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Behavioral Symptoms in the Variants of Primary Progressive Aphasia

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Abstract

Introduction: Primary progressive aphasia is a neurodegenerative syndrome mainly associated with frontotemporal lobar degeneration or Alzheimer disease pathology. It is characterized by a prominent, isolated language deficit, and is classified in 3 clinical variants: nonfluent/agrammatic variant, semantic variant, and logopenic variant. Behavioral symptoms can emerge on primary progressive aphasia and its phenomenology may be useful as a surrogate of the underlying pathology.

The aims of this study are to assess the typology and severity of the behavioral symptoms between the clinical variants of primary progressive aphasia and to compare neuropsychiatric profiles of these variants with those found in the typical forms of frontotemporal lobar degeneration and Alzheimer disease. The relationship with biological variables is also explored.

Methods: We prospectively recruited patients followed in the dementia consultation at the Centro Hospitalar e Universitário de Coimbra and fulfilling the current diagnostic criteria for primary progressive aphasia and its variants, as well the typical forms of frontotemporal lobar degeneration (behavioural variant) and amnesic-Alzheimer disease. 94 patients were included: 21 with primary progressive aphasia (9 with nonfluent variant, 3 with semantic variant, and 9 with logopenic variant), 40 with behavioral variant of frontotemporal dementia, and 33 with Alzheimer disease. Behavioral symptoms were assessed with the neuropsychiatric inventory and the frontal behavioral inventory. The biomarkers in the liquor were also evaluated.

Results: The results obtained on the two scales (neuropsychiatric inventory and frontal behavioral inventory) are similar, with semantic variant presenting the higher scores, and being statistically comparable to behavioral variant of frontotemporal dementia. On the neuropsychiatric

inventory, the nonfluent and logopenic variants presented scores quite similar between them and the Alzheimer disease group, and considerably lower than the behavioral variant of frontotemporal dementia and semantic variant. On the frontal behavioral inventory, the logopenic variant obtained an increment of the mean scores, and presented statistically higher scores than the Alzheimer disease group.

Relatively to the behavioral items evaluated on each scale, the semantic variant presented higher scores on almost all of them, on both scales. The most notorious difference between the semantic and the other variants was on: appetite and eating disorders, aberrant motor behavior and agitation/aggression, concerning to neuropsychiatric inventory, but no statistical significance was achieved between the variants. More significant results were found on the frontal behavioral inventory, particularly on: inattention, indifference, loss of insight, with the nonfluent variant presenting with lower scores; and inflexibility, with both nonfluent and logopenic variants presenting with lower scores.

The behavioral scales were not correlated to disease duration at any diagnostic group, with the exception of logopenic, positively correlated with frontal behavioral inventory total score. No correlation was either found between those scales and the cerebrospinal fluid biomarkers at any diagnostic group.

Discussion and Conclusions: Semantic variant is associated with more severe behavioral disturbances than other variants of primary progressive aphasia, being comparable with behavioral variant of frontotemporal lobar degeneration on many items, whereas nonfluent and logopenic variants, present with significant less behavioral symptoms, with a pattern more similar to Alzheimer disease. Only the frontal behavioral inventory allowed to differentiate the primary progressive aphasia variants on 4 items, suggesting that it can be a better scale to apply on those patients. The behavioral scales were not correlated neither with the disease duration nor

with the biomarkers of neurodegeneration in the cerebrospinal fluid, and are more likely to be associated with the underlying pathology, instead of being symptoms of the disease progression.

Key words

Primary progressive aphasia; Frontotemporal lobar degeneration; Alzheimer Disease; Semantic variant primary progressive aphasia; Nonfluent agrammatic variant primary progressive aphasia; Logopenic variant primary progressive aphasia; Neuropsychiatric Inventory; Frontal Behavioral Inventory.

Resumo

Introdução: A afasia primária progressiva é um síndrome neurodegenerativo maioritariamente associado a patologia de degenerescência lobar fronto-temporal ou de doença de Alzheimer. Apresenta-se como um défice de linguagem proeminente e isolado com três variantes clínicas: agramatical/não-fluente, semântica e logopénica. As alterações do comportamento podem emergir na afasia primária progressiva e a sua fenomenologia pode ser útil como indicadora da patologia de base.

O objetivo deste estudo é avaliar a tipologia e gravidade das alterações comportamentais entre as variantes clínicas da afasia primária progressiva e comparar os perfis neuropsiquiátricos destas variantes com os encontrados nas formas típicas de degenerescência lobar fronto-temporal e doença de Alzheimer. A relação com algumas variáveis biológicas também será investigada.

Métodos: Foram recrutados prospectivamente doentes da consulta de demência do Centro Hospitalar e Universitário de Coimbra e que preenchiam os critérios diagnósticos atuais para afasia primária progressiva e suas variantes, bem como para as formas típicas de degenerescência lobar fronto-temporal (variante do comportamento) e doença de Alzheimer amnésica. Foram incluídos 94 doentes: 21 com afasia primária progressiva (9 com variante não-fluente, 3 com variante semântica, e 9 com variante logopénica), 40 com variante do comportamento de degenerescência lobar fronto-temporal e 33 com doença de Alzheimer. As alterações do comportamento foram avaliadas com o inventário neuropsiquiátrico e com o inventário de comportamento frontal. Também foram quantificados os biomarcadores do liquor.

Resultados: Os resultados obtidos através das duas escalas (inventário neuropsiquiátrico e inventário de comportamento frontal) são semelhantes, sendo a variante

semântica da afasia primária progressiva, aquela que apresenta *scores* mais elevados em ambas as escalas, sendo estatisticamente comparável à variante do comportamento da degenerescência lobar fronto-temporal. No inventário neuropsiquiátrico, as variantes não-fluente e logopénica apresentam pontuações semelhantes entre si, comparáveis à doença de Alzheimer, e consideravelmente inferiores aos obtidos na variante do comportamento da degenerescência lobar fronto-temporal e na variante semântica da afasia primária progressiva.

Relativamente aos parâmetros comportamentais avaliados em cada escala, a variante semântica apresentou os *scores* mais elevados em praticamente todos, em ambas as escalas. As diferenças mais notórias, no inventário neuropsiquiátrico, entre a variante semântica e as outras variantes, obtiveram-se nos seguintes parâmetros: apetite e distúrbios da alimentação, comportamento motor aberrante e agitação/agressão, contudo, não foi atingida significância estatística. Resultados mais significativos foram obtidos no inventário de comportamento frontal, particularmente nos seguintes parâmetros: inatenção, indiferença, perda de *insight*, onde a variante não-fluente apresentou as pontuações mais baixas; e na inflexibilidade, onde as variantes não-fluente e logopénica obtiveram os *scores* mais baixos.

