The Canadian Journal of Neurological Sciences (2023), **50**, 845–852
doi:10.1017/cjn.2022.332

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

The Rossy Progressive Supranuclear Palsy Centre: Creation and Initial Experience

Blas Couto[1], Susan Fox[1,2], Maria Carmela Tartaglia[1,2,3,4], Ekaterina Rogaeva[4], Jeffrey Antwi[1], Puja Bhakta[1], Gabor G. Kovacs[1,2,4,5,6] and Anthony E. Lang[1,2,4]

[1]Edmond J. Safra Program in Parkinson's Disease, Rossy Progressive Supranuclear Palsy Centre and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada, [2]Department of Medicine, Division of Neurology, University Health Network and the University of Toronto, Toronto, Ontario, Canada, [3]Memory Clinic, Toronto Western Hospital, Toronto, Ontario, Canada, [4]Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada, [5]Department of Laboratory Medicine and Pathobiology and Department of Medicine, University of Toronto, Toronto, Ontario, Canada and [6]Laboratory Medicine Program & Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada

ABSTRACT: ***Objective:*** To describe the development and initial experience of a clinical research program in progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) in Canada: The Rossy PSP Centre, to share the data acquisition tools adopted, and to report preliminary results. ***Methods:*** Extensive demographic and longitudinal clinical information is collected every 6 months using standardized forms. Biofluids are collected for biobanking and genetic analysis, and many patients are enrolled in neuroimaging research protocols. Brain donation is an important component of the program, and standardized processing protocols have been established, including very short death to autopsy times in patients undergoing medical assistance in dying. ***Results:*** Between Oct 2019 and Dec 2021, 132 patients were screened, 91 fulfilling criteria for PSP and 19 for CBS; age 71 years; 41% female; duration 5 years, age-of-onset 66 years. The most common symptoms at onset were postural instability and falls (45%), cognitive-behavioral changes (22%), and Parkinsonism (9%). The predominant clinical phenotype was Richardson syndrome (82%). Levodopa and amantadine resulted in partial and short-lasting benefit. ***Conclusions:*** The Rossy PSP Centre has been established to advance clinical and basic research in PSP and related tauopathies. The extent of the clinical data collected permits deep phenotyping of patients and allows for future clinical and basic research. Preliminary results showed expected distribution of phenotypes, demographics, and response to symptomatic treatments in our cohort. Longitudinal data will provide insight into the early diagnosis and management of PSP. Future steps include enrollment of patients in earlier stages, development of biomarkers, and fast-tracking well-characterized patients into clinical trials.

RÉSUMÉ : Le centre de recherche Rossy sur la paralysie supranucléaire progressive : la mise sur pied et la première expérience. ***Objectif :*** L'étude visait à dépeindre l'élaboration d'un programme de recherche clinique sur la paralysie supranucléaire progressive (PSP) et le syndrome corticobasal (SCB) au Canada, et à décrire la première expérience : le centre de recherche Rossy sur la PSP; à mentionner les outils d'acquisition de données adoptés, et à faire état des résultats préliminaires. ***Méthode :*** Une collecte exhaustive de données démographiques et d'information clinique longitudinale est réalisée tous les 6 mois à l'aide de formulaires uniformisés. On procède également à une collecte de liquides biologiques à des fins de mise en banque de matériel biologique et d'analyse génétique, et bon nombre de patients participent à des études soumises à des protocoles de recherche en neuro-imagerie. Par ailleurs, le don de cerveau constitue un élément important du programme, et des protocoles uniformisés de traitement ont été établis, notamment en ce qui concerne une durée très courte de délai entre le moment de la mort et l'autopsie chez les patients qui ont fait une demande d'aide médicale à mourir. ***Résultats :*** Entre octobre 2019 et décembre 2021, 132 patients ont été sélectionnés : 91 d'entre eux respectaient les critères de la PSP et 19, ceux du SCB; l'âge moyen était de 71 ans; il y avait 41 % de femmes; l'âge moyen au moment de l'apparition des symptômes était de 66 ans, et la durée moyenne de la maladie, de 5 ans. Les symptômes les plus fréquents au début étaient une instabilité posturale et les chutes (chez 45 % des patients), des changements cognitifs et comportementaux (22 %) et le parkinsonisme (9 %). Le phénotype clinique prédominant était le syndrome de Richardson (82 %). Enfin, la lévodopa et l'amantadine ont permis un soulagement partiel, mais de courte durée. ***Conclusion :*** Le centre de recherche Rossy sur la PSP a été mis sur pied afin de faire progresser la recherche clinique et la recherche fondamentale sur la PSP et les tauopathies connexes. L'étendue de la collecte de données cliniques est telle qu'elle permet une détermination approfondie des phénotypes des patients et qu'elle ouvre la voie à des travaux futurs de recherche clinique et fondamentale. Les résultats préliminaires ont confirmé, dans la cohorte à l'étude, la distribution attendue des

Corresponding author: Anthony E. Lang, MD, FRCPC, Edmond J. Safra Program in Parkinson's Disease, Rossy Progressive Supranuclear Palsy Centre and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada. Email: anthony.lang@uhnresearch.ca

Cite this article: Couto B, Fox S, Tartaglia MC, Rogaeva E, Antwi J, Bhakta P, Kovacs GG, and Lang AE. (2023) The Rossy Progressive Supranuclear Palsy Centre: Creation and Initial Experience. *The Canadian Journal of Neurological Sciences* **50**: 845–852, https://doi.org/10.1017/cjn.2022.332

© The Author(s), 2023. Published by Cambridge University Press on behalf of Canadian Neurological Sciences Federation. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

phénotypes, les données démographiques et les réactions aux traitements symptomatiques. Quant aux données longitudinales, elles jettent la lumière sur la pose précoce du diagnostic de la PSP et la prise en charge qui s'impose. Enfin, parmi les nouvelles étapes à venir figurent la recherche et la sélection de patients à des stades plus précoces de la maladie, la découverte de biomarqueurs et l'élaboration d'un processus de participation accélérée et bien caractérisée de sujets à des essais cliniques.

Keywords: Neurodegenerative diseases; Progressive Supranuclear Palsy; Biomarkers; Corticobasal degeneration; Movement disorders

(Received 20 July 2022; final revisions submitted 19 November 2022; date of acceptance 24 November 2022; First Published online 5 January 2023)

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder that causes a mixed constellation of motor and behavioral symptoms associated with the deposition of pathological 4-Repeat tau protein following a sequential distribution in the brain but showing distinct regional predominance of pathology based on the clinical phenotype.[1] To date, there are no proven therapies to slow or prevent disease progression, and management is symptomatic and supportive but limited in efficacy.

PSP is uncommon and affects 5 in 100,000,[2] although postmortem studies suggest that it may be more common than currently appreciated.[3,4] Making a diagnosis of PSP is based on clinical criteria. As such, expertise in recognizing and managing the disease is generally within the scope of tertiary centers in Canada with specialized movement disorder or behavioral neurology clinics. Even in such referral centers, care can be fragmented due to the requirement of multiple sub-specialties to address the multiple systems affected by PSP. Clinical research is also challenging due to diagnostic difficulties and rapid clinical deterioration. An important contribution to this problem is the relatively recent recognition of clinical phenotypic heterogeneity and the relatively poor diagnostic accuracy in life, apart from the more classical cases of the Richardson syndrome (PSP-RS) variant.[5,6] The commonest of these non-RS phenotypes include variants dominated by corticobasal syndrome (PSP-CBS), parkinsonism (PSP-P), frontal behavioral abnormalities (PSP-F), progressive freezing of gait (PSP-PFG), speech and language dysfunction (non-fluent aphasia; PSP-SL), and prominent early postural instability (PSP-PI). The related 4R-tauopathy corticobasal degeneration is equally heterogeneous in presentation and even more often misdiagnosed.[7,8] To our knowledge, there exists no program in Canada that focuses on PSP, embedding clinical and basic research in clinical care. Although there are specific programs for atypical parkinsonism or frontotemporal dementia in tertiary referral centers in the US, there are very few that have been specially endorsed by the CurePSP Foundation as Centers of Care (which includes a high commitment to multimodal and standardized clinical assessments and provides interdisciplinary care) and none in Canada that are dedicated to the combination of clinical and basic research.

To improve management and clinical research in PSP and related tauopathies, with the support of the Rossy Foundation, we have recently established a dedicated clinical research program with research embedded in care, the *Rossy PSP Centre*. We present here the design and operationalization of the program for the diagnosis, long-term follow-up, and development of a research cohort with careful phenotyping of patients with probable PSP and CBS for improved clinical-pathological correlations. Additional goals are the possible description of new phenotypes and the discovery of new fluid and tissue biomarkers with the support of postmortem assessment of patients enrolled in the research program.

Methods

Rossy PSP Centre's Program Design

Aim and Mission

A Mission statement for the Rossy PSP Centre at the Toronto Western Hospital (TWH), University Health Network (UHN), was formulated: To establish a world-class clinical and basic research program in PSP and related Atypical Parkinsonian disorders with the primary goal of advancing the understanding of these complex neurodegenerative diseases and eventually contributing to the development of effective disease-modifying therapies. Critical components of the program are the provision of best available care and embedding research in clinical care, availing patients of the latest research studies including clinical trials of experimental therapies, the recruitment of bright young investigators to the field as fellows in training and an open and sharing approach to collaborative research with the internationally renowned members of the Program's Scientific Advisory Board (SAB) and other experts throughout the world.

In terms of program design, a Scientific Advisory Committee and an external advisor have proven crucial to shape the consistency of clinical and research goals and their integration with similar past and ongoing international initiatives. Members of the SAB and external advisors include the following experts: A. Boxer (US), L. Golbe (US), G. Hoglinger (Germany), I. Litvan (US), I. Mackenzie (Canada), H. Morris (UK), and M. Samuels (US). Recently, the program has been granted Center of Care status by the CurePSP Foundation.

Goals and Design

The program's clinical goal is to provide diagnostic and management recommendations to the patient, the family, and to the referring physician. In case the patient is under the care of a general neurologist or other movement disorders/behavioral neurology specialist, the program encourages the patient to retain this care while providing recommendations on treatment and referrals to additional professionals required from the allied-health team (i.e., speech/language pathologists, occupational therapy, physiotherapy, urology, and other pertinent medical specialties). The program's scientific goal is to conduct a prospective, longitudinal observational study of the clinical presentation and progression of PSP and other possible tauopathies with deep phenotyping of patients using a variety of clinical assessments, imaging studies (magnetic resonance imaging (MRI), positron emission tomography) and biological samples (e.g., blood, saliva, skin biopsy and skin oil, cerebrospinal fluid (CSF)). The visit schedule with the list of scales and questionnaires administered are presented in Table 1. Funding for the Rossy Centre was received in 2019, and the clinical arm of the program was initiated in October of that year (following hiring of a fellow, research assistant, and research coordinator). In consultation with other programs in Europe and the United States, the faculty established the formal clinical

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press

Table 1: Visit schedule with the list of scales and questionnaires administered

	Initial visit	6 months of follow-up	12 months of follow-up
Intake history form	×		
Follow-up history intake form		×	×
Review of medication	×	×	×
Health history assessment	×		
Full neurological exam	×		
Focused neurological exam		×	×
ARTFL LEFFTDS[33] clinical phenotype checklist	×	×	×
PSP clinical features[5]	×	×	×
PSP clinical deficits scale[34]	×	×	×
MDS-UPDRS I–IV[35]	×	×	×
PSP rating scale[36]	×	×	×
MOCA (v 7.1–7.3)[37]	×	×	
CGI-severity	×	×	×
CGI-change		×	×
Family history	×		
Demographics	×		
Epworth sleepiness scale[38]	×	×	×
Clinical Dementia Rating scale[39]	×	×	×
Geriatric depression rating scale[40]	×		×
Hamilton anxiety scale[41]	×		×
Neuropsychiatric inventory[42]	×	×	×
Social norms questionnaire	×		×
Schwab and England	×	×	×
TorCA[43]	×		×
PDQ-39[44]	×	×	×
PSP-QOL[45]	×	×	×
EQ-5D-3L[46]	×	×	×
CBFS[47]	×	×	×
RSMS[48]	×	×	×
Zarit caregiver[49]	×	×	×
Exposure and risk questionnaire[50]	×	×	×

ARTFL, Advancing Research and Treatment in Frontotemporal Lobar Degeneration; LEFFTDS, Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's disease Rating Scale; MoCA, Montreal Cognitive Assessment; CGI, clinical global impression; TorCA, Toronto Cognitive Assessment; PDQ, Parkinson's disease questionnaire; EQ-5D-3L, EuroQoL, 5-dimension 3 levels; CBS, corticobasal syndrome; RSMS, The Revised Self-Monitoring Scale.

evaluation tools/protocols during the planning phases and applied these immediately on initial patient intakes using paper documentation while plans were being made for the electronic database. The final choice of the database vendor was made over the first year of the clinical program, and once this was finalized, all the clinical data were subsequently entered. In parallel with the clinical assessments and care provided in the program, research ethics board submissions were made for the ongoing use of the clinical data for research purposes as well as collection of biological samples for a variety of research purposes including biomarkers and genetics. The time required from the initial planning stages to the current fully functioning clinical program has been approximately 2.5 years.

Clinical Assessments

Initial visits have a duration of 120–180 minutes including a first clinical assessment by a neurology fellow, a discussion with the faculty physician, and a final encounter/interview with the research coordinator where the scheduling of further appointments and completion of additional evaluations are done. Follow-up visits (between 90 and 120 minutes) are held every 6 months during the first year and then every 12 months. Their main goal is the collection of clinical data regarding the progression of the disease. As part of follow-up, a virtual interview is held by the research assistant (see below Pre-clinical interview and questionnaires). Clinical data collections have been chosen to harmonize with those obtained by other large consortia on PSP to facilitate data sharing.

The clinical diagnosis is made by application of the MDS-PSP criteria,[5] and clinical features are documented in specific forms as well as the primary, secondary, and tertiary most likely diagnoses together with the clinician's confidence level in each of these (percentage). The flow chart presented in Figure 1 shows the path of each patient from referral to the program through follow-up options and inclusion in different clinical research opportunities offered.

Pre-clinical Interview and Questionnaires

The MDS-UPDRS part II, Clinical Dementia Rating scale, and the Epworth sleepiness scale are assessed virtually in a pre-clinical meeting with patient and relative. In addition to these, scales of quality of life, behavioral symptoms, and information about family history, previous medication use, and occupational exposures are collected during this visit (see Table 1).

Biobanking for Detection and Development of Biomarkers Biofluid Specimen and Skin Biopsy

All patients are asked to participate in biobanking, which includes blood, saliva, skin (3–5 mm punch biopsies of cervical skin), and cerebrospinal fluid.

Genomic Analyses

PSP is genetically heterogeneous; however, this has been investigated in only a few studies mainly limited to cohorts of European ancestry. The strongest PSP-association signal is reported for variants in *MAPT* mapped to the inversion region linked to the H1/H2 tau-haplotype.[9] Therefore, all study participants are assessed for H1/H2 haplotype. Notably, genome-wide association studies of Parkinson's disease (PD) have also detected a highly significant association with the H1-haplotype of *MAPT*,[10,11] pointing to an overlap in disease mechanisms between PD and PSP (also clinically evident in PSP-P patients). Thus, study participants are also assessed for mutations in PD-related genes. Genetically characterized autopsy tissues could reveal new gene candidates derived from the neuropathologically well-characterized cases. Hence, our priority is to start with a genetic study of pathologically confirmed cases of PSP and other tauopathies and contrast these with other neurodegenerative disorders such as PD, multiple system atrophy, dementia with Lewy bodies, and Alzheimer's disease. During the first 2 years of the Rossy

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press

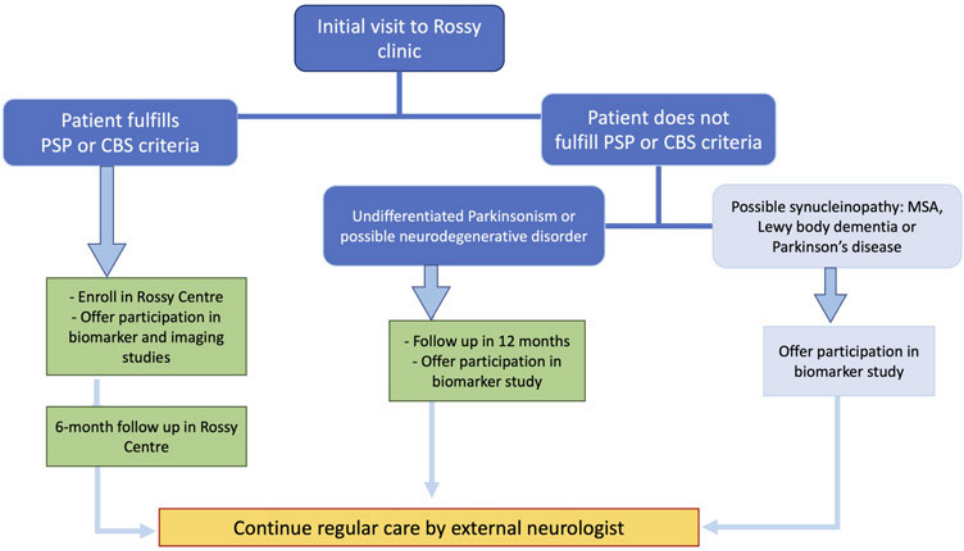


Figure 1: Patient's path through clinical care and research within the Rossy Program.

program, we generated a DNA collection from 384 well-characterized autopsy cases (collected before the establishment of the Rossy Centre). For the ongoing genetic analysis of this brain cohort, we selected the most modern genome-wide Illumina array tailored to study neurological diseases (GDA-NeuroBooster Bead Chip 8+v1.0). Specifically, the Neuro Booster array is based on the global diversity array backbone that provides genotypes for about two million variants (https://www.illumina.com/products/by-type/microarray-kits/infinium-global-diversity.html) including up to 95,000 custom content variants relevant to neurological disease (https://github.com/GP2code/Neuro_Booster_Array). Keeping in mind that novel genetic variations cannot be detected by the Neuro Booster array, we have also established a collaboration with Dr. Z. Gan-Or from McGill University (Montreal, Canada) who is currently genotyping our brain DNA collection using next-generation targeted sequencing of 51 parkinsonism-related genes, including the *MAPT* locus. In addition to these prioritized genetic studies, we will also be conducting epigenetic studies given the influence of DNA methylation (DNAm) at CpG-sites as a key epigenetic regulator of gene expression that can influence clinical presentation, including age of onset and rate of progression (see Discussion).

Brain Donation

The Rossy program has been associated with the launching of a more active neurodegenerative diseases brain donation program offered to all patients and families in the movement disorders and behavioral neurology programs at TWH. The option of brain donation is also discussed in a supportive, respectful fashion with all patients expressing an interest in considering medical assistance in dying (MAID) and this has permitted a very short death to autopsy time (typically 6 hours or less) that has made it possible to successfully culture neurons and glia for future research studies. We have established standardized protocols for handling, processing, staining, and storing of brains and necessary infrastructure supporting the neuropathology laboratory for the prospective brain collection. The strategy includes preparing formalin-fixed paraffin-embedded tissue samples from both hemispheres, including corresponding regions that are sampled for deep freezing (−80 Celsius degrees) for biochemical, seeding assay,[12] transcriptomic and genomic/epigenomic studies. In addition, the laboratory is prepared to process double or half hemispheric large blocks. In addition to detailed written neuropathology reports, computer-based data collection comprises a detailed diagnostic sheet and an extensive evaluation sheet to document various pathologies including immunoreactivities using immunostaining for neurodegenerative disease-related proteins, the latter used to generate heat maps of pathologies.[13,14] Establishment of post-mortem MRI imaging has also been organized. Our approach to brain sampling and evaluation will be reported in a separate paper. Finally, we have established a preliminary agreement with CurePSP to fund the harvesting, transportation, and evaluation of PSP brains from other centers in Canada.

Staff Working at the Rossy Program

The human resources in the program include one program coordinator, one research assistant, and at least five physicians with neurology specialty: three movement disorders sub-specialists, one behavioral-cognitive sub-specialist, one neuropathology specialist (also movement disorders neurology specialist) and a designated Rossy movement disorders fellow as well as other movement disorders/behavioral neurology fellows seeing patients in the program on a rotational basis.

Ethical Review and Approval

The entire clinical and research protocol was approved by the Research Ethics Board of the UHN, and patients and caregivers sign an approved informed consent form to participate in research within the Rossy program.

Data Collection and Storage

The information collected at each visit is uploaded into the DAta Driven Outcome System (DADOS) digitized platform (Techna Institute, UHN, Toronto, Canada). DADOS is a platform used by several research clinics affiliated to the UHN. This provides a set of digitized forms organized in a structure of folders per visit and per type of administration (self-answered by patient/caregiver, administered by research coordinator or by physician). They can be accessed online by the staff of the program who are given a password and username. Pictures of source data can be scanned and uploaded. Collated data can be analyzed at any time. Data storage

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press

Table 2: Results of the screened patients' demographics, disease features, and phenotypes

Age mean in years (SD)	71 (7.4)
Female %	41
Mean disease duration	5
Mean age of symptom onset (SD)	66.8 (7)
Clinical predominant phenotype (*n*)*	
Richardson's syndrome (RS)	91
Corticobasal syndrome	19
PSP-Progressive Gait Freezing	8
Possible speech/language variant (SL)	1
PSP-Frontal predominant	1
PSP-Parkinsonism predominant	2
Motor neuron disease (PLS pattern)	1
Additional clinical phenotypes (*n*)	
Possible speech/language variant (SL)	7
PSP-Frontal predominant	4
Predominant ocular motor-PSP	3
PSPS-RS	33.36 (14)
MDS-UPDRS-III	39.25 (13)
Clinical Global Impression, severity	3.10 (0.9)

SD, standard deviation; Age, disease duration and age of symptoms onset in years; PLS, primary lateral sclerosis; PSP-RS, progressive supranuclear palsy rating scale; MDS-UPDRS-III, Movement disorders society endorsed Unified Parkinson Disease rating scale, part 3.
*Twenty-seven patients fulfilled criteria for more than one variant (listed as primary and secondary phenotypes), and all of them later developed Richardson syndrome: 10 patients with CBS manifested additional RS or SL/progressive aphasia variants, 15 patients had a non-Richardson and Richardson phenotype, and two patients fulfilled criteria for three variants.

in DADOS uses different formats including text, numeric, image counts with a password-protected access. The actual programmed PSP DADOS database will be shared with other academic clinics wishing to establish a comparable clinical research program. Use of the DADOS platform will facilitate sharing of relevant clinical assessments, environmental history, and cognitive-behavioral symptoms data to promote data collaboration with similar academic clinics, clinical registries, and research initiatives on PSP. Responsibility of protecting patient data throughout any sharing process will be assumed by the PI/applicant of the proposal/request.

Results

Referrals have been accepted, both from external and internal physicians to UHN. The combined pool of internal referrals came from the Movement Disorders Clinic that has followed about ~300 patients with PSP since 2011 and the Memory Neurology Clinic of the TWH with another ~200 patients in follow-up. However, considering the median survival of 7.8 years and a mean disease duration at the time of referral of about 5.6 years, many of these patients were either too advanced to attend the clinic or lost to follow-up by the time the Rossy program launched, resulting in internal referrals involving patients seen for the first time after 2016. In 27 months, between October 2019 and December 2021, a total of 132 patients were screened. Criteria for clinical PSP were fulfilled by 110 patients. Details on the number of follow-up visits

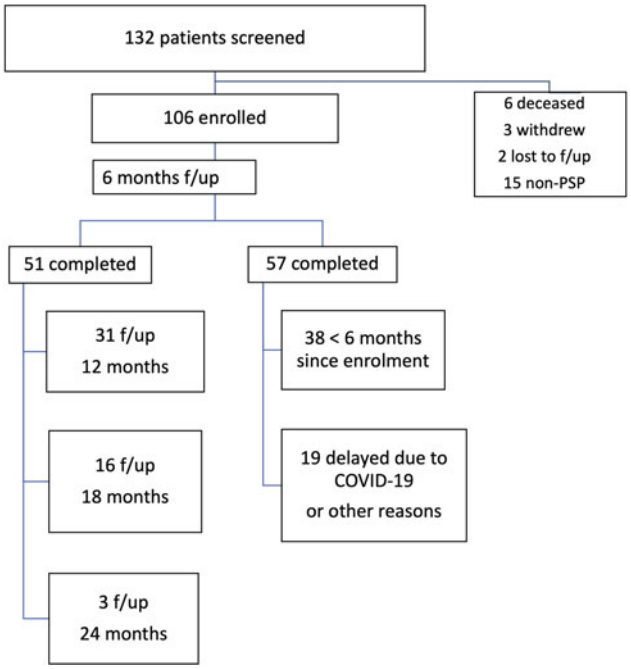


Figure 2: Enrollment and follow-up visits.

and excluded patients are provided in Figure 2. Demographics, clinical features, and predominant phenotype of the probable PSP are shown in Table 2. Initial dominant complaint at presentation was postural instability and falls in 45%, cognitive-behavioral changes in 22%, Parkinsonism in 9%, and tremor or myoclonus in 7%, as well as oculomotor abnormalities in 7% and bulbar symptoms in 7%.

In terms of management, diverse symptomatic treatments were attempted for motor and non-motor symptoms. Levodopa use was documented in 74 patients (mean dose 500–600 mg per day) and amantadine in 54 patients (mean dose 250 mg per day). Response was defined based on patient's report as (i) mild subjective benefit in either balance, stiffness, or general wellbeing including more alertness; (ii) moderate benefit of these features but no impact in daily living functionality; (iii) considerable improvement in balance, stiffness, gait, or cognition and with a relevant impact in daily living functionality; (iv) no improvement or worsening of balance or overall function. Moderate and persistent subjective response to levodopa was recorded in less than 25% of the patients without a clear change in motor signs on examination. In those who reported response to amantadine, it was generally mild (less than 40% benefit in motor and cognitive symptoms) and with a duration shorter than 2 months. In addition, botulinum toxin injections were indicated for the treatment of dystonia in patients with disabling blepharospasm/eyelid-opening apraxia (10 patients, response rate 70%), limb dystonia with pain or hygiene limitations in upper extremities (3 patients, response rate 100%), or foot dystonia interfering with walking (3 patients, response rate 33%). Sialorrhea was treated with atropine 1% drops, ipratropium bromide 0.03% spray, or botulinum toxin injections to the parotid and submandibular salivary glands (seven patients, response rate 85%).

Treatment of non-motor symptoms included the management of mood/behavioral and sleep issues. For these, pharmacological measures included selective-serotonin reuptake inhibitors drugs for symptoms of depression, anxiety, and emotional lability and

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press

irritability in about 40% of patients, and agents such as melatonin, and mirtazapine for insomnia in 14%. One patient with disabling pseudobulbar affect obtained marked benefit from the combination of dextromethorphan and quinidine prepared by a local pharmacy. Non-pharmacological treatment included periodic referral to allied-health specialists: speech/language pathology every 12 months in the 91 patients with dysphagia, and for communication issues related to dysarthria or language impairment; occupational therapy in 91 patients to address home safety and walking aid recommendations; physiotherapy for deconditioning, falls prevention and for range of motion in the case of immobility. Palliative care referral for patients in later stages of the disease is done by the social worker of the Memory clinic (five done until this time) or through the patient's family physician.

Since the clinic was opened in Oct 2019, 7 of the 110 assessed patients have died; all of them have donated their brains for research including three following medical assistance in dying (MAID). This represents 10% of the total of 70 brain donations received to the whole Brain donation program during that time.

The Rossy Centre has a policy completely supportive of data sharing whenever requested by centers with shared and aligned research goals and reasonable justification is provided. All data collected and analyzed will be treated as confidential and the potential identifying information removed and anonymized. Standard operating procedures will be instated for each external data request and signature of a data sharing agreement between institutions.

Discussion

This article summarizes the design and first 2 years of experience of the Rossy PSP Centre at the Movement Disorders Clinic of the TWH. The goals of the program include improving the diagnosis, treatment, and quality of life of people with PSP and related disorders and to advance both clinical and basic research in this group of inexorably progressive and inevitably fatal neurodegenerative diseases. A total of 132 patients have been screened in 27 months, and about a hundred have been enrolled with various clinical presentations fulfilling MDS criteria of possible or probable PSP, and over 50% have already completed a first follow-up visit despite the intervening COVID pandemic. It is important to note that during this time, several research initiatives derived from this cohort have been conducted including epidemiological study of the cohort, the development of reliable diagnostic biomarkers,[15] testing and validation of current diagnostic criteria, evaluation of a virtual version of the PSP Rating Scale,[16] and the description of a "protracted course PSP."[13] An evaluation of the response to pharmacologic and non-pharmacologic treatments is under preparation for peer-reviewed publication.

The strengths of the program are its design utilizing the most recent clinical criteria and the deep phenotyping of the patients. An important goal is that increasingly larger numbers of patients will be seen at earlier disease stages with a broader representation of PSP variants. This is an important goal since a strong bias towards over-representation of the most common Richardson's syndrome (RS) variant exists in previous clinical and clinical-pathological studies.[3] For example, RS accounted for 53% of an initial series that clustered symptoms in two variants (RS and PSP-Parkinsonism)[17] but a series containing patients with the six currently described variants showed an incidence of only 24% of RS at presentation.[4] Although our preliminary results show that 91 patients fulfilled criteria of a Richardson syndrome, this number includes those patients who developed this even after having a different presentation at onset. Following the recommendations of use of the MDS-PSP criteria,[18] RS is the most prevalent and with highest positive predictive value ("probable" PSP) compared to other phenotypes such as speech/language variant at onset. To mitigate for this finding, the Rossy program includes careful historical documentation of primary, secondary, and tertiary clinical phenotypes for each patient. Table 1 shows the frequency of the secondary phenotypes; many cases did not start with a RS but, as is typically the case, later evolved to this but before the initial visit to the Rossy program. This decrease in phenotypic diversity has been reported with other clinical and pathologically confirmed cohorts.[4,19] Further attempts to increase a broader representation of PSP variants include screening of all referrals to our movement disorders and behavioral neurology programs for possible PSP variants (e.g., behavioral variant frontotemporal dementia, non-fluent primary progressive aphasia, CBS, primary freezing of gait), and these are directed to the Rossy program for initial assessment. Finally, we expect that as the general awareness of this new program in the neurologic community increases this will enhance referral of a broader clinical profile.

The longitudinally collected data will provide insight into the diagnosis and management of PSP and allow the creation of trial-ready cohorts of patients to be fast-tracked to participate in future trials of experimental disease-modifying therapies. For example, the variability in clinical presentation of PSP could be attributed to genetic polymorphisms in *SLC2A13*[20] and *TRIM11* loci,[21] in agreement with our recent study suggesting that a longer PSP duration might be related to homozygosity for the rs564309-C allele at *TRIM11*.[13] The catalog of significant findings by genome-wide association studies[22] includes 35 common variants, the most consistent being the association of PSP with the *MAPT* gene variant rs807072[9] and the H1/H2 tau-haplotype. Genetic investigations of autopsy cases have been prioritized during the first 2 years of the program, and in a second stage, epigenetic factors such as DNA methylation regulating gene expression and potential prognostic biomarker[23,24] will be studied in variants of PSP as we have tested in other neurodegenerative diseases.[25,26] The results of these studies may assist in explaining clinical heterogeneity in PSP and may provide important considerations in the design of future disease-modifying clinical trials.

The new staging of pathology of PSP and the continuous search for diagnostic biomarkers (in blood and plasma, skin, and CSF), including seeding amplification assays,[15,27] exosomes derived from neurons and glia,[28–31] as well as studies of tau using cryo-EM,[32] guarantee advances in our knowledge over the next few years and will contribute to the development of biomarkers for therapy trials. The brain donation program provides feedback for the clinical phenotyping, including understanding protracted course[13] and rapidly progressive forms of PSP, allows comparative studies with neuroimaging, and provides an invaluable resource for tissue-based research in PSP.

Acknowledgements. The authors would like to thank the Rossy Foundation and family for their generous support and the patients and their families involved in the program. The funding has supported a dedicated fellow, full-time research assistant, part-time research coordinator, programming, and ongoing support of the database as well as ongoing clinical and basic research projects. Initial funding has been provided for a 10-year period.

Statement of Authorship. B.C.: Data curation, Writing-Original draft preparation.

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press

S.F.: Conceptualization; Supervision; Data curation, Writing – Reviewing and Editing.

M.C.T.: Conceptualization; Supervision; Data curation, Writing – Reviewing and Editing.

E.R.: Conceptualization; Writing – Reviewing and Editing.

J.A.: Data curation, Writing – Reviewing and Editing.

P.B.: Data curation, Writing – Reviewing and Editing.

G.G.K.: Conceptualization; Supervision; Data curation, Writing – Reviewing and Editing.

A.E.L.: Conceptualization; Supervision; Data curation, Writing – Reviewing and Editing; Funding acquisition.

Conflicts of Interest. The authors deny any conflict of interest regarding the data described in this article.

Disclosures. Dr. Lang has served as an advisor for AbbVie, AFFiRis, Alector, Amylyx, Biogen, BioAdvance, BlueRock, BMS, Denali, Janssen, Jazz, Lilly, Novartis, Paladin, Retrophin, Roche, Sun Pharma, and UCB; received honoraria from Sun Pharma, AbbVie and Sunovion; received grants from Brain Canada, Canadian Institutes of Health Research, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, Parkinson Foundation, Parkinson Canada, and W. Garfield Weston Foundation; received publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press. Dr. Tartaglia has served as an advisor for Denali and received grants from the Canadian Institutes of Health Research, and National Institute of Neurological Disorders and Stroke. Dr. Fox receives clinic support from the Edmond J Safra Foundation for Parkinson's Research; Parkinson Foundation; research funding from Michael J Fox Foundation for Parkinson Research, NIH (Dystonia Coalition); Parkinson Canada; honoraria from the International Parkinson and Movement Disorder Society; consultancy/speaker fees from Alexion, Bial, Pharma 2B, Sunovion, and Paladin. Royalties from Oxford University Press. Dr. Kovacs receives funding from the Rossy Family Foundation and Edmond Safra Philanthropic fund; received funding from Michael J. Fox Foundation, Parkinson Canada and Canada Foundation for Innovation; publishing royalties Wiley, Cambridge University Press, and Elsevier; previously received consulting fees from Biogen; declares a shared patent for 5G4 synuclein antibody with Roboscreen GmbH. The authors BC, PB, JA, and ER have nothing to declare.

References

1. Kovacs GG, Lukic MJ, Irwin DJ, et al. Distribution patterns of tau pathology in progressive supranuclear palsy. Acta Neuropathol. 2020;140 :99–119.
2. Giagkou N, Höglinger GU, Stamelou M. Progressive supranuclear palsy. Int Rev Neurobiol. 2019;149:49–86.
3. Golbe LI. A clinician's guide to progressive supranuclear palsy. New Brunswick, NJ: Rutgers University Press; 2018.
4. Respondek G, Kurz C, Arzberger T, et al. Which ante mortem clinical features predict progressive supranuclear palsy pathology? Mov Disord. 2017;32:995–1005.
5. Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord. 2017;32:853–64.
6. Ali F, Botha H, Whitwell JL, Josephs KA. Utility of the Movement Disorders Society Criteria for progressive supranuclear palsy in clinical practice. Mov Disord Clin Pract. 2019;6:436–9.
7. Saranza GM, Whitwell JL, Kovacs GG, Lang AE. Corticobasal degeneration. Int Rev Neurobiol. 2019;149:87–136.
8. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013;80:496–503.
9. Hoglinger GU, Melhem NM, Dickson DW, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011;43:699–705.
10. Spencer CC, Plagnol V, Strange A, et al. Dissection of the genetics of Parkinson's disease identifies an additional association 5' of SNCA and multiple associated haplotypes at 17q21. Hum Mol Genet. 2011;20:345–53.
11. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet. 2014;46:989–93.
12. Martinez-Valbuena I, Visanji NP, Kim A, et al. Alpha-synuclein seeding shows a wide heterogeneity in multiple system atrophy. Transl Neurodegener. 2022;11:7.
13. Couto B, Martinez-Valbuena I, Lee S, et al. Protracted course progressive supranuclear palsy. Eur J Neurol. 2022;29:2220–31. DOI 10.1111/ene.15346.
14. Di Luca DG, Slow EJ, Martinez-Valbuena I, Lang AE, Kovacs GG. Dream enactment behavior disorder associated with pallido-nigro-luysian degeneration and tau proteinopathy. Mov Disord Clin Pract. 2021;8:594–9.
15. Martinez-Valbuena I, Visanji NP, Olszewska DA, et al. Combining skin α-synuclein real-time quaking-induced conversion and circulating neurofilament light chain to distinguish multiple system atrophy and Parkinson's disease. Mov Disord. 2022;37:648–50.
16. Wills AM, Pantelyat A, Espay A, et al. A modified progressive supranuclear palsy rating scale for virtual assessments. Mov Disord. 2022;37:1265–71.
17. Williams DR, Holton JL, Strand C, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. Brain. 2007;130:1566–76.
18. Grimm MJ, Respondek G, Stamelou M, et al. How to apply the movement disorder society criteria for diagnosis of progressive supranuclear palsy. Mov Disord. 2019;34:1228–32.
19. Sánchez-Ruiz de Gordoa J, Zelaya V, Tellechea-Aramburo P, et al. Is the phenotype designation by PSP-MDS criteria stable throughout the disease course and consistent with tau distribution? Front Neurol. 2022;13:827338.
20. Jabbari E, Koga S, Valentino RR, et al. Genetic determinants of survival in progressive supranuclear palsy: a genome-wide association study. Lancet Neurol. 2021;20:107–16.
21. Jabbari E, Woodside J, Tan MMX, et al. Variation at the TRIM11 locus modifies progressive supranuclear palsy phenotype. Ann Neurol. 2018;84: 485–96.
22. Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res. 2019;47:D1005–D12.
23. Xi Z, Zhang M, Bruni AC, et al. The C9orf72 repeat expansion itself is methylated in ALS and FTLD patients. Acta Neuropathol. 2015;129:715–27.
24. Zhang M, Ferrari R, Tartaglia MC, et al. A C6orf10/LOC101929163 locus is associated with age of onset in C9orf72 carriers. Brain J Neurol. 2018;141: 2895–907.
25. Zhang M, McKeever PM, Xi Z, et al. DNA methylation age acceleration is associated with ALS age of onset and survival. Acta Neuropathol. 2020;139: 943–6.
26. Zhang M, Tartaglia MC, Moreno D, et al. DNA methylation age-acceleration is associated with disease duration and age at onset in C9orf72 patients. Acta Neuropathol. 2017;134:271–9.
27. Tarutani A, Miyata H, Nonaka T, et al. Human tauopathy-derived tau strains determine the substrates recruited for templated amplification. Brain. 2021;144:2333–48.
28. Ngolab J, Trinh I, Rockenstein E, et al. Brain-derived exosomes from dementia with Lewy bodies propagate α-synuclein pathology. Acta Neuropathol Commun. 2017;5:46.
29. Jiang C, Hopfner F, Katsikoudi A, et al. Serum neuronal exosomes predict and differentiate Parkinson's disease from atypical parkinsonism. J Neurol Neurosurg Psychiatry. 2020;91:720–9.
30. Ohmichi T, Mitsuhashi M, Tatebe H, Kasai T, Ali El-Agnaf OM, Tokuda T. Quantification of brain-derived extracellular vesicles in plasma as a biomarker to diagnose Parkinson's and related diseases. Parkinsonism Relat Disord. 2019;61:82–7.
31. Stuendl A, Kraus T, Chatterjee M, et al. α-synuclein in plasma-derived extracellular vesicles is a potential biomarker of Parkinson's disease. Mov Disord. 2021;36:2508–18.
32. Shi Y, Zhang W, Yang Y, et al. Structure-based classification of tauopathies. Nature. 2021;598:359–63.
33. Boeve B, Bove J, Brannelly P, et al. The longitudinal evaluation of familial frontotemporal dementia subjects protocol: framework and methodology. Alzheimers Dement. 2020;16:22–36.

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press

34. Piot I, Schweyer K, Respondek G, et al. The progressive supranuclear palsy clinical deficits scale. Mov Disord. 2020;35:650–61.
35. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129–70.
36. Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain. 2007;130:1552–65.
37. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
38. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540–5.
39. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull. 1988;24:637–9.
40. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17:37–49.
41. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50–5.
42. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308–14.
43. Freedman M, Leach L, Carmela Tartaglia M, et al. The Toronto Cognitive Assessment (TorCA): normative data and validation to detect amnestic mild cognitive impairment. Alzheimers Res Ther. 2018;10:65.
44. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. J Neurol. 1998;245 Suppl 1: S10–4.
45. Schrag A, Selai C, Quinn N, et al. Measuring quality of life in PSP: the PSP-QoL. Neurology. 2006;67:39–44.
46. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199–208.
47. Lang AE, Stebbins GT, Wang P, et al. The Cortical Basal ganglia Functional Scale (CBFS): development and preliminary validation. Parkinsonism Relat Disord. 2020;79:121–6.
48. Toller G, Ranasinghe K, Cobigo Y, et al. Revised Self-Monitoring Scale: a potential endpoint for frontotemporal dementia clinical trials. Neurology. 2020;94:e2384–e95.
49. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980;20:649–55.
50. Grinnon ST, Miller K, Marler JR, Lu Y, Stout A, Odenkirchen J, Kunitz S. National Institute of Neurological Disorders and Stroke Common Data Element Project - approach and methods. Clin Trials. 2012;9(3):322–9.

https://doi.org/10.1017/cjn.2022.332 Published online by Cambridge University Press