CLINICAL SCIENCE

Verbal fluency in Alzheimer's disease, Parkinson's disease, and major depression

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OBJECTIVE: To compare verbal fluency among Alzheimer's disease, Parkinson's disease, and major depression and to assess the sociodemographic and clinical factors associated with the disease severity.

METHODS: Patients from an outpatient university center with a clinical diagnosis of Alzheimer's disease, Parkinson's disease or major depression were studied. Severity was staged using the Hoehn & Yahr scale, the Hamilton Depression scale and the Clinical Dementia Rating for Parkinson's disease, major depression, and Alzheimer's disease, respectively. All subjects were tested with the Mini-Mental State Examination, the digit span test, and the verbal fluency test (animals). We fit four types of regression models for the count variable: Poisson model, negative binomial model, zero-inflated Poisson model, and zero-inflated negative binomial model.

RESULTS: The mean digit span and verbal fluency scores were lower in patients with Alzheimer's disease (n = 34) than in patients with major depression (n = 52) or Parkinson's disease (n = 17) (p<0.001). The average number of words listed was much lower for Alzheimer's disease patients (7.2 words) compared to the patients presenting with major depression (14.6 words) or Parkinson's disease (15.7 words) (KW test = 32.4; p<0.01). Major depression and Parkinson's disease groups listed 44% (ROM = 1.44) and 48% (ROM = 1.48) more words, respectively, compared to those patients with Alzheimer's disease; these results were independent of age, education, disease severity and attention. Independently of diagnosis, age, and education, severe disease showed a 26% (ROM = 0.74) reduction in the number of words listed when compared to mild cases.

CONCLUSIONS: Verbal fluency provides a better characterization of Alzheimer's disease, major depression, and Parkinson's disease, even at later stages.

KEYWORDS: Verbal fluency; cognition; diagnosis; neuropsychology.

INTRODUCTION

The increasing life expectancy of the population has lead to a growing number of elderly individuals with major depression (MD) and dementia worldwide and this trend has prompted research on the early recognition and differential diagnosis of these entities in primary care settings.[1,2] Brief and valid tests, and cognitive batteries have been developed to screen for[2,3] and differentiate the diagnoses to better understand the general profiles of these patient groups.[4,5]

The verbal fluency test is a one-minute evaluation that assesses executive functions as well as linguistic abilities.[6,7] Two subtests are usually applied, the semantic (mainly on animals)[7,8,9] and the phonetic categories (number of words begining with the letters F, A, and S in one minute).[14,15] Sociodemographic factors may influence the test performance, especially education[6,7,9-12] and age.[6,9,12]

Executive dysfunction is a neuropsychological constituent of dementing illnesses and MD.[13] Parkinson's disease (PD) patients usually show executive deficits early in the disease course, including deficits in information processing, the use of internal cues for attention and creation of orientation strategies.[14] The same deficits are applied to patients with MD, who also present with psychomotor retardation, apathy, and fluency deficits.[15] Neurodegenerative diseases also present with marked changes in the ability to generate and understand words, sentences, and language as a whole. In both Alzheimer's disease (AD) and PD, the verbal fluency

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test results usually differ from those of healthy elderly,[16,17] although the neural pathways may differ between diseases in terms of the differences in the test.[18-21] Several studies have evaluated verbal fluency in these three diseases separately, but only a few have compared the test results among the three disorders. This direct comparison could provide further data that would allow these disorders to be characterized in a quick and valid way from a cognitive standpoint. Therefore, we studied whether verbal fluency scores would differ between AD, PD, and MD patients. We hypothesized that AD patients would exhibit the lowest scores while there would be no significant differences between PD and MD scores. We also assessed which sociodemographic and clinical factors influenced the results.

MATERIALS AND METHODS

Patients from an outpatient university center who had a clinical diagnosis of AD according to DSM-IV[22] and NINCDS-ADRDA,[23] PD according to the United Kingdom Parkinson Disease Society Brain Bank[24] and the Unified Parkinson's disease rating scale (UPDRS),[25] and MD according to DSM-IV criteria using the Structured Clinical Interview for DSM Disorders (SCID) were recruited for the study from an outpatient university center. Subjects with comorbid psychiatric, neurological, or clinical disorders were excluded from the sample, as well as those patients who presented with important physical limitations and visual or hearing impairment. None of the PD patients included in this study had a clinical diagnosis of dementia after thorough clinical, biochemical and neuroimaging examinations. A total of 103 patients older than 45 years of age were included in the final sample (n = 34 AD, n = 17 PD, and n = 52 MD).

To stage the severity of each disorder, the Brazilian validated versions of the Hoehn & Yahr scale[26] (stages 1 to 3), the Hamilton Depression scale[27] (cutoff scores - mild: 8-13; moderate: 14-18; severe: 19-22), and the Clinical Dementia Rating[28] were used for PD, MD, and AD patients, respectively. All subjects were assessed with a sociodemographic interview and the Mini Mental State Examination (MMSE),[29] the digit span subtest of the WAIS-R,[30] and the verbal fluency test using the animal category.[31]

The MMSE is a brief screening test for cognitive capabilities that evaluates orientation (spatial and time), attention, concentration, memory, calculation, language, and praxis. The score ranges from 0 to 30, with higher scores indicating better performance.[32]

The digit span subtest[30] assesses immediate memory and attention. A series of number sequences are presented to the subject. In the first portion of the test, the subject is asked to reproduce the exact sequence, whereas in the second portion he/she is asked to repeat the sequence backwards.[29]

The verbal fluency test is a one-minute assessment in which the patient is asked to name as many animals as he can.[11] Repeated words are not counted towards the final score.

A descriptive statistic was initially calculated for the demographic and clinical characteristics of the patients for each diagnosis. The statistical significance of differences between means was estimated with the Kruskal-Wallis test. The exploratory analysis of verbal fluency scores suggested an excess of zeros in the frequency distribution of this variable. We fitted four types of regression models for the count variable: the Poisson model (PRM), the negative

binomial model (NRBM), the zero-inflated Poisson model (ZIP) and the zero-inflated negative binomial model (ZINB). Tests, plots and fit statistics were performed, and the ZINB model yielded the best results. This model assumes that the studied population comprises two sets of individuals: one consisting of subjects with a high propensity to list words and another consisting of individuals with a high chance of having difficulty listing at least one word. The ZINB model assumes that various underlying processes can be involved in producing zero and non-zero counts. The exponential transformation of the coefficient of the negative binomial component (count part) estimates the average number of listed words associated with the selected explanatory variables. However, the exponential transformation of the coefficient provided by the logistic component (inflate part) of the model estimates the odds ratio for the chance of belonging to the group of individuals with difficulty listing at least one word.[33,34]

The alpha dispersion parameter was calculated for the count model. If this parameter is close to zero, the model converges to a Poisson distribution. The Vuong test was used to compare the zero-inflated negative binomial to the standard negative binomial model.[34] The Akaike's information criterion (AIC), Bayesian information criterion (BIC) and Likelihood Ratio (LR) chi-squared statistics were also used to compare the goodness of fit between the different models. The analysis was conducted using Stata 10.0.

This study was approved by the Ethics Committee of the Institute of Psychiatry of the Federal University of Rio de Janeiro, and all participants signed informed consent forms before any procedures.

RESULTS

The study population consisted of 103 patients. Table 1 presents the distribution of the group according to demographic and clinical characteristics.

Most patients were women and had less than 9 years of education. MD was the largest diagnostic group, and the disease was considered severe in approximately 1/5 of the sample. The mean MMSE of the AD patients was the lowest and was significantly different from the other diagnoses (p<0.001). The mean Digit Span and verbal fluency scores of the AD patients were smaller and lower, respectively, compared to the scores for those patients with MD and PD (p<0.001). Table 2 shows the pattern of disease severity for the individuals in each disease group. While AD and MD patients were classified predominantly as mild cases, those patients with PD were predominantly in the moderate group.

Verbal fluency test results differed between diagnostic groups. The average number of words listed was much lower for AD patients (7.2 words) than for those patients presenting MD (14.6 words) or PD (15.7 words). This difference was statistically significant (KW test = 32.4; p<0.01).

Table 3 presents the parameters for the count and inflate components of the ZINB model. For the count component (average number of words listed), the MD and PD groups had 44% (ratio of means [ROM] = 1.44) and 48% (ROM = 1.48) more words listed, respectively, in one minute compared to AD patients. This association was independent of age, education, severity and attention.

The PD and MD groups only differed by 2% in the average number of words listed, and this difference did not reach statistical significance (p = 0.80).

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Table 1 - Demographic and clinical characteristics of the patients (n = 103).

Characteristics	Diseases		
	Alzheimer's N = 34	Depression N = 52	Parkinson's N = 17
Gender (female)			
N (%)	24 (70.6)	45 (86.5)	5 (29.4)
Age (years)[*]			
Mean (SD[1])	74.3 (8.9)	71.4 (5.9)	64.2 (9.3)
Median	76.5	70.5	64.0
Range	54-90	60-87	45-77
Years of education[2]			
Mean (SD)	5.7 (3.9)	7.8 (3.9)	7.9 (4.9)
Median	5.0	7.5	6.0
Range	1-17	2-16	3-15
MMSE[***]			
Mean (SD)	14.0 (8.8)	27.1 (3.0)	25.6 (3.5)
Median	15.0	28.0	25.0
Range	0-30	17-30	21-30
Digit Span Test[3]			
Mean (SD)	4.7 (3.1)	8.9 (3.0)	9.3 (3.1)
Median	4.5	8.5	9.0
Range	0-11	4-18	5-14
Verbal Fluency Test (words)[4]			
Mean (SD)	7.2 (6.0)	14.6 (3.7)	15.7 (5.8)
Median	7.0	14.0	15.0
Range	0-21	7-26	6-27

([§]) Standard deviation.
(*) Age: Alzheimer's disease vs. depression: p = 0.04; depression vs. Parkinson's disease: p = 0.003; Alzheimer's vs. Parkinson's disease: p<0.001.
(**) Years of education: Alzheimer's disease vs. depression: p = 0.005; depression vs. Parkinson's disease: p = 0.79; Alzheimer's vs. Parkinson's disease: p = 0.09.
(***) MMSE (Mini-Mental State Examination): Alzheimer's disease vs. depression or Parkinson's disease: p<0.001; depression vs. Parkinson's disease: p = 0.09.
(****) Digit span test: Alzheimer's disease vs. depression or Parkinson's disease: p<0.001; depression vs. Parkinson's disease: p = 0.63.
(*****) Verbal fluency test: Alzheimer's disease vs. depression or Parkinson's disease: p<0.001; depression vs. Parkinson's disease: p = 0.35.

The degree of severity within each diagnostic category was also inversely associated with verbal fluency. Severe cases, independently of diagnosis, age and education, showed a 26% (ROM = 0.74) reduction in the number of words listed compared to mild cases. We observed no statistically significant difference in verbal fluency results between the moderate and mild cases.

The performance on the digit span test was associated with verbal fluency as measured in the two components of the model. For each one-point increase in the digit span, there was a 6% (ROM = 1.06) increase in the number of words listed in one minute. Only the digit span test influenced verbal fluency in the inflate component of the ZINB model (chance of not listing at least one word). We observed a 62% reduction in the chance of being unable to

Table 2 - Disease severity according to diagnosis.

Diagnosis	Mild form N (%)	Moderate form N (%)	Severe form N (%)
Alzheimer's disease	16 (47.1)	9 (26.5)	9 (26.5)
Major Depression	24 (53.3)	14 (31.1)	7 (15.6)
Parkinson's disease	3 (17.7)	9 (52.9)	5 (29.4)

Table 3 - Zero-inflated negative binomial regression of verbal fluency scores according to demographic and clinical variables.

Variable	ROM*	95% CI	P-value
Count for verbal fluency score.			
Diagnosis			
Alzheimer's disease	Reference		
Depression	1.44	1.20 to 1.73	<0.001
Parkinson's disease	1.48	1.15 to 1.89	0.002
Disease severity			
Mild	Reference		
Moderate	0.96	0.82 to 1.11	0.58
Severe	0.74	0.60 to 0.92	0.01
Digit Span test	1.06	1.04 to 1.09	<0.001
Age	1.00	0.99 to 1.01	0.78
Education (years)	0.95	0.89 to 1.02	0.14
Gender (female)	0.88	0.75 to 1.04	0.14
OR** of verbal fluency score = 0			
Digit Span test	0.38	0.21 to 0.70	0.002
Constant	3.77	0.63 to 22.37	0.14

Log alpha = -3.93 (p< 0.001); alpha = 0.02.
Vuong test of ZINB vs. standard negative binomial: z = 2.23 (Pr>z = 0.01).
(*) The ratio of means expresses the difference in the number of words listed in one minute as a ratio.
(**) Odds ratio.

list at least one word for each one-point increase in the digit span test score (OR = 0.38).

Although age and education were not associated with verbal fluency in this sample, they were retained in the final model as a confounding control.

When the MMSE scores were included in the model, diagnosis and severity lost their association with verbal fluency due to collinearity. Digit span remained associated with higher verbal fluency (ROM = 1.04; p = 0.01).

The log of the alpha and Vuong tests were statistically significant, suggesting data dispersion and an excess of zeros and increasing the appropriateness of the ZINB model compared to the negative binomial model for these data. Figure 1 depicts the fit of the PRM, NBRM, ZIP and ZINB regression models. Although the figure shows a very similar pattern of residuals for both ZINB and ZIP models, AIC and LR chi-squared statistics suggested that the ZINB model presents a slightly better fit than ZIP.

DISCUSSION

As expected, the performance of AD patients in the verbal fluency test was significantly lower than the performance observed in both PD and MD patients. The AD group averaged half the number of words observed for PD and MD patients. Our results also showed that disease severity has a direct impact on verbal fluency, regardless of the diagnosis, age, educational level, or gender. Overall, patients in the more severe stage generated 26% fewer words than those patients in the mild and moderate stages. Moreover, attention and concentration seem to play an important role in performance because the digit span test both reduces the chance of being unable to say at least one word and also increases the average number of listed words.

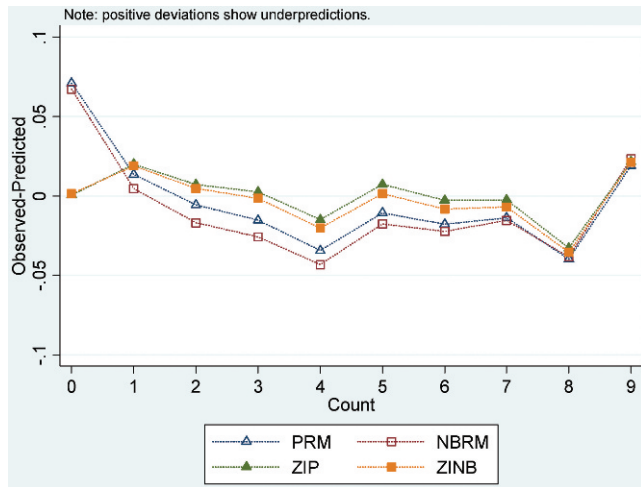Healthy elderly people with lower levels of education in Brazil are expected to generate a mean of nine words, as

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Note: positive deviations show underpredictions.

Figure 1 - Poisson (PRM), negative binomial (NBRM), zero-inflated Poisson (ZIP) and zero-inflated negative binomial (ZINB) regression models. The best model is closest to the zero horizontal line.

opposed to 13 words by those healthy elderly with more than eight years of education.[30] Thus, the results for the PD and MD groups in our study are within the normal ranges for the Brazilian elderly population. These results are consistent with research that found that AD patients have a decreased performance in verbal fluency compared to non-demented PD patients[35] and MD elderly.[21] The preservation of functional areas related to language and semantic knowledge is key to achieving a normal performance on the verbal fluency test.[36] However, subcortical disorders, such as PD, and disorders, such as MD, which are related to a decreased activity in orbital[13,37] and dorsal lateral frontal areas,[13,37] could show some impairment of verbal fluency by different mechanisms from the one shown by AD patients. Two recent meta-analyses have shown that semantic verbal fluency is significantly reduced in AD patients when compared to MD and PD patients.[14,21] In addition, one of these studies presented data confirming that semantic fluency in depression is not only related to executive impairment but could also be a sign of a broader impairment in terms of neural circuits.[21]

Similar to other studies,[18,19] we found that verbal fluency decreases as the three diseases progress in severity. This result then raises the question of whether the verbal fluency test would also be able to better characterize these three entities at later stages of the disease. As shown in Table 3, we found that differences in semantic verbal fluency are present even at the more severe stages.

This study has some limitations that should be acknowledged. The cross-sectional design does not allow us to make a conclusion on the nature of the real outcome of verbal fluency as the diseases progress in severity. Longitudinal studies measuring verbal fluency can provide a more complete picture than the present paper. Another important limitation is that the measurement of severity of the three disorders requires distinct instruments. In fact, the severity of dementia is mostly assessed based on cognitive and functional status, whereas PD is rated by taking motor symptoms into account, and MD severity relies on the intensity of emotional and physiological symptoms. The

small number of participants and the absence of a healthy control group are other important limitations of this study. However, to the best of our knowledge, this is the first study to assess and compare verbal fluency among AD, PD, and MD patients. This study presented the clinically relevant finding that verbal fluency is worse in AD patients when compared to MD and PD patients, even when the three disorders are at their most severe stages.

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