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The applause sign and neuropsychological profile in progressive supranuclear palsy and Parkinson's disease

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ABSTRACT

Background: The applause sign has been associated with various neurodegenerative diseases. We investigate its validity in the differential diagnosis of progressive supranuclear palsy and Parkinson's disease, and its relationship with neuropsychological tests.
Patients and methods: 23 patients with progressive supranuclear palsy and 106 patients with Parkinson's disease were included and administered the following scales: progressive supranuclear palsy rating scale, unified Parkinson's disease rating scale (UPDRS), mini-mental state examination (MMSE), frontal assessment battery (FAB), neuropsychiatric inventory and three-clap test.
Results: 73.9% with progressive supranuclear palsy and 21.7% with Parkinson's disease showed a positive applause sign. Only a positive applause sign, UPDRS II score and disease duration were found to be predictors of progressive supranuclear palsy. Both patient-groups showed statistically significant correlations between the applause sign and neuropsychological tests: in progressive supranuclear palsy patients MMSE correlation coefficient: 0.62 (p: 0.002) and FAB correlation coefficient: 0.48 (p: 0.02), and in Parkinson's disease patients MMSE correlation coefficient: 0.47 ($p < 0.001$) and FAB correlation coefficient: 0.43 ($p < 0.001$). Verbal fluency and inhibitory control (FAB) and writing and orientation in time (MMSE) discriminated between patients with normal and positive applause sign.
Conclusions: A positive applause sign is not specific to progressive supranuclear palsy and may also be observed in Parkinson's disease patients with altered cognition, and it's related to cortical frontal abnormalities such as language disorders and inhibitory control.

1. Introduction

An impaired three-clap test (positive applause sign) is considered indicative of neurodegenerative disease [1,2]. It is believed to be due to an executive dysfunction that can be observed in lesions on both frontal lobes as well as in basal ganglia disorders. Some publications point to its utility in differential diagnosis between progressive supranuclear palsy (PSP) and Parkinson's disease (PD) [2]. Other research, however, records no difference in frequency between the different atypical parkinsonisms [3].

The aim of the present work is to analyze the utility of the applause sign (AS) in the differential diagnosis between PSP and PD, and as part of this to identify the characteristics of PD patients with abnormal AS. We also study the relationship of AS with neuropsychiatric symptoms and neuropsychological test scores, in particular the frontal assessment battery (FAB), which is considered a useful tool in detecting frontal lobe disorders [4].

2. Methods

2.1. Patient selection

Twenty-three patients with a diagnosis of PSP were studied (12 women, 11 men) with a mean age of 72.9 ± 6.9 and a mean of 3.3 ± 2.3 years of disease duration at the time of the study; 78% (18 patients) had a diagnosis of probable PSP and the remaining 22% (5 patients) of possible PSP, according to the clinical criteria set out by the NINDS-PSP international workshop [5]. The two diagnostic groups of PSP were separated for the analysis of general characteristics and were thereafter analyzed as a whole. The control group was a sample of 106 patients (50 men, 56 women) with a diagnosis of PD according to the London Brain Bank criteria [6]. The mean age

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of this group was 67.8 ± 11.6 years, with a mean of 6.9 ± 5.6 years of disease duration.

All patient data was made anonymous and an informed consent approved by the local ethics committee was requested before participation in the study. Patients with a diagnosis of other atypical parkinsonisms such as multiple system atrophy, corticobasal degeneration and vascular parkinsonism were excluded.

2.2. Patient assessment

The following tests were administered to all patients: the PSP rating scale (only PSP patients), the unified Parkinson's disease rating scale (UPDRS I-IV), the mini-mental state examination (MMSE), the FAB, the neuropsychiatric inventory (NPI) and the three-clap test (AS). In the latter test, the patient is asked to clap as fast as possible three times in a row, the examiner demonstrates the normal three clap response before the patient performs the test. Scores are allocated according to the number of claps: a score of 3 for three claps, 2 for four claps, 1 for between five and ten and a score of 0 when the patient is incapable of stopping or claps more than ten times. A number of claps greater than three was considered positive.

The neuropsychiatric inventory [7] is a semi-structured interview administered to a knowledgeable informant including screening questions on 12 behavioural domains; delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, abberant motor behaviour, nighttime behavioural disturbance and appetite/weight changes. If the answer is positive the problematic behaviour is rated in frequency from 1 (less than once per week) to 4 (once or more per day) and the severity from 1 (mild) to 3 (severe). The total domain score is the product of frequency multiplied by severity, and the total score of the NPI is the sum of all domain scores. Demographic variables were also obtained including age, sex and treatment.

