Parkinsonism and Related Disorders 19 (2013) 436–440

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

# Disability in atypical parkinsonian syndromes is more dependent on memory dysfunction than motor symptoms

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ARTICLE INFO

*Article history:*
Received 24 October 2012
Received in revised form
12 December 2012
Accepted 8 January 2013

*Keywords:*
Corticobasal syndrome
Progressive supranuclear palsy
Primary progressive aphasia-nonfluent variant
Activities of daily living
Functional disability
Apraxia
Memory
Cognitive deficits
Behavioural changes

ABSTRACT

*Background:* There is a gap in the systematic description and investigation of functional disability in corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Additionally, the relations between disability, apraxia, cognitive and behavioural changes are not well understood in atypical parkinsonian syndromes.
*Methods:* Fifty patients were included in this study (CBS = 18; PSP = 11), including a subgroup of primary progressive aphasia-nonfluent variant (PPA-nfv = 21) who were used as a control group given the clinico-pathological overlap. Functional disability (basic and instrumental activities of daily living), general cognition and behavioural changes were evaluated at baseline, with a subgroup of patients being reassessed after 16 months.
*Results:* The corticobasal syndrome group had the most marked disability in basic activities in comparison to progressive supranuclear palsy and primary progressive aphasia-nonfluent variant. Longitudinal decline was marked for all three groups. In a linear regression examining factors behind functional disability in CBS and PSP, memory dysfunction emerged as the main factor (48.5%), followed by apraxia (14.9%) and atypical parkinsonian symptoms (9.6%).
*Conclusions:* Memory dysfunction is the most important factor in functional disability in CBS and PSP, which has to be taken into consideration in disease management, prognosis and planning of services to fully address patients' and families' needs.



## 1. Introduction

Corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) are two closely related neurodegenerative diseases which overlap clinically and pathologically, with a significant proportion of both CBS and PSP cases due to tau protein deposits [1].

Of the two, CBS is arguably the most debilitating as patients have limb apraxia, parkinsonism, and prominent cognitive dysfunction [2,3]. PSP patients also present with atypical parkinsonism (such as rigidity and frequent falls), which is accompanied by executive dysfunction [4]. Although marked changes in functional ability are expected, little research has been conducted into the degree of disability experienced in these diseases. Moreover, there is no clear understanding how the recognised marked cognitive and behavioural deficits affect performance of activities of daily living (ADLs).

Descriptive studies of people with CBS have identified problems with money transaction, calculations, speech and handwriting, as well as the ability to manipulate objects and dress due to apraxia [5–7]. These suggest that both basic ADLs and instrumental ADLS (more complex such as meal preparation, managing finances) are possibly affected from an early stage. In PSP, the literature is even scarcer. A drug trial used ADL decline as an outcome measure, and showed no improvement for those receiving the drug [8]. Two case studies have mentioned functional decline in PSP: difficulty with speech [9,10], which subsequently caused difficulties using the telephone and reading aloud [9], while another case was reported to be able to drive a car, manage finances and use the computer even after 3 years post onset [10]. Research into functional decline in PPA-nfv is also in its early days. The first study to explore functional decline specifically in PPA-nfv was conducted within the FTD context. Ninety percent of the PPA-nfv participants experienced

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http://dx.doi.org/10.1016/j.parkreldis.2013.01.002

no change in basic ADLs, as opposed to majority scoring moderate-to-severely impaired instrumental ADLs [11]. No correlation was found between the ADL measure and general cognition [11] or the clinical dementia rating scale (CDR) [12], which perhaps is not surprising given that the CDR was not developed to detect changes in FTD. A 12-month follow-up revealed significant decline in both BADLs and IADLs for the PPA-nfv group, more marked so in IADLs [13].

To complicate matters, CBS and PSP are also accompanied by language deficits, which overlap greatly with primary progressive aphasia-nonfluent variant (PPA-nfv). Interestingly, both CBS and PSP syndromes can be preceded by a PPA-nfv picture [14], with distortion of speech output and/or agrammatism in the context of otherwise well preserved general cognitive abilities [15]. PPA-nfv is categorised under the frontotemporal dementia (FTD) umbrella [16] and has a close clinical-pathological relation to CBS and PSP [14,17]. For this reason, a sample of early PPA-nfv patients was used as a control comparison group in this study.

The aims of the study were to: 1) explore the nature of functional disability in CBS and PSP, and contrast them with PPA-nfv, given their clinical-pathological overlap; 2) examine which clinical motor, cognitive, or behavioural changes were behind functional disability in CBS and PSP; 3) verify if longitudinal changes in functional scores were similar to global cognitive decline. We hypothesised that CBS patients would show more functional deficits than the PSP group, which in turn would be more severe than the PPA-nfv group; we expected to identify apraxia as the main contributor to functional disability in CBS and PSP, and to find an association between functional and cognitive decline.

## 2. Methods

### 2.1. Patients

Fifty patients participated in the study (CBS = 18; PSP = 11; PPA-nfv = 21). Patients were recruited from the Frontier Research Group in Sydney, and were assessed either in the research clinic or their own home. Patients were included if they: 1) fulfilled the criteria for PPA-nfv [16], CBS [3], or PSP [4]; 2) had an informant who could give a reliable account of the patients' behaviour and everyday routine; 3) had undergone the Addenbrooke's cognitive examination revised (ACE-R) [18] and the Cambridge behavioural inventory-revised (CBI-R) [19] within 6 months of ADL assessment, and 4) had no confounding variables such as major depression or major physical disability such as being wheelchair bound at home. Each participant had undergone an MRI scan and was excluded if they demonstrated significant cerebrovascular disease (infarcts or confluent white matters change). Functional assessment was conducted by a senior research occupational therapist (EM) or occupational therapy student (NC or JJ).

Estimated disease duration was obtained from the first signs of symptoms as reported by the informant at time of the diagnosis. The study was approved by the Northern Hospital Network Human Research Ethics committee and consents were obtained from patients and/or carers.

### 2.2. Instruments

#### 2.2.1. Functional assessment: DAD

Activities of daily living (ADL) were assessed using the disability assessment for dementia (DAD) [20]. The DAD is an informant-based assessment tool completed via an interview with the carer to assess functional disability in BADLs (e.g. dressing, eating) and IADLs (e.g. meal preparation, housework). In addition, the DAD further categorises functional components of the task into components of initiation, planning and execution. Importantly, the total score is corrected to 100 to prevent gender bias, e.g. activities which were not part of the patient's premorbid repertoire are not included in the scoring. As a result, the patient is compared to themselves, to their previous level of functional ability, prior to symptom onset. Higher scores on the DAD reflect greater functional ability.

#### 2.2.2. Apraxia and parkinsonian features

Apraxia was measured with a standardised clinical assessment that was conducted by one of the neurologists (JRH or JB). A score of 0 denoted no apraxia, 1 = mild, 2 = moderate and 3 = severe. Apraxia was assessed in 5 areas: orobuccal, upper limb (left and right) meaningful and meaningless gestures, where a maximum score of 15 reflected severe apraxia.

Atypical parkinsonian features were also evaluated by one of the neurologists and scores were standardised as follows: 0 = normal; 1 = mild; 2 = moderate and 3 = severe. Areas evaluated were: gait disturbance, postural instability, and upper limb (left and right) rigidity and bradykinesia, where a maximum score of 15 referred to marked parkinsonism.

#### 2.2.3. Brief cognitive assessment: ACE-R

The ACE-R evaluates global cognitive dysfunction, and was designed to detect early changes [21]. It consists of five cognitive domains: attention/orientation (18 points), memory (26 points), fluency (14points), language (26 points) and visuospatial skills (16 points) totalling 100, with higher scores denoting better cognitive functioning.

#### 2.2.4. Behavioural assessment: CBI-R

The Cambridge behavioural inventory-revised (CBI-R) [19] is an informant-based assessment tool consisting of 45 questions used to assess and discriminate behavioural changes in neurodegenerative diseases. The CBI-R covers ten domains: memory, challenging behaviour, everyday skills, self care, motivation/apathy, mood, eating behaviour, abnormal beliefs, stereotypic motor behaviours and sleep. Behaviours are rated on a 0–4 frequency scale, with higher scores denoting greater dysfunctional behaviour [22]. For the purpose of this study, we focused on behavioural changes and excluded the domains of functional performance (everyday skills, self care and eating behaviour), as these were already assessed in detail using the DAD.

### 2.3. Data analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows. Kolmogorov–Smirnoff tests revealed that main variables of interest were normally distributed, favouring a parametric approach to the data. One-way analyses of variance, followed by $t$ tests, were applied to determine between group differences in ADL, cognitive ability and behavioural changes. Pearson correlations were conducted within groups to identify associations that may exist between ADL and behavioural performance. The $r_s$ value threshold was set at 0.5684 for group size of 20 participants [23]. Bonferroni corrections of $p < 0.01$ was applied for multiple comparisons.

For the longitudinal analysis, a mixed design 3 × 2 × 2 ANOVA was applied, including the 3 diagnostic groups, 2 time points (baseline and follow up) as well the 2 main variables of interest, DAD and ACE-R.

Lastly, to identify which variables were the best contributors to the variance on the DAD scores, we applied a multiple regression analysis (stepwise method) using the DAD as the dependent variable. The $p$ value was set at 0.05 unless otherwise stated.

## 3. Results

### 3.1. Group demographics

Patients were matched for age, education and disease duration (Table 1). A male predominance was present in the PSP and PPA-nfv groups.

### 3.2. Functional assessment

To investigate ADL performance across all groups, DAD scores were broken down into the following components: total DAD, BADL, IADL, and performance component areas of initiation, planning and execution (Table 2).

#### 3.2.1. DAD total scores

An ANOVA revealed a significant group difference on the total DAD (Table 2); post hoc tests revealed a significant difference between CBS and PSP patients, and CBS and PPA-nfv patients, where CBS patients were the most disabled group.

**Table 1**
Group demographics for patients with CBS, PSP and PPA-nfv regarding sex, age, education and disease duration.

| | CBS ($n$ = 18) | PSP ($n$ = 11) | PPA-nfv ($n$ = 21) | |
|---|---|---|---|---|
| Sex, % male | 42% | 64% | 67% | – |
| Age, years | 68 (6.3) | 66.5 (3.53) | 69.1 (10.85) | n.s. |
| Education, years | 10.6 (2.8) | 11.6 (3.55) | 11.9 (3.96) | n.s |
| Disease duration, years | 4.1 (1.40) | 3.0 (1.00) | 3 (1.73) | n.s. |

*Note*. Values represent means with standard deviation in parentheses, except for the variable 'sex' CBS = corticobasal degeneration; PSP = progressive supranuclear palsy; PPA-nfv = progressive nonfluent aphasia.