As escalas de avaliação do comportamento não se correlacionaram com a duração da doença em nenhum dos grupos de diagnóstico, à exceção da variante logopénica, positivamente correlacionada com o *score* total do inventário de comportamento frontal. Também não foi encontrada correlação entre as escalas e os biomarcadores do liquor em nenhum dos grupos de diagnóstico.

Discussão e Conclusões: A variante semântica está associada a alterações do comportamento mais severas do que as outras variantes da afasia primária progressiva, sendo comparável à variante do comportamento da degenerescência lobar fronto-temporal em vários parâmetros, enquanto as variantes não-fluente e logopénica, apresentaram significativamente

menos sintomas comportamentais, com um padrão comportamental semelhante à doença de Alzheimer.

O inventário de comportamento frontal foi o único instrumento que discriminou com significância estatística em 4 parâmetros as variantes afásicas, o que sugere que esta poderá ser uma escala mais adaptada a estes doentes.

As escalas de comportamento não se correlacionaram nem com a duração da doença nem com os biomarcadores de neurodegenerescência do liquor, apresentando-se como marcadores de patologia e não de gravidade.

Palavras-Chave

Afasia Primária Progressiva; Demência Frontotemporal; Doença de Alzheimer; Variante Semântica da Afasia Primária Progressiva; Variante Agramática/Não-fluente da Afasia Primária Progressiva; Variante Logopénica da Afasia Primária Progressiva; Inventário Neuropsiquiátrico; Inventário de Comportamento Frontal

Contents

Introduction

Primary progressive aphasia (PPA) is a clinical syndrome that consists on a prominent, isolated language deficit, caused by a neurodegenerative disorder, mainly associated with frontotemporal lobar degeneration (FTLD) or Alzheimer disease (AD) pathology.(1) PPA is classified in 3 clinical variants: nonfluent/agrammatic variant (nonfluent PPA), semantic variant (semantic PPA), and logopenic variant (logopenic PPA).(2)

Nonfluent PPA presents with agrammatism in language production and/or effortful speech. Impaired comprehension of syntactically complex sentences may also be present, with spared single-word comprehension and spared object knowledge. Tau positive FTLD pathology is the underlying cause most often associated with nonfluent PPA.(2,3)

Semantic PPA core features are progressive anomia and impaired single-word comprehension. Impaired object knowledge and surface dyslexia or dysgraphia may also be present, with spared repetition and speech production. Ubiquitin/TDP43-positive FTLD pathology is the most frequent in semantic PPA.(1,2)

Logopenic PPA presents with impaired single-word retrieval in spontaneous speech and naming, as well as sentence repetition deficit. Single-word comprehension, object knowledge and motor speech are frequently spared, without frank agrammatism.(2) AD is the most common underlying pathology of logopenic PPA.(2,4)

Despite the frequent association between a type of pathology and the clinical presentations of PPA, it can be initially hard to clinically identify the neurodegenerative process on the base of the PPA. The identification of clinical predictors that differentiate FTLD and AD pathology in PPA has been subjected to considerable interest since an accurate diagnosis is important for rational therapy and genetic counselling.(3)

Behavioral symptoms are of great importance, as they are a major source of disability, patient distress and caregiver burden, contributing greatly to the level of care required.(5) Scales based on a caregiver interview such as the Neuropsychiatric Inventory (NPI) and the Frontal Behavioral Inventory (FBI) were developed for the quantification of these symptoms.(6)

Over time, behavioral symptoms similar to behavioral variant of frontotemporal dementia (bvFTD) become more prominent on PPA.(7,8) In fact, approximately 75% of patients with PPA eventually develop those symptoms (9) and, Particularly on semantic PPA, they can also be present on early stages of the disease.(10–12)

Previous studies comparing the behavioral profiles in different variants of PPA found that semantic-PPA was associated with significantly more behavioral dysfunction than the other variants of PPA, specifically more disinhibition, aberrant motor behavior, and eating disorders. Nonfluent-PPA or logopenic-PPA had lower levels of behavioral dysfunction, similar to those present in AD.(13)

When comparing semantic PPA with nonfluent PPA, former studies conclude that the semantic PPA group developed more frequent and intense agitation, which was clearly associated with the presence of delusions/hallucinations.(10) In contrast, the nonfluent PPA group had a higher frequency of depression.(10)

A better understanding of the behavioral symptoms and the identification of specific patterns in the clinical variants of the PPA would aid not only in their differential diagnosis but also in a better assessment and treatment of the patients.

The aim of this study is to assess the prevalence, frequency and severity of the behavioral symptoms between the clinical variants of PPA and to compare neuropsychiatric profiles of these variants with those found in the typical forms of FTLD (bvFTD) and AD. The relationship with biological variables is also explored.

Methods

Patients

We prospectively recruited patients followed in the Dementia consultation at the Centro Hospitalar e Universitário de Coimbra and fulfilling the current diagnostic criteria for PPA and its variants(2), bvFTD(14) and AD(15).

We included 94 patients: 21 with PPA: 9 with nonfluent PPA (2 men and 7 women), 3 with semantic PPA (1 man and 2 women) and 9 with logopenic PPA (4 men and 5 women), 40 with bvFTD (27 men and 13 women) and 33 with AD (10 men and 23 women).

At baseline they were extensively characterized using formal neuropsychological evaluation as well as specific cognitive and functional staging scales, including the Minimental-State Examination (MMSE).

CSF Biomarkers Determinations

In 43 patients, CSF samples were collected as part of their routine clinical diagnosis investigation. Pre-analytical and analytical procedures were done in accordance with the Alzheimer's Association guidelines for CSF biomarker determination.(16) Briefly, CSF samples were collected in sterile polypropylene tubes, immediately centrifuged at 1800 g for 10 min at 4ºC, aliquoted into polypropylene tubes and stored at –80oC until analysis. CSF amyloid β 1-42 peptide (Aβ42), total tau (t-tau) and phosphorylated tau (p-tau) proteins were measured separately by commercially available sandwich ELISA kits (Innotest, Innogenetics / Fujirebio, Ghent, Belgium).(17) All samples were analyzed in duplicate and performed sequentially in a clinical routine setting. External quality control of the assays was performed under the scope of the Alzheimer's Association Quality Control Program for CSF Biomarkers. (16) This data was correlated with behavioural features.

Behavioral assessment

Behavioral symptoms were assessed using the Portuguese validated versions of two psychiatric scales: the Neuropsychiatric Inventory (NPI)(18) and the Frontal Behavioral Inventory (FBI) scales.(18) The NPI was created by Cummings in 1994(19) to characterize the complex neuropsychiatric symptoms in dementia, mainly AD. It is a caregiver-based behavioral questionnaire that includes 12 items (delusions, hallucinations, agitation/aggression, depression, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, sleep disturbances, and eating disorders) and is the gold-standard for the assessment of neuropsychiatric symptoms in dementia.(20) Each item is scored by the caregiver on frequency (1 – rarely to 4 – very often) and severity (1 – mild to 3 – severe). The NPI total score is based on the sum of the frequency multiplied by the severity of each behavioral domain. Each item possible scores between 0 and 12 with a maximum score of 144. The NPI also evaluates the amount of caregiver distress engendered by each of the neuropsychiatric disorders. A total NPI score and a total caregiver distress score are calculated, in addition to the scores for the individual symptom domains.(5,19,21)

The FBI, created by Kertesz in 1996(22), is also a caregiver based questionnaire with 24 items divided into two categories: FBI negative behavior and FBI disinhibition score. FBI negative behavior includes: apathy, aspontaneity, indifference, inflexibility, personal neglect, disorganization, inattention, loss of insight, logopenia, aphasia and verbal apraxia, perseveration and obsessions (stereotypy), and comprehension (semantic deficit). FBI disinhibition score includes: irritability, excessive jocularity, poor judgment and impulsivity, inappropriateness, hoarding, restlessness or roaming, and aggression. The informant is asked about the extent of the symptoms in the domain on a 4-point scale from 0 (none) to 3 (severe, most of the time). The FBI total score is based on the sum of each item, with a maximum score of 72.(22,23)

Data analysis

Group comparison of demographic variables was performed using One-Way ANOVA test for age, education and age of onset. To find if there was an association between gender and family history with the diagnostic group, the Fisher Exact Test was performed.

The Kruskal Wallis test was performed to analyse if the diagnostic group influence the score of MMSE, NPI and FBI (total score and individual items), as they were non-normally distributed variables. When statistical difference was found, pairwise comparisons were made using the Mann-Whitney U test. The same procedure was made to study the CSF biomarkers across the diagnostic groups.

Pearson correlation was carried out to find if there was an association between the neuropsychiatric scales MMSE score or the disease duration. All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS version 19.0.0 for Windows), and all hypotheses were tested at an α level of 0.05 (2-tailed).

Results

Group demographics

Demographic characteristics of our population as well as the major clinical features of this sample are described in Table 1. The mean age at evaluation was 70.1 ± 8.2 years, while the mean age of disease onset (first symptoms) was 66.1 ± 8.6 years. The mean level of education was low (6.4 ± 4.4 years) and 21 out of the 94 patients (22,3%) had a positive family history. There were no significant differences between diagnostic groups for the mean age (p=0.236), mean age of onset (p=0.288), number of years of education (p=0.789) or family history (p=0.103). Conversely, the same analysis showed a significant difference for gender (p=0.015), mainly due to the nonfluent PPA group, where the observed values for females exceed the expected.

Table 1 - Demographic and clinical data of the studied population

	bvFTD	**AD**	**Nonfluent PPA**	**Semantic PPA**	**Logopenic PPA**
Number of cases	40	33	9	3	9
Age, years (p=0.236)	67.9 ± 6.9	71.9 ± 8.0	70.9 ± 10.0	68.7 ± 4.9	72.7 ± 11.6
Age of onset, years (p=0.288)	64.3 ± 7.8	68.9 ± 8.2	63.3 ± 8.4	64.3 ± 4.6	68.0 ± 10.7
Disease duration, years (p=0.281)	3.2 ± 2.1	5.2 ± 3.7	4.5 ± 4.7	4.3 ± 3.2	5.4 ± 3.0
Gender, male/female **(p=0.015)** *	24/13	10/23	2/7	1/2	4/5
Education, years (p=0.789)	5.9 ± 3.9	7.2 ± 5.1	6.7 ± 4.2	5.3 ± 5.9	5.9 ± 3.9
Family history, positive/negative, n (p=0.103)	12/28	6/27	2/7	1/2	0/9

Results are expressed as means ± standard deviation. * Significant difference across the groups (p<0.05)

Behavioral analysis

In Table 2 we present the mean scores and standard deviations obtained with the application of the cognitive and behavioral scales, and the significant differences observed across groups.

Table 2 - Cognitive and behavioral scares of the studied population

	bvFTD	AD	Nonfluent PPA	Semantic PPA	Logopenic PPA
MMSE* (p=0.000)	23.8 ± 5.4	19.5 ± 5.8	18.4 ± 6.1	9.7 ± 8.3	11.0 ± 7.5
NPI total score* (p=0.001)	21.1 ± 12.7	10.7 ± 10.9	11.7 ± 11.3	32.0 ± 15.5	12.3 ± 9.3
Caregiver distress* (p=0.001)	15.5 ± 8.2	8.7 ± 8.1	7.7 ± 7.1	20.7 ± 8.1	7.3 ± 5.9
FBI total score* (p=0.001)	26.5 ± 7.9	13.9 ± 10.6	15.3 ± 9.0	34.7 ± 13.6	21.4 ± 8.0
FBI negative behavior* (p=0.000)	20.5 ± 5.5	11.3 ± 8.3	12.3 ± 7.2	25.7 ± 7.8	17.4 ± 6.4
FBI disinhibition score* (p=0.000)	6.5 ± 4.5	2.6 ± 3.3	3.0 ± 3.5	9.0 ± 6.2	3.4 ± 2.8

Results are expressed as means ± standard deviation. * Significant difference across the groups ($p<0.05$)

NPI total score showed significant differences across groups (p=0.001) (Table 2). The mean scores on NPI total score are represented on Figure 1 and further commented.

