

Over these two days, scientific advances and promising therapeutics for the treatment of PSP took center stage, uniting the research community and offering patients and families new hope.

Diaz remarked, “For a rare-disease symposium, this representation is impressive, and I’m excited and proud. Our focus at CurePSP is to help our amazing community of patients, families, and volunteers. We aim to connect them to important discoveries and to the scientists that facilitate these discoveries.”

Many supporters played a role in the success of the meeting including the Light of Day Foundation, Union Chimique Belge (UCB), Aprinoia Therapeutics, Applied BioMath, NeuroTau, and Pinteon Therapeutics.

The prevalence of PSP has been estimated between 5.8 to 6.5 per 100,000 [1-3], but research discussed at the conference suggests this number could be double [4]. The cause of PSP is unknown, but advanced age and environmental factors have been shown to contribute [1, 5, 6]. A protein referred to as tau is also believed to play a major role in the disease [7, 8].

PSP is a brain disorder that affects movement, vision, behavior, and cognition. The motor and behavioral syndromes that are observed in PSP are caused by the death of cells in specific regions of the brain. What causes these cells to die? How do we prevent this from happening? These are just a couple of questions that were discussed at the symposium.

Contributions That Transformed PSP Research

The conference opened with remarks by Lawrence I. Golbe, MD, chair of the CurePSP Scientific Advisory Board, CurePSP’s director of clinical affairs, and member of the foundation’s Board of Directors. Golbe highlighted philanthropic contributions that have transformed research related to PSP. Of note, Jay Troxel, Chuck Peebler, and Abe Pollin were credited for their contributions. Also, Irene Litvan, MD, University of California, San Diego, was commended for receiving the first NIH grant devoted exclusively to PSP, a significant milestone. Golbe commented on how this funding and these transformational donations have contributed to the foundation of the world’s largest PSP Brain Bank, the start of the PSP Genetics Consortium, and the production of a valuable body of knowledge.

Kristophe Díaz, PhD

The Extraordinary Times
The Genetics of PSP

Knowledge about genetic variants that increase risk for PSP or control the progression of PSP is critical. These topics were a major focus of the symposium. The identification of these genes will allow us to identify biomarkers, model disease, and design better clinical trials and possibly individualized drug studies.

The PSP Genetics Consortium is supported by nine institutions and 15 investigators and aims to identify new risk alleles for PSP and discover novel targets and pathways involved in PSP pathogenesis. Jeffrey Friedman, MD, PhD, Friedman BioVentures, emphasized the importance of collaborations to reach these goals. “The more resources we can put together, the more likely we are to come up with therapeutic leads, diagnostics, and modifiers of therapy. In every step along the way, bringing people together can enhance the effort.” Friedman also discussed the importance of data sharing, joint analysis of data, and a commitment to promote the careers of junior investigators such as Timothy Chang, MD, PhD, at the University of California, Los Angeles.

In work supported by the Consortium, Chang discussed research on rare genetic variants in PSP. Chang presented studies that assessed rare variants within protein coding regions, promoter regions, and distal noncoding regions in PSP. With over 2,000 samples sequenced in a genome-wide association study (GWAS), variants involved in cell-cell interaction and cell-cell communication in the brain (PCDHGA10) were identified. Also, variants involved in apoptosis related to an inflammatory response (GSDMA) and viral response (BIRC7) were found.

Huw Morris, MD, University College London, UK, also presented on recent advances in the genetics of PSP. In research funded in part by CurePSP, common variants influencing the risk of tauopathy progression in PSP have been found, and a number of genes that play a role in increased susceptibility to PSP have been identified: specifically, MOBP, STX6, EIF2AK3, SLCO1A2, and DUSP10. Studies are still needed to determine the biological relevance of these genes in PSP.

Morris highlighted the PROSPECT study. A major goal of this study is to identify biomarkers that can improve the accuracy of PSP diagnosis. Morris and colleagues identified a variant that differentiates classical PSP-Richardson Syndrome (RS) from non-Richardson phenotypes. The new subtypes are almost as common as classic PSP-RS and share midbrain atrophy as a common hallmark. The findings suggest that PSP prevalence may be twice as common as what has been previously estimated.

