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Monash-Alfred protocol for assessment of atypical parkinsonian syndromes (MAP-APS)

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ABSTRACT:

Introduction Atypical parkinsonian syndromes (APS) are rare neurodegenerative syndromes for which parkinsonism is one significant feature. APS includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal syndrome (CBS). The diagnosis of APS remains reliant on clinical features with no available diagnostic or prognostic biomarker. Clinical scales remain the gold standard assessment measures in clinical trials and research. The lack of standardised approach for research cohorts has contributed to shortcomings in disease understanding and limits collaboration between researchers. The primary objectives of this study are to (1) establish an assessment protocol for parkinsonian syndromes and (2) to implement it at a single site to establish the viability and utility of populating a clinical and biological databank of patients with APS.

Methods The Monash Alfred Protocol for Assessment of APS was devised by expert consensus within a broad multidisciplinary team. Eligible patients are diagnosed as possible or probable PSP, MSA or CBS by a consultant neurologist with expertise in movement disorders. Participants will be assessed at recruitment and then annually for up to 3 years; individuals within 5 years of index symptom onset will also undergo a once-off 6-month assessment.

Ethics and dissemination Each participant or their legally authorised representative will provide informed written consent prior to commencement of the study. Data will be stored on a locally hosted Research Electronic Data Capture database.

Trial registration number Australian New Zealand Clinical Trials Registry (ANZCTN 12622000923763).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atypical parkinsonian syndromes (APS) are a heterogenous group of disorders sharing parkinsonism as a core clinical feature. There is no widely agreed on assessment protocol for clinical research in APS.

WHAT THIS STUDY ADDS

⇒ Monash Alfred Protocol for Assessment of APS proposes a standardised set of routinely used clinical scales for longitudinal assessment in APS which is meaningful enough for deep clinical phenotyping and biomarker discovery but succinct enough to run in parallel to routine clinical assessment with minimal additional resource requirements.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This protocol will assist clinician researchers in establishing cohorts of patients with APS. Furthermore, standardisation of data collection will facilitate data sharing and collaboration between research groups enhancing research output in this area.

INTRODUCTION

Parkinsonism is a common clinical phenotype in neurology, incorporating extrapyramidal rigidity, decrementing bradykinesia and rest tremor. Causative aetiologies include idiopathic Parkinson disease (PD), dementia with Lewy bodies (DLB), vascular parkinsonism and 'atypical parkinsonian syndromes' (APS). APS are rare neurodegenerative syndromes for which parkinsonism is one significant feature, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal syndrome (CBS).[1] Each of these conditions are distinct with respect to the associated proteinopathy, clinical features and clinical trajectory. Disease-modifying therapies are not currently available for any of these conditions. Challenges in providing accurate and timely diagnosis, and a lack of sensitive disease monitoring instruments, impact clinical care and research progress in these populations.

The distinction and diagnosis of APS is primarily reliant on clinical features,[1] without readily available ancillary testing in clinical practice. Crucially, multiple years of manifest symptoms and clinical follow-up are often required before an APS diagnosis can be made due to the poor sensitivity and specificity of current diagnostic criteria to detect and differentiate diseases in the earliest stages.[2] Early diagnostic confidence is paramount to

allow potential therapeutics to be used both in trials and clinical practice early in the disease course. Ameliorating uncertainty could also improve the experience during a patient's diagnostic odyssey. Lastly, substantial clinical heterogeneity is evident within each APS leading to the differentiation of a number of subphenotypes with prognostic implications. Effective and efficient understanding of an individual patient's clinical profile is crucial to delivering best care.

Clinical scales are the current gold-standard trial outcome measures but are limited in their sensitivity to subtle clinical changes and suffer from rating reliability issues.[3 4] Current trials thus require large sample sizes and extended trial periods, which increase cost and reduce feasibility of studies. Although research and understanding of this group of disorders continues to expand, these issues remain critical unmet needs. Several limitations of current research practise have likely contributed to this. First, research within APS is often limited to small cohorts or case series, with reliance on retrospective disease rating via medical record review or similar means.[5] Furthermore, the relative rarity, heterogeneity and evolving diagnostic criteria have contributed to differences in study populations over time.[5] Compounding the issue of data uniformity is the diversity of scales, questionnaires and assessments used between research groups. Standardised approaches to acquisition of data and implementation of a minimum data set with systematic serial data collection parallel to clinical care would address many of these challenges.

We are unaware of any publicly available registry protocols for prospective cohort studies in APS. Numerous protocols, such as the Parkinson Progressive Marker Initiative[6] exist for longitudinal disease assessment and deep clinical phenotyping of idiopathic PD. However, these tend to be resource and time intensive, and focus specifically on PD. Development, distribution and uptake of a standardised protocol that is pragmatic and minimises resource demand, while providing sufficient data to perform deep clinical phenotyping and detect change over time, will benefit research output, clinical monitoring and further disease understanding in this patient population.

The Monash-Alfred Protocol for Assessment of Parkinsonism (MAP-APS) establishes a minimum set of clinical, cognitive, patient-reported and biosampling procedures. The protocol will aid clinician-researchers to establish standardised research databases, aggregate and share data and harmonise research efforts between groups. We have developed this protocol with an emphasis on resource and time efficiency so that it can be administered parallel to routine clinical assessment with minimal additional resource requirement.

PRIMARY OBJECTIVES

1. Establish an atypical parkinsonian syndrome research protocol that:
   a. Has the potential to detect clinically meaningful change over time using familiar clinical assessments.
   b. Contains only essential biological samples.
   c. Is pragmatic and minimises time and resource allocation.
   d. Is minimally burdensome on caregivers and patients with an expected level of disability.
2. Implement the protocol at a single-site to establish the viability and utility of populating a clinical and biological databank of APS patients with minimal resource allocation.

METHODS

Overview

The MAP-APS was developed by consensus among movement disorder clinicians and researchers at the Alfred Hospital and Monash University (Melbourne, Australia) with qualifications in neurology, radiology, psychiatry, neuropsychology, cohort and clinical trial design and/or biobanking. The protocol uses assessments that are common in clinical contexts, and which can typically be administered in full by a neurology trainee or divided between a neurology trainee and a research nurse (or equivalent). The full battery requires approximately 2 hours to administer the initial assessment, exclusive of MRI, which can be undertaken in parallel to a standard clinical follow-up.

Our single-site validation study will recruit from the Movement Disorders Service at Alfred Health (Melbourne, Australia). Eligible patients are diagnosed as possible or probable PSP, MSA or CBS by a consultant neurologist with expertise in movement disorders. Participants will be assessed at recruitment and then annually for up to 3 years; individuals within 5 years of initial symptoms will also undergo a once-off 6-month assessment. Each participant or their legally authorised representative will provide informed written consent prior to commencement of the study. This study is registered with the Australian and New Zealand Clinical Trials Registry. Patient and public involvement was not sought for the design and initial implementation of this study.

SCHEDULE OF ASSESSMENTS (TABLE 1)

Demography and medical history

Patient demographic and sociodemographic data is collected at baseline. Key demographics include age, sex, height, weight, educational attainment and prior or current occupation. Family history of neurological illnesses is recorded at baseline. Comorbidities and clinical milestones are collected via clinical history, including admission to acute or subacute hospital, period of residential respite care or admission to permanent residential care facility in the last 6 months or from the previous study visit. Finally, home care supports are recorded at each study visit considering both informal (spouse, family,

Table 1 Schedule of activities

	Initial assessment	Follow-up
Consent	X	
General activities		
Demographics	X	
Sociodemographic information	X	
Family history	X	
Comorbid conditions	X	
Height/weight/body mass index	X	
Clinical milestones	X	
Current home supports	X	
Neurological and motor assessments		
Primary clinical diagnosis and subdiagnosis	X	X
Neurological examination	X	X
MDS-UPDRS section Ia and III	X	X
Relevant disease rating scale (PSP-RS, UMSARS, MDS-UPDRS-IV)	X	X
MDS-UPDRS section Ib and II	P	P
Hoehn and Yahr	X	X
Modified Rankin Scale	X	X
Historical features of diagnosis	X	
Falls history	X	X
Non-motor assessments		
Neuropsychiatric history	X	
Neuro-QoL depression	P	P
Neuro-QoL anxiety	P	P
Neuro-QoL cognitive function	P	P
Neuro-QoL behavioural control	P	P
EQ-5D	P	P
Cognitive battery		
MoCA	X	X
Frontal Assessment Battery	X	X
Categorical fluency (animals)	X	X
Treatment assessments		
Parkinson's disease specific medication	X	X
LEDD	X	X
Psychiatric medication history	X	X
Concomitant medication history	X	X
'Advanced' treatment consideration	X	
Bio-samples		
Research blood samples	X	X
MRI-brain	X	X

EQ-5D, European Quality of Life – 5 dimension; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society – Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment Battery; P, patient completed; PSP-RS, Progressive Supranuclear Palsy Rating Scale; UMSARS, Unified Multiple System Atrophy Rating Scale; X, investigator completed.

friends or other) and formal (local or federal funding) sources.Table 1

Neurological and motor assessments

Primary diagnosis is confirmed by neurological assessment and recorded on entry and at each subsequent study visit according to current diagnostic guidelines for PD, PSP, MSA and CBS.[7–10] Diagnostic certainty is recorded for PSP (two levels: possible and probable) and MSA (two levels: possible and probable) according to the same guidelines. Finally, a dominant phenotypic diagnosis for PSP (eg, PSP-Richardson syndrome, PSP-predominant parkinsonism, PSP-progressive gait freezing, PSP-CBS, PSP-predominant frontal presentation, PSP-predominant speech and language)[9 11] and for MSA (eg, MSA-parkinsonian or cerebellar) is recorded when possible, according to current diagnostic guidelines.

Neurological examination and motor assessment comprises the Movement Disorder Society – Unified Parkinson Disease Rating Scale (MDS-UPDRS) section III for each participant[12] and the relevant, validated clinical disease rating scale matched to diagnosis for PSP and CBS (Progressive Supranuclear Palsy Rating Scale; PSP-RS),[13] for MSA (Unified Multiple System Atrophy Rating Scale; UMSARS)[14] or for PD: MDS-UPDRS section IV.[12] In the event of a primary diagnosis being revised on a subsequent study visit (eg, from PSP to MSA) the relevant disease rating scale to current diagnosis will be employed. The inclusion of the MDS-UPDRS III for all patients yields standardised data while minimising additional time spent for physical examination when performed in conjunction with either the PSP-RS or UMSARS. Additional motor assessment includes MDS-UPDRS section Ib and II.[12] Clinician assessed functional status is measured using the Hoehn and Yahr Scale (which remains recommended by the International Parkinson and Movement Disorders Society and is used in clinical trials) and Modified Rankin Scale.[15 16]

Historical features of diagnosis are assessed via questionnaire and include the index symptom and its onset time, the time of diagnosis and occupational status at that time. Initial subjective response to levodopa is documented. A history of alpha-synuclein prodromal features including constipation, anosmia, rapid eye movement sleep behaviour disorder and depression or anxiety are documented at baseline only.[17] Finally, falls are assessed with clinical history at each visit. We document all near and actual falls in the preceding 6 months and if falls are present then the mechanism of falls. If the mechanism is freezing of gait, we further assess responsiveness to levodopa therapy via history.