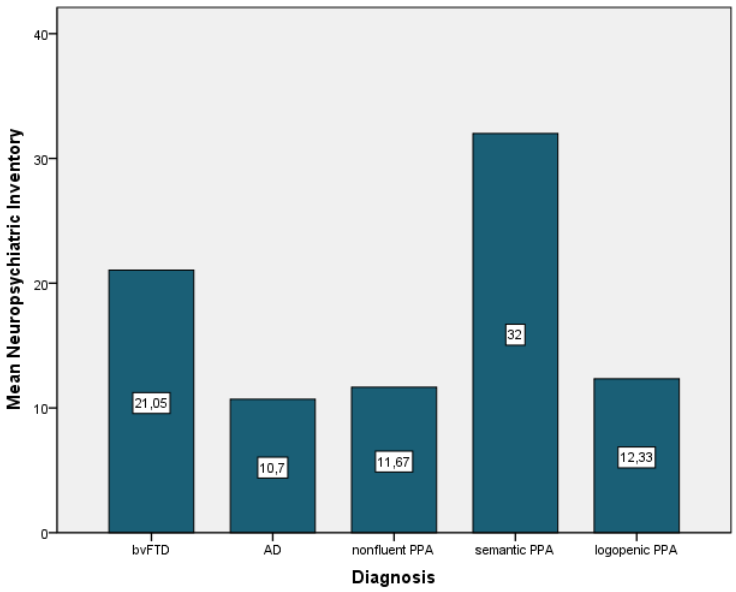

Figure 1 - NPI total score across diagnostic groups

Semantic PPA group is the one with higher total score on NPI, being comparable to bvFTD and both are statistically different from AD (p=0.017)/(p=0.000). Conversely, the nonfluent PPA and logopenic PPA groups presented scores that are quite similar between them and AD, and considerably lower than the bvFTD and semantic PPA groups, but without reaching significance (Table 3).

Table 3 - Pairwise comparisons of the NPI total score across the diagnostic groups

	AD	Nonfluent PPA	Semantic PPA	Logopenic PPA
bvFTD	**.000** *	.056	.166	.070
AD		.829	**.017** *	.442
Nonfluent PPA			.052	.691
Semantic PPA				.052

* Significant difference across the groups (p<0.05)

The NPI-Caregiver distress mean values were also different between diagnostic groups (p=0.001) (Table 2) and the behavioural profile (data not presented) was similar to the one observed on NPI total score, but also achieved statistical significance in the comparison between the semantic PPA and both the nonfluent PPA (p=0.033) and the logopenic PPA groups (p=0.040).

FBI total scores also showed significant differences across groups (p=0.000) (Table 2) and are further represented on Figure 2. In general, the results are equivalent to those obtained with the NPI: higher values on semantic PPA, followed by bvFTD, logopenic PPA, nonfluent PPA and AD. As it can be observed on Figure 2, the main difference comparing to NPI total score, resides on the substantial increment of the psychopathology of the logopenic PPA variant. In fact, the logopenic PPA group achieved statistically significant higher scores than the AD group (p=0.019) (Table 4).

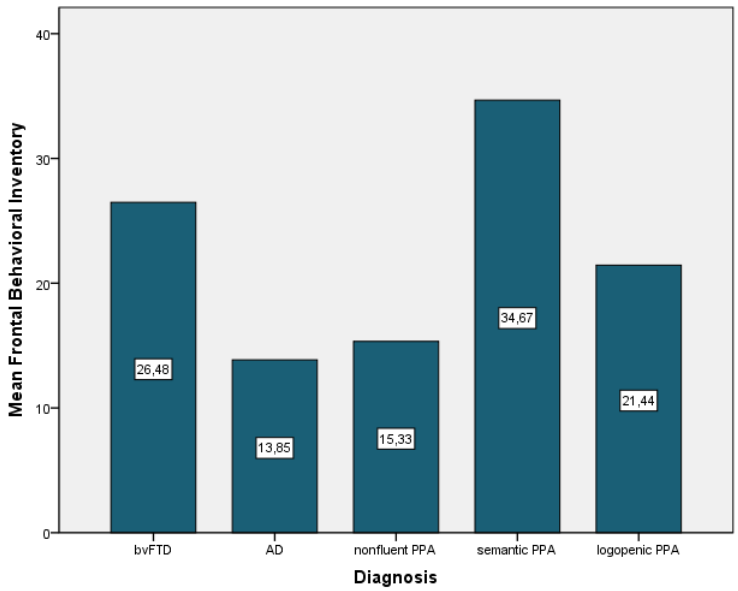

Figure 2 - FBI total score across diagnostic groups

Table 4 - Pairwise comparisons of the FBI Total Score across the diagnostic groups

	AD	Nonfluent PPA	Semantic PPA	Logopenic PPA
bvFTD	**.000** *	**.003** *	.272	.052
AD		.549	**.024** *	**.019** *
Nonfluent PPA			.052	.133
Semantic PPA				.096

* Significant difference across the groups ($p<0.05$)

In order to explain this discrepancy between behavioural scales we considered separately the two main components of FBI (FBI Negative Behavior and FBI Disinhibition Score). By comparing the graphs presented on Figure 3, it is possible to conclude that the increment observed on the FBI total score of the logopenic PPA group is mainly due to the FBI negative behavior domain score.

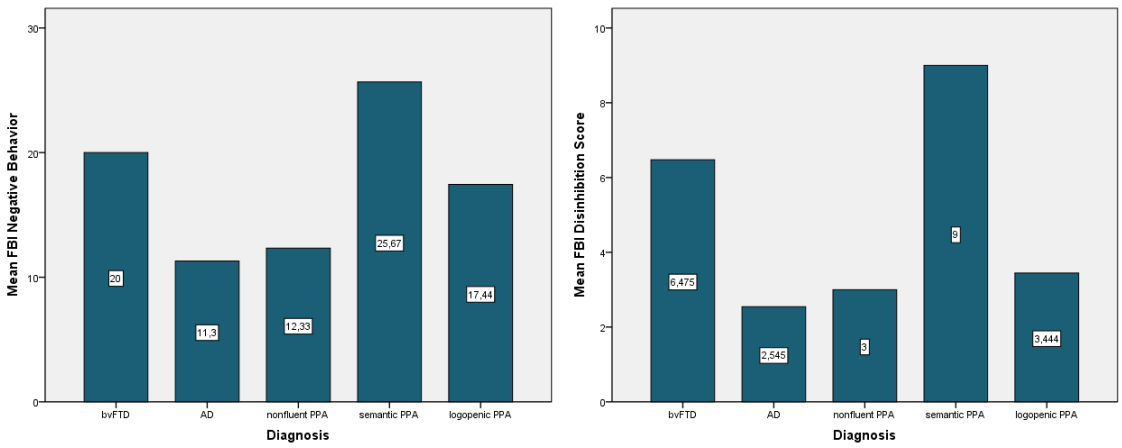

Figure 3 - FBI Negative Behavior and FBI Disinhibition Score across diagnostic groups

Profile of symptoms

Relatively to NPI items, represented on Figure 4, none of the patients with the clinical variants of PPA experienced hallucinations, and delusions were referred in just one patient. Sleep and night time behavior disorders were only observed on nonfluent PPA and logopenic PPA groups. Disinhibition and irritability/lability were only seen on logopenic PPA and semantic PPA groups.

Globally, semantic PPA group presented higher scores on all of the other evaluated items, with the exception of apathy/indifference, where the higher scores were observed on the logopenic PPA group. The most notorious difference between the semantic PPA and the other variants was on the following items: appetite and eating disorders, aberrant motor behavior and agitation/aggression.

When comparing with bvFTD (data not showed), the nonfluent PPA and logopenic PPA groups presented significantly lower scores on apathy/indifference ($p=0.000$)/($p=0.035$), disinhibition ($p=0.005$)/($p=0.016$) and appetite and eating disorders ($p=0.005$)/($p=0.016$). In the comparison with AD (data not showed), semantic PPA presented significantly higher scores on appetite and eating disorders ($p=0.025$).

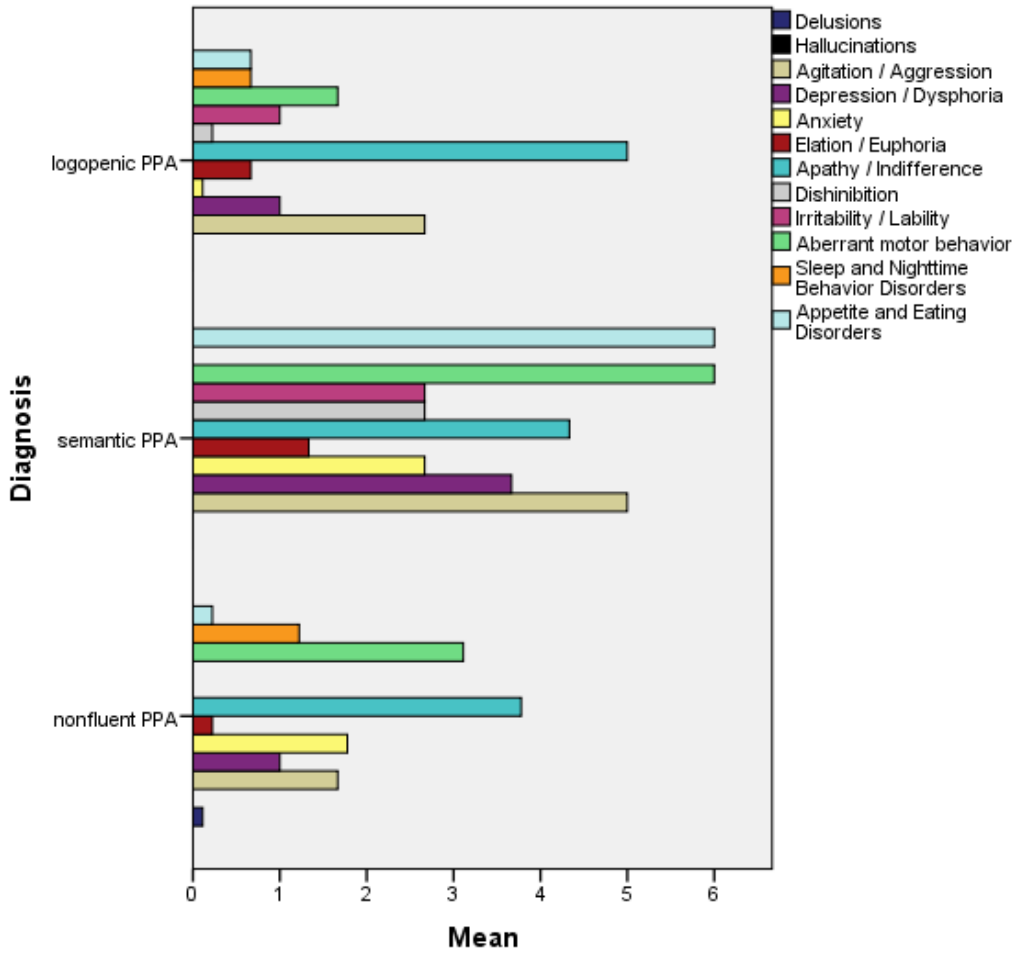

Figure 4 - Severity of the NPI items across the clinical variants of PPA

On FBI negative behavior items, represented on Figure 5, semantic PPA showed the greatest severity on all the items, with the exception of logopenia, with higher scores on logopenic PPA group, and aphasia and verbal apraxia, absent on semantic PPA e higher scored on nonfluent PPA group, as expected.