Karen Strauss Cook Research Scholars John Crary, MD, PhD, and Ana Pereira, MD, Mount Sinai, New York, looked specifically at the genetics that lead to sporadic PSP. Using brain banks from around the world, Crary found tissue from over 300 patients with sporadic PSP that were not included in the original GWAS. GWAS of this novel PSP cohort confirmed an association between tau and PSP; identified 130 differentially expressed genes, and identified 35 differentially spliced genes.

Looking at the single-cell level, Pereira indicated that there may be dysfunction in cholesterol metabolism and remyelination. Of note, Pereira discussed the novel activation of an astrocyte population unique to PSP, and this data suggested dysregulation in unfolded protein response (EIF2 signaling).

In the past 18 months, there have been setbacks in PSP clinical trials. Adam Boxer, MD, PhD, University of California, San Francisco, a keynote speaker at the symposium, encouraged scientists to “focus research in areas that will reignite an interest in therapeutics for PSP.” Boxer encouraged scientists to decrease the risk involved in clinical trials by generating data that will give confidence in the outcome of a program. Boxer focused specifically on the need for PSP biomarkers. “Although there are a variety of informative biomarkers for Alzheimer’s disease, there is no PSP biomarker. If we had one, this may help to de-risk a clinical trials program.” Boxer further discussed ways to pave the road for success: “Scientists need to improve understanding of tau biology in PSP, understand the limitations of preclinical models, and fast track promising therapies to human trials.” The use of innovative trial designs would also be beneficial.

In his concluding remarks, Boxer highlighted the importance of clinical trials to PSP patients and their families. “Our patients want to be our copilots. They want to be part of these exciting missions to test new therapies. It is incredibly meaningful for patients to have clinical trials, and it gives them hope.”
Molecular Imaging of 4R Tauopathies

Gil Rabinovici, MD, University of California, San Francisco, emphasized Boxer’s calling for PSP-relevant biomarkers and focused specific attention on positron emission tomography (PET) radiotracers. Rabinovici gave a comprehensive overview of the radiotracers used in 4R tauopathies, and of these, 18F-PI-2620 and 18F-PMP-222 have the most promise for PSP. “The initial studies need replication, and PET-to-pathology correlations need confirmation if they are going to be used in drug trials.”

Rabinovici was most excited on a focused effort that is underway to optimize imaging of 4R tauopathies. In collaboration with the National Institute of Neurological Disorders and Stroke and the Rainwater Charitable Foundation, a team of scientists has created the Center Without Walls for Imaging Proteinopathies with PET. Activities supported by this initiative hold tremendous potential for identifying completely novel PET radiotracers. Rabinovici stated that this work “could be transformative not only for 4R tau but also in how we develop PET ligands in the future.”

Identification of a biomarker for PSP would be a major advancement for PSP research.
Judith Steen, PhD, Harvard Medical School, used a proteomic approach to study neurodegeneration. Specifically, Steen used a novel method called FLEXITau to quantify post-translational modifications to the tau protein in the Alzheimer's disease (AD) brain.

What was exciting about Steen's work was the novel identification of acetylation and ubiquitination of the tau protein. “These modifications were abundant, and almost every patient with AD had these modifications. Interestingly, the acetylation and ubiquitination correlated with symptoms indicating that this may be the switch to becoming symptomatic.” Steen also noted that in control tissue, the C-terminus of tau was unmodified. In AD tissue, the C-terminus became increasingly modified, and this correlated with Braak staging.

Steen also focused research on the prion-like behavior of tau. Specifically, what are the distinct features of tau that cause it to acquire prion-like behavior? Steen noted that specific regions of tau (1N and 2N) prevent aggregation, and isoforms that do not have these regions are more prone to aggregation (such as 0N4R). She stated that the tau prion seed is created by multiple processive steps.

Following Steen’s presentation, Diaz gave closing remarks and reflected on Boxer’s comments about the importance of PSP patients in research endeavors. In his presentation, Boxer had said, “Patients are the copilots of these difficult adventures, and we are thrilled that many research leaders recognize that and involve the patient voice at a much earlier stage in their thought process. In the future, we hope to work with many researchers, scientists, and technologists to empower this patient voice toward true milestones.”

REFERENCES: