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Editorial

The Rossy Progressive Supranuclear Palsy Centre: PSP Coming Full Circle

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In June 1963, Steele, Richardson, and Olszewski presented their clinical and pathological findings of a parkinsonian condition distinct from Parkinson's disease in Atlantic City, New Jersey at meetings of the American Neurological Association and the American Association of Neuropathologists. Their original paper was published the following year.[1] They reported on seven cases who came to autopsy and included two more surviving cases with similar clinical features. All cases were male with onset in the sixth or seventh decade. Survival was poor, with death occurring within 7 years of symptom onset. Onset was "... insidious with vague changes in personality, visual or speech troubles, altered facies or unsteady gait ... ophthalmoplegia was constant, striking, and usually early ... a loss of conjugate vertical gaze to command and in following and attraction [saccadic] movements." They noted preservation of the oculocephalic reflex, axial rigidity of the neck and upper trunk with six of their cases having "a striking extensor posturing of the head and neck," and "none of the patients developed parkinsonian tremor."[1] Brain pathology showed a more widespread pathology with neurofibrillary tangles and cell loss involving the basal ganglia, brainstem, and cerebellum. Steele et al. called this condition progressive supranuclear palsy (PSP) and thought it was unlikely to be new but had not been reported with this level of clinical and pathological documentation.

Clinical research diagnostic criteria for PSP were published in 1996. The three categories of diagnostic certainty were possible, probable, and definite (autopsy-confirmed). The key features were early-onset vertical gaze impairment and history of falls within the first year of symptom onset.[2] In 2005, using principal component analysis, Williams et al. identified two clinical subtypes of pathologically verified PSP which they named PSP-Richardson's syndrome (PSP-RS) (after the original description) and PSP-parkinsonism (PSP-P).[3] More than half of their cases were PSP-RS, with the classic early-onset postural instability, supranuclear gaze impairment, and cognitive impairment. One-third were PSP-P, with tremor, asymmetric onset, better response to levodopa, and longer survival – these cases were often misdiagnosed as Parkinson's disease. A minority (14%) did not fit into either category.[3] They acknowledged that it was not possible to identify clinical syndromes (e.g. primary gait freezing) based on characteristics (e.g. gait initiation failure) that were not included in the data set analyzed. In 2014, Respondek and colleagues reported on a cohort of autopsy-confirmed PSP cases with retrospective chart analysis.[4] There was marked heterogeneity of clinical features, with only 24% presenting as PSP-RS. Over half the cases showed either overlapping features or not fitting proposed criteria for previously described phenotypes. Within the first 2 years of symptom onset, fewer than one-third of PSP cases exhibited supranuclear gaze palsy, and only about half reported falls. Principal component analysis identified the three most common clinical constellations as oculomotor dysfunction and falls (i.e. PSP-RS), parkinsonism, and frontal and cognitive dysfunction; however, this explained only 37% of the clinical variance.[4] Additionally, the less common phenotypes of progressive non-fluent aphasia, corticobasal syndrome, and pure akinesia with gait freezing were present in their cohort.

Revised diagnostic criteria for PSP were published in 2017 including three levels of clinical certainty: probable, possible, and suggestive.[5] Höglinger et al. proposed that "definite" PSP be reserved only for cases with neuropathological confirmation. Application of these diagnostic criteria is relevant and increases the sensitivity to detect PSP; applying the new criteria for "suggestive" of PSP reduced the average time to diagnosis from 3.6 years to 2.2 years.[6]

In a span of just over half a century, our understanding of PSP has changed dramatically. After its initial identification as a unique clinical and pathological entity, it was recognized that the canonical clinical description only applies to a minority of cases with pathologically verified PSP.

Advances have required collaborations between clinicians, pathologists, and basic scientists across institutions, countries, and continents. Combining data collected from different sites for retrospective analysis is challenging. It is expected there will be some missing values, as not every site will have recorded information the same way or have ready access to the same investigations. Using mathematical modeling for an unbiased approach is useful to detect patterns we would otherwise not have been identified; however, it is only as good as the data collected.

The work of collecting human brain tissue for analysis requires the cooperation of patients, families, clinicians, and pathologists in

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addition to adequate financial and other resources. While brain banks are valuable, they obtain biological material and clinical documentation from multiple sources resulting in heterogeneous information. Clinically well-characterized autopsy-verified cases followed longitudinally are crucial to advancing our understanding knowledge of diseases, particularly neurodegenerative conditions. Programs of this nature are labor-intensive and not for the faint of heart.[7,8]

The group at the Toronto Western Hospital received a generous grant from the Rossy family to establish a world-class center for PSP and atypical parkinsonian conditions.[9] The program was endorsed by the CurePSP Foundation as a Centre of Care, one of the few in North America. The program is extremely well-resourced, including dedicated funding for a program coordinator, a research assistant, and a designated Rossy movement disorders fellow. The time allotted for an initial visit is 2–3 hours. Follow-up visits are booked for every 6 months for the first year and then annually, with an allotted time of 1½ to 2 hours with the primary goal of collecting clinical data regarding disease progression.[9]

In addition to highly detailed clinical assessments including questionnaires and rating scales as part of longitudinal follow-up, MRI, positron emission tomography, and biological specimen collection (including cerebrospinal fluid, blood, saliva, and skin biopsy) are offered. Brain autopsy is also discussed with patients and families.

Other programs in the United States and Europe were consulted early on, and it took nearly 2½ years from inception to initiating a fully functional clinical program. From the opening of the Rossy PSP Centre in October 2019 until December 2021, Couto and colleagues screened 132 patients, with 91 fulfilling criteria for PSP.[9] The most common phenotype was Richardson syndrome.

Standardized, prospective data collection with detailed evaluations is essential to gain a better understanding of PSP and related conditions. It is fitting that a Canadian site is poised to be a world leader in PSP research as the story comes full circle. The seminal 1964 publication was the collaborative work from the University of Toronto by Dr. Steele, an Assistant Resident in Neuropathology, Dr. Richardson, an Associate Professor in Medicine, and Dr. Olszewski, a Professor of Neuropathology. I wish the current group at Toronto Western Hospital and those who follow much success in this ambitious and inspiring endeavor.

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