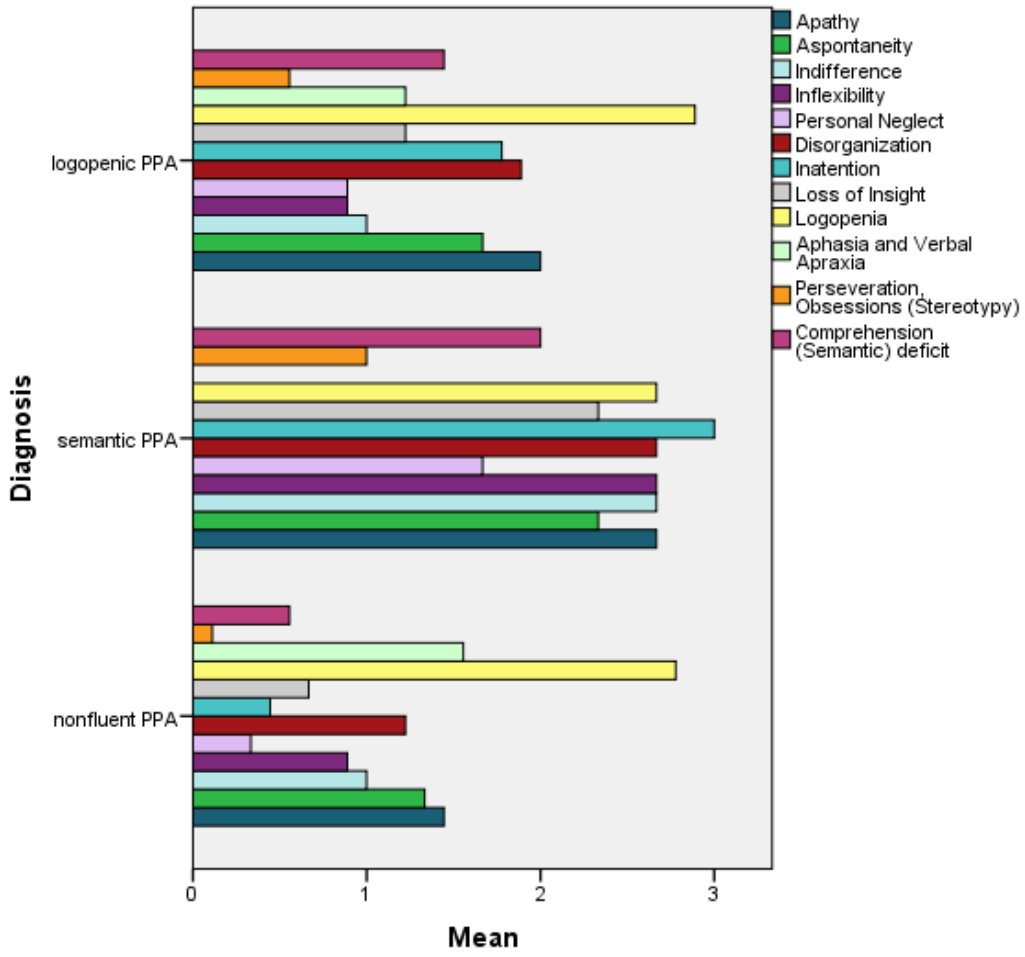

Figure 5 - Severity of the FBI Negative Behavior items across the clinical variants of PPA

The items with statistically significant differences across groups are: inattention, when comparing logopenic PPA (p=0.025) and semantic PPA (p=0.011) with nonfluent PPA; indifference, when comparing semantic PPA with nonfluent PPA (p=0.045); inflexibility, when comparing semantic PPA with nonfluent PPA (p=0.021) and logopenic PPA (p=0.035); and loss of insight, when comparing semantic PPA with nonfluent PPA (p=0.045).

The nonfluent PPA group presented statistically significant lower scores, when comparing with bvFTD group, on 8 out of 12 items: apathy (p=0.000), aspontaneity (p=0.002), indifference (p=0.007), inflexibility (p=0.0001), personal neglect (p=0.002), disorganization

(p=0.023), inattention (p=0.009), loss of insight (p=0.001), poor judgment and impulsivity (p=0.002), and inappropriateness (p=0.041), similar to the AD group (data not showed).

The logopenic PPA group presented statistically significant lower scores, when comparing with bvFTD group, on 5 out of 12 items: apathy (p=0.000), aspontaneity (p=0.001), indifference (p=0.017), inflexibility (p=0.001), loss of insight (p=0.012) and poor judgment and impulsivity (p=0.000), also being similar to the AD group on those items (data not showed).

Relatively to FBI disinhibition score, presented on Figure 6, alien hand and/or apraxia and hypersexuality were not referred on any clinical variant of PPA. Aggression and hyperorality/food fats were not seen on the nonfluent PPA group. On all the items, the semantic PPA group presented the higher scores, and the nonfluent PPA and logopenic PPA groups revealed a similar profile.

The nonfluent PPA group showed significant lower scores, when compared with bvFTD, on: poor judgment and impulsivity (p=0.002) and inappropriateness (p=0.041), being comparable with the AD group. Both semantic PPA and logopenic PPA groups revealed significant higher scores on hyperorality/food fads when compared with AD group (p=0.001)/(p=0.006).

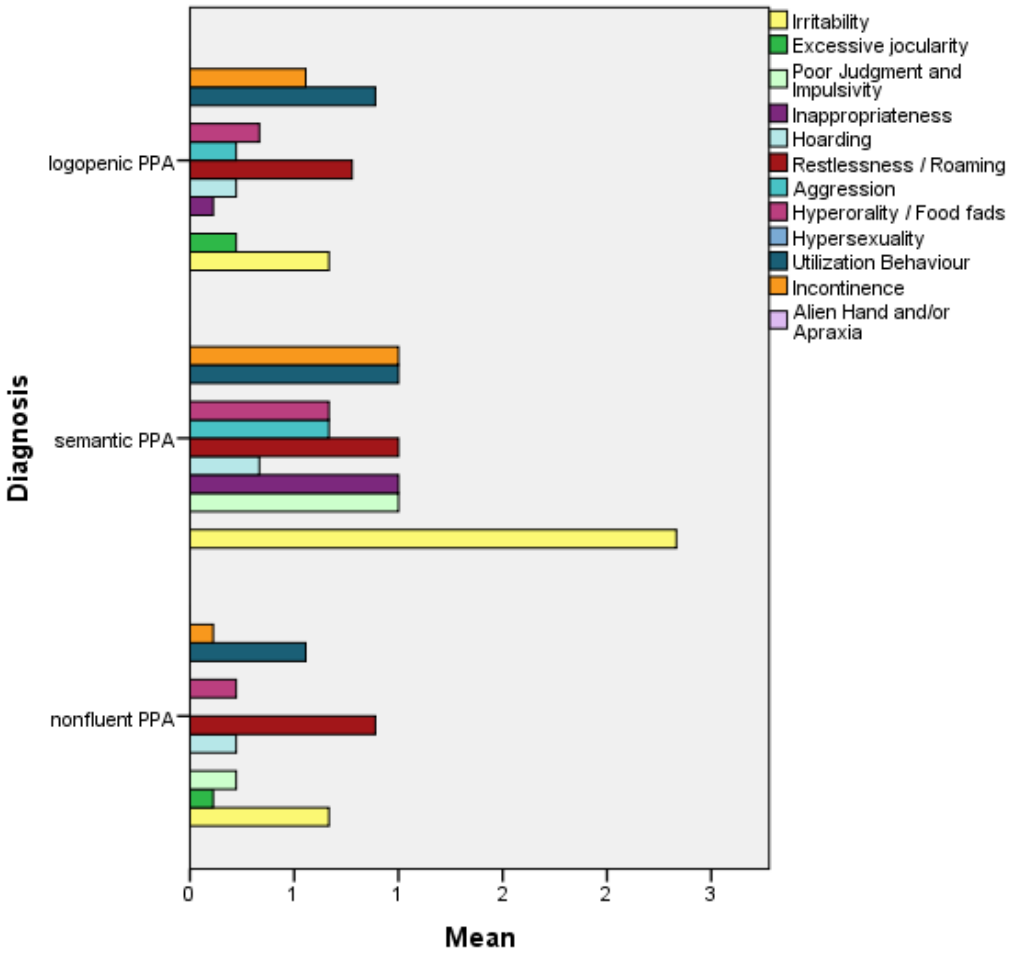

Figure 6 - Severity of the FBI Disinhibition score items across the clinical variants of PPA

Relation between behavioral changes and biological variables

Disease Duration

A positive statistically significant correlation between the disease duration and the FBI total scores was found for the logopenic PPA group (p=0.042, Pearson correlation=0.772).

With the exception mentioned above, NPI total score, caregiver distress, FBI total score, FBI negative behavior and FBI disinhibition score were not significantly correlated to disease duration for the diagnostic groups.

Mini Mental State Examination

The mean scores on MMSE are represented on Figure 7. Statistically significant differences were found across the diagnostic groups (p=0.000) (Table 2).

As it can be seen on Figure 7, all the diagnostic groups (AD, nonfluent PPA, semantic PPA and logopenic PPA) present lower scores on MMSE when comparing with bvFTD group. Comparisons between the diagnostic groups are represented on Table 5. All the patients presenting with PPA showed significantly lower scores on MMSE when compared with bvFTD: nonfluent PPA (p=0.018), semantic PPA (p=0.011) and logopenic PPA (p=0.000). When comparing with the AD group, the nonfluent PPA group presented with similar MMSE scores, whereas logopenic PPA and semantic PPA groups showed lower scores, although only statistically significant on the logopenic PPA group (p=0.008), because of the low number of cases seen in the semantic PPA group.

Relatively to the clinical variants of PPA, semantic PPA and logopenic PPA groups revealed lower scores on MMSE, comparing to nonfluent PPA, although only statistically significant between the logopenic PPA and the nonfluent PPA groups (p=0.034).

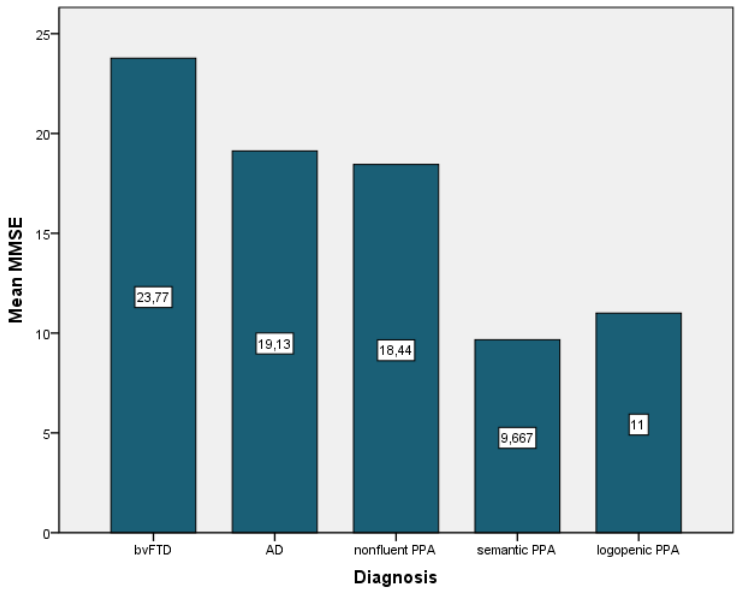

Figure 7 - Mean Score of MMSE across diagnostic groups

Table 5 - Pairwise comparisons of MMSE score across the diagnostic groups

	AD	Nonfluent PPA	Semantic PPA	Logopenic PPA
bvFTD	**.000** *	**.018** *	**.011** *	**.000** *
AD		.598	.053	**.008** *
Nonfluent PPA			.114	**.034** *
Semantic PPA				.710

* Significant difference across the groups ($p<0.05$)

CSF biomarkers

On Table 6 are represented the mean values and standard deviation of the CSF biomarkers for the studied population.

Statistically significant differences were found on CSF Aβ42 across the diagnostic groups (p=0.04). The difference is significant between the bvFTD group when comparing with AD (p=0.005) and with logopenic PPA group (p=0.004), with those two groups presenting

significant lower levels of CSF Aβ42. Additionally, the logopenic PPA group also achieve statistical significance when compared with the nonfluent PPA group (p=0.027).

Table 6 - Mean values and standard deviation of the CSF biomarkers on the studied population

	bvFTD	AD	Nonfluent PPA	Semantic PPA	Logopenic PPA
CSF Aβ42* (p=0.004)	795.7 ± 251.9	581.1 ± 159.2	611.0 ± 81.4	691.0 ± 491.4	342.2 ± 162.9
CSF t-tau (p=0.069)	293.9 ± 185.1	602.0 ± 304.7	343.7 ± 202.4	432.9 ± 290.0	473.0 ± 272.3
CSF p-tau (p=0.058)	73.1 ± 179.5	84.9 ± 59.3	42.1 ± 26.7	55.0 ± 16.7	226.0 ± 333.7

Results are expressed as means ± standard deviation. * Significant difference across the groups ($p<0.05$)

No association was found between CSF t-tau protein p-tau proteins and the behavioral scales (NPI total score, FBI total score, FBI negative behavior and FBI disinhibition) at any diagnostic group.

Discussion and Conclusions

The primary goal of this study was to compare the profile and severity of the behavioral of symptoms in the clinical variants of PPA and identify features that best differentiate each other, using NPI and FBI scales.

It stood out that psychotic symptoms (delusions and hallucinations) are either rare or absent on our sample, which was also observed on previous studies.(8,13,24–26) The same was verified for alien hand and/or apraxia and hypersexuality, which in the latter can be attributed to a lack of information given by the caregiver regarding this item.

The most severe behaviors, evaluated by the NPI scale, were apathy/indifference for nonfluent PPA and logopenic PPA groups, and aberrant motor behavior plus appetite and eating disorders for semantic PPA group. On what concerns to the negative domain of FBI scale, the most severe symptoms were: logopenia for both nonfluent PPA and logopenic PPA groups, and inattention for semantic PPA group. Relatively to the disinhibition domain of FBI, the most severe were: restlessness and roaming on nonfluent PPA group, irritability on semantic PPA group and utilization behavior on logopenic PPA group.

In general, the behavioral symptoms presented a much higher severity on semantic PPA comparing with the other variants of PPA, particularly on appetite and eating disorders, aberrant motor behavior and agitation/aggression. These findings overlap those in previous studies of PPA behavioral changes, mainly for semantic PPA and nonfluent PPA.(8,13)

We did not find the statistical differences that we expected across the PPA subgroups using the NPI items, specifically disinhibition and appetite and eating disorders, which proven to differentiate semantic PPA from the other groups on previous works.(13,26) However, in our sample, there was no differentiating items to logopenic PPA and nonfluent PPA groups

when directly compared with each other, which was in accordance with the existing literature. (13,26)

In our results, the FBI scale allowed us to find statistically significant differences among the PPA variants on 4 items (inattention, indifference, inflexibility, and loss of insight), suggesting that it can be a better scale to apply on this group of patients. However, as few studies are available, more research is needed.

Our second aim was to compare neuropsychiatric profiles of these variants with those found in the typical forms of bvFTD and AD, as behavioral symptoms can emerge on PPA as a surrogate of the underlying pathology. Besides, it has been proposed that the differences in behavioral symptoms possibly reflect distinct and specific sites of anatomic involvement. The tendency for semantic PPA to show behavioral changes like those of bvFTD has been associated with atrophy on anterior temporal lobes, mainly left sided, but also on orbitofrontal, medial frontal and insular regions.(13,27) Also, the damage of the uncinate fasciculus, a pathway between the anterior part of the temporal lobe and the orbitofrontal region, that was correlated with semantic processing deficits, has recently been associated with behavioral deficits.(9) It was also demonstrated that semantic PPA have the most severe damage on the uncinate fasciculus, when compared with the other variants of PPA.(9) In contrast, nonfluent PPA and logopenic PPA do not involve medial and orbital frontal structures, what may explain the relative absence of behaviors like those present in bvFTD. Nonfluent PPA and logopenic PPA are associated with left perisylvian atrophy, with frontal predominance in nonfluent PPA(27) and parietal predominance on logopenic PPA.(13)

Congruent with that hypothesis, we found that the semantic PPA group had significantly higher scores than AD patients on NPI and FBI total scores, and FBI negative behavior, being comparable with bvFTD group. The nonfluent PPA group scored significantly lower on FBI scale when compared with bvFTD group, being the PPA group that demonstrated less

behavioral changes, and comparable with AD group. Finally, an increment of the mean score of the logopenic PPA variant was verified on FBI scale, due to is negative domain, presenting similar scores as the bvFTD group, and statistical significant difference was found on FBI total score and FBI negative behavior when compared with AD group.

Strictly based on this analysis, some similarities emerged between semantic PPA and bvFTD and between nonfluent PPA and AD, while the logopenic PPA variant presents a transitional profile between AD and bvFTD. Nonetheless behavioral analysis profile revealed that nonfluent PPA parallels semantic PPA on the most severe behavioral symptoms, despite those behaviors being rarer and less severe on nonfluent PPA. Combining these results, we propose that on most cases, these variants share the same baseline neurodegenerative pathology, FTLD.

When compared with bvFTD group, nonfluent PPA and logopenic PPA patients presented significantly lower scores on a lot of behavioral items (apathy, indifference, disinhibition, appetite and eating disorders, aspontaneity, inflexibility, loss of insight, poor judgment and impulsivity). The nonfluent PPA group demonstrated even more differences, presenting with lower scores on additional items (personal neglect, disorganization, inattention and inappropriateness), being comparable with AD patients.

These results are consistent with previous descriptions(28) suggesting that semantic PPA is associated with more severe behavioral disturbances than other variants of PPA, being comparable with bvFTD on many items,(13) whereas nonfluent and logopenic PPA, present with significant less behavioral symptoms than bvFTD, with a pattern more similar to AD.

Additionally, we studied a few variables capable of influence the behavioral symptoms and potentially indicate the underlying pathology.

The differences found on MMSE score were as expected, as it is heavily dependent on language skill and PPA patients have major difficulty in the language domain. These results are congruent with previous studies that found out that MMSE overestimates the level of dementia severity in PPA patients.(29)

With the exception of the logopenic PPA group, where a statistically significant association between the disease duration and the FBI total scores were found, being higher scores on FBI associated with greater disease duration, on the remain diagnostic groups, NPI and FBI scores were not related to disease duration, which is also consistent with previous data. (8,13) As so, symptoms evaluated by those scales are more likely to be markers of the underlying pathology, instead of disease progression. In the evaluation of CSF biomarkers, the logopenic PPA group presented a similar profile to the AD group, with both having significantly lower levels of CSF Aβ42 when comparing with bvFTD group. This provides a support for an AD underlying pathology in logopenic PPA.

Regarding the behavioral analysis no association was found between t-tau and p-tau CSF proteins, used on this case as severity markers, and NPI and FBI scores at any diagnostic group, which reinforces the fact that those behavioral scales do not associate with disease severity but may be related to the underlying pathology.

There are clinical implications of this study, emphasizing different treatment, care and support needs for both patients and caregivers of each PPA group. It may have diagnostic implications as well. On the early course of PPA syndrome, the emerging of behavioral symptoms may be a clue supporting the diagnosis of semantic PPA and tools like NPI and FBI are important to assess this.

The incorporation of behavioral features analysis and the assessment of their severity more systematically will allow better diagnostic and accurate focus on the appropriate therapeutic intervention, improving the quality of life for patients and their families.

In general, caregivers of FTLD patients have been recognized as bearing a greater burden and being more distressed than caregivers of AD patients.(30) On our sample we observe that on the semantic PPA and bvFTD groups, caregivers presented higher levels of distress, comparing to other diagnostic groups. This enforces the need for appropriate psychosocial education and care support for patients and their caregivers.

One limitation of this study is the relatively small sample sizes. We believe that with bigger samples, more statistical significant difference across groups would emerge. Besides, the fact that FBI and NPI are dependent on the reliability of the caregivers doesn't allows us to discard the possibility of a discrepancy between the patient behavioral changes and the informant's report, which can be influenced by their won psychological status and distress. Also, it is difficult in some cases to distinguish if a specific behavior emerged by the progression of the disease or if it was part of patient's baseline personality.

In conclusion, our study confirms that PPA variants are heterogeneous concerning the phenomenology and severity of the behavioural symptoms. At the same time, the behavioural profile of each variant seems to be related to the underlying pathology pointing out for an association between the semantic and the nonfluent variants with frontotemporal degeneration, while the logopenic variant is more ambivalent, emerging as an inconsistent or transitional phenotype between AD and FTLD. These assumptions are corroborated by CSF biomarkers and should be considered in differential diagnosis and rational treatment.

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