Quality of life and neuropsychiatric status

Impact on activities of daily living is assessed with the MDS-UPDRS section 1a.[12] General function and quality of life is further assessed by the European Quality of Life, 5-dimension, 5-level questionnaire.[18] Neuropsychiatric history is assessed by clinical history noting previous and current diagnoses of depression, anxiety, psychosis, neurodevelopment or personality disorders. Current and former treatments include medical, psychological and other. Additional patient-reported outcome measures include Neuro-QoL V.1.0 short forms (eight items each) on depression, anxiety, emotional and behavioural

control and subjective cognition. Self-reported cognitive function is assessed with the MDS-UPDRS section 1a and Neuro-QoL V.2.0 short form on general cognitive function.[19]

Cognitive assessment

Cognitive function is objectively assessed on level 1 of the MDS taskforce definition for cognitive assessment[20] and is comprised of several screening tests, including the Montreal Cognitive Assessment (MoCA),[21] the Frontal Assessment Battery (FAB)[22] and categorical fluency (animals). Instrument selection considered the ability of these tests to delineate between underlying diagnoses of participants with parkinsonism.[23]

The MoCA is a short-form cognitive screening test commonly used in clinical practice that can be administered in 10 min. It is comprised of six components and scored 0–30 in totality, with lower scores indicating worse performance. It assesses multiple cognitive domains including executive function, memory, attention, language and abstraction yielding a good impression of global cognitive function.[21] Similarly, FAB is a short-form cognitive screening test commonly used in clinical practice and can be administered in 10 min. The FAB is composed of six subtests scored 0–3 with a total score range of 0–18 with higher scores indicating worse performance. Each subtest assesses executive functions.[22] Categorical fluency (animals) is a measure of verbal fluency. Participants are asked to list aloud items from a particular category in 60 s. Individual scores are calculated on the correct number of items within the chosen category.

Medication and treatment

Medication history is taken with a focus on three separate entities. First, current dopaminergic therapy is documented with the agent, dose and frequency of each. A levodopa daily equivalent dose is recorded. Neuropsychiatric medication history is taken for commonly used drug classes, including any previous exposure to dopaminergic antagonist medication. A concomitant medication history is documented at baseline and follow-up. Previous consideration for 'advanced' treatment options are documented which include deep brain stimulation or continuous levodopa infusion therapies (apomorphine or Duodopa).

Biological samples

Blood sampling is taken at each study visit for all participants. Collection includes three 8 mL EDTA tubes and one 8 mL serum separator tube (SST) with clot activator. One EDTA tube and SST are processed immediately after sampling via centrifugation according to standard practices and 500 µL aliquots of serum, plasma and buffy coat are stored in cryovials at −80°C. Whole blood is stored in EDTA tubes at −80°C. Archive quality DNA samples are extracted from these samples using Qiagen Gentra Puregene Blood Kit and standard practices.

MRI-brain scanning at 3-Telsa is performed on all participants without contraindication at each study assessment. Sequences include three-dimensional (3D) T1-weighted (1.0 mm isotropic resolution) and 3D FLAIR (1.0 mm isotropic), 2D transverse T2-weighted (0.5 mm in-plane, 4 mm slices), 2D diffusion-weighted (3-direction, b1000, 1.1×1.1×4.0 mm and 30-direction, b1000, 2.0 mm isotropic) and 3D susceptibility-weighted imaging (0.8×0.8×2.0 mm). Postmortem pathological diagnosis is desirable for all participants and should be obtained and recorded where possible.

Data availability, collection and quality

Study data is collected, managed and stored using a Research Electronic Data Capture (REDCap) database[24] hosted at Alfred Health, Melbourne, Australia. REDCap is a secure, web-based software platform designed to support data capture for research studies. The REDCap webtool is used during clinical assessments to input data directly assessment. This approach minimises the potential for both missing data and transcription error and promotes efficiency of data collection. Furthermore, patient-reported outcome measures are completed by patient and caregiver digitally and recorded directly to the database. REDCap allows for real time data-monitoring and coordinating participant follow-up assessments. A complete data dictionary will be made available by the authors on request in writing to the corresponding author.

CONCLUSION

We present a research protocol for use in patients with parkinsonian movement disorders for longitudinal cohort assessment. The protocol is short enough for implementation in clinical settings ancillary to standard clinical practise, but robust enough to provide meaningful data for longitudinal clinical monitoring and biomarker discovery in APS.

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Ethics approval This study involves human participants and was approved by Alfred Health Ethics Committee, 157/19. Participants gave informed consent to participate in the study before taking part.

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