2.3. Statistical analysis

A descriptive study of all quantitative variables was carried out, showing the mean and standard deviation for each. Percentages were used for qualitative variables. The normality and homogeneity of the variance were confirmed using Kolmogorov-Smirnov and Levene's tests, respectively. The chi-squared test was used for comparing dichotomous qualitative variables and Fisher's exact test when the sample was small, quantitative variables were compared with Student's *T* test. For examining partial correlations, the Pearson correlation coefficient was used, controlled by patient age and disease duration. An ANCOVA model was also created, using the AS score as the dependent variable and the scores from the different scales as co-variables. For analysing the various subitems of the FAB and NPI scales, stepped linear regression methods were used, with the AS score as the dependent variable.

Finally a stepped linear regression model was created with the diagnosis of PSP as the dependent variable. For this regression model the applause sign was classified as present or absent, the MMSE and the FAB scores were dichotomized according to previously established cut-off values for pathologic scores (MMSE < 25 and FAB < 15) and the remaining test scores were dichotomized according to the median (NPI > 6, UPDRS I > 3, UPDRS II > 17, UPDRS III > 35 and UPDRS IV > 2).

The Statistical Package for the Social Sciences 18 software for Windows (SPSS inc©-Chicago ILL) package was used for the statistical analysis.

3. Results

A total of 129 patients were included, 23 with PSP and 106 with PD. There was no significant difference in the age between the two groups, but the PSP patients presented significantly lower MMSE, FAB and UPDRS IV, with higher UPDRS II and III as well as shorter disease duration (Table 1).

Of the 23 patients with a diagnosis of PSP, 73.9% had a positive AS (Fig. 1). There was no correlation between the scores on the PSPRS scale and the AS, MMSE or FAB. Of the 106 patients with PD diagnosis, 83 (78.3%) scored 3 in the AS (Fig. 1). The PD patients with pathologic AS presented significantly lower scores on FAB and MMSE, but there was no significant differences in age, disease duration, NPI or UPDRS scores compared with those with a normal AS (Table 2). There is a similar weak but statistically significant correlation between the AS and the MMSE score (cc: 0.47; $p < 0.001$) and the FAB score (cc: 0.43; $p < 0.001$).

Analysing the full cohort statistically significant correlations were found between the AS and the MMSE (correlation coefficient (cc): 0.62; $p = 0.002$), the FAB (cc: 0.48; $p = 0.02$) and the UPDRS II (cc: 0.47; $p = 0.03$). We observed no significant correlations with the total scores of the NPI, UPDRS I, III or IV. Using 25 as the cut-off point for the MMSE and 15 for the FAB, nine patients with a positive AS (50%) had a normal MMSE. However, only one patient with a positive AS scored normal in the FAB, whilst the majority (18 patients) produced an abnormal result ($p = 0.04$, Fisher's exact test).

In the linear regression study using the AS as the dependent variable, four variables were selected as determining variables: verbal fluency and inhibitory control, both from the FAB, and to a lesser degree, irritability and agitation from the NPI scale ($F = 18.173$; $p < 0.001$). The linear regression analysis was repeated, this time with the MMSE subscores; three subscores were selected: writing, orientation to time and to a lesser degree, attention (calculation) ($F = 27.627$; $p < 0.001$).

Finally a stepwise logistic regression analysis was preformed with the diagnosis of PSP (possible or probable) as the dependent variable and as co-variables the age, disease duration, applause sign, MMSE, FAB, NPI and UPDRS I-IV. The co-variables were dichotomized as previously described. Only three variables were selected as predictive of a diagnosis of PSP, namely the applause sign, the disease duration and UPDRS II (Table 3). The risk of presenting PSP is 6.5 times higher in those with a positive applause sign and 9 times higher in those with a UPDRS II higher than 17. As expected longer disease duration lowers the risk of PSP, with a 28% lower risk per year.

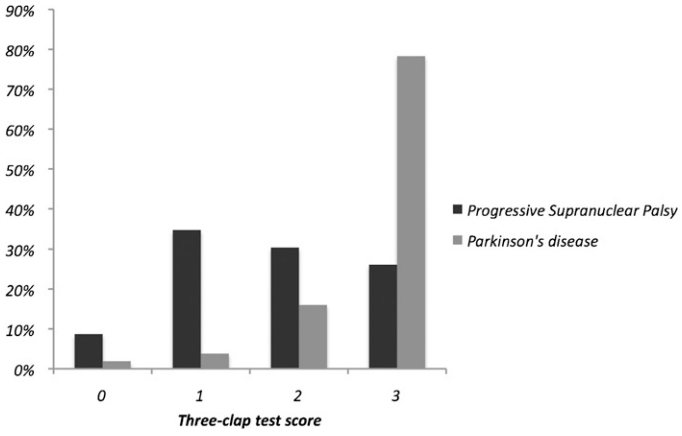

Fig. 1. The graph shows the applause sign scores of patients with Parkinson's disease and progressive supranuclear palsy (percentages).