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Neuropsychiatric Aspects of Primary Progressive Aphasia

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Abstract

Few studies have reported neuropsychiatric symptoms (NPS) in Primary Progressive Aphasia (PPA), a neurodegenerative disorder that primarily affects the left hemisphere. Depression is associated with left-sided stroke, but it remains unclear if depression and other NPS are also associated with PPA. The authors compared the frequency of NPS in 55 cases of PPA with 110 cognitively normal persons matched for age, sex and education. Depression, apathy, agitation, anxiety, appetite change, and irritability are associated with PPA. Hallucinations, delusion and night time behavior were not associated with PPA.

INTRODUCTION

Primary Progressive Aphasia (PPA) is a neurodegenerative disorder characterized by an isolated and gradual dissolution of language function[1]. Cases of PPA-like aphasias *along with* behavioral disturbances were first noted by Pick in 1892[2], but it was almost one hundred years later, in 1982, when PPA was more adequately defined by Mesulam[1]. To diagnose PPA, memory, visual processing, and personality of the individual are relatively intact and language dysfunction is the salient feature for about the first 2 years of the disease[3-6]. Subsequently, as the disease progresses other cognitive domains may become impaired leading to PPA-plus, although the language dysfunction remains the prominent impairment[7]. This particular isolation of language dysfunction is what distinguishes PPA from behavioral variant frontotemporal dementia (bvFTD)[8, 9] and typical forms of Alzheimer's dementia[7]. PPA is classified into agrammatic (PPA-G), semantic (PPA-S), and logopenic (PPA-L) variants[10, 11]. Additionally, each PPA variant has a different probability of association with Alzheimer disease vs frontotemporal lobar degeneration[10].

Even though there is a growing interest in the investigation of the nosology, neuropsychology, and neuropathology of PPA, little is known about the neuropsychiatric aspects of PPA[8,12]. Banks and Weintraub compared the frequency of NPS in PPA with that of bvFTD[13, 14]. We conducted a similar study, but we sought to examine as to whether NPS occurs in PPA over and above expected in the general population by conducting a case-control study in which the controls were sampled from an ongoing population-based study. Our study is likely to contribute to the budding literature on the neuropsychiatric aspects of PPA. This is important as NPS may be clinical markers for various phases of the underlying neurodegenerative disorder manifesting with PPA and subsequently in PPA-plus[13].

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METHODS

The study was approved by Mayo Clinic and Olmsted Medical Center Institutional Review Board (IRB).

Study design

Case-Control Study.

Participants

55 cases of PPA were *individually* matched by age, sex, and education at a ratio of 1:2 with 110 cognitively normal persons sampled from an ongoing population-based study.

Definition of Cases

A consensus panel of behavioral neurologists, neuropsychologists and nurses made a diagnosis of PPA based on Mesulam's criteria : insidious onset and gradual progression of primary language problem such as word-finding, object naming, or word comprehension impairments as manifested during conversations or as assessed through formal neuropsychological testing, all limitations of daily activities are attributable to the language impairment with in about the first two years of the illness, additionally no significant impairment in other cognitive domains with in the first two years (acalculia and ideomotor apraxia may be present within the first two years of the illness), absence of "specific" causes such as stroke or tumor as ascertained by neuroimaging, other domains possibly affected after the first 2 years but language remains to be the predominant cognitive impairment[4].

Definition of Controls

The controls are participants of the Mayo Clinic Study of Aging, which is a population-based study of aging and mild cognitive impairment (MCI) in Olmsted County, Minnesota[15]. Elderly persons are recruited using stratified random sampling from the target population of nearly 10,000 elderly individuals living in Olmsted County on the prevalence date of October 1, 2004. The sampling involved equal allocation of men and women in two age strata, 70 to 79 years old and 80 to 89 years old. Each participant in the Mayo Clinic Study of Aging underwent the following three baseline face-to-face evaluations: (1) a neurological evaluation by a behavioral neurologist; (2) a risk factor assessment by a nurse or study coordinator; and (3) neuropsychological assessments of memory, executive function, language and visuospatial skills. The tests are administered by a psychometrist and the results are interpreted by a neuropsychologist. The interview by the nurse or study coordinator includes administration of the Clinical Dementia Rating Scale (CDR)[16] to the participant and to an informant as well as collection of neuropsychiatric data. An expert consensus panel of physicians, nurses and psychologists meets on a weekly basis and reviews the neurological, nursing data and neuropsychological data and classifies a person as cognitively normal or not[15].

Measurement of Neuropsychiatric Symptoms

The NPS of all cases and controls were measured by the Neuropsychiatric Inventory (NPI), with the exception of 1 case and 2 controls whose NPS were measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q). The NPI and NPI-Q measure twelve behavioral domains including depression, apathy, irritability, agitation, anxiety, disinhibition, delusions, aberrant motor behavior, euphoria, hallucinations, night-time behaviors, and appetite/eating change. Both NPI and NPI-Q have been shown to be reliable and valid scales[17, 18].

An experienced research nurse or psychometrist administered the NPI to a spouse or other informant for all study participants. The information was gathered through a series of screening questions for each of the 12 behavioral domains. If the informant answered a question affirmatively, the specific behavior was further queried for frequency (range 1 to 4) and severity (score of 1 to 3). The product of frequency and severity gave the composite score (maximum 12) for each of the 12 behaviors. Adding the total scores of the 12 behavioral domains gave the total NPI score.

Statistical Analysis

We compared the neuropsychiatric profiles of cases and controls by using odds ratios (OR) and the corresponding 95% confidence intervals (95% CI). The OR and 95% CI were computed by multi-variable logistic regression analysis. Statistical testing was done at the conventional 2-tailed alpha level of 0.05. All analyses were performed by using SAS (Cary, NC). The cases (n = 55) and controls (n = 110) were individually matched by age, sex, and education, hence, by design there was no difference between cases and controls in these three variables. Functional ability as measured by CDR was entered in the model as a covariate. Therefore, the design and analysis of the study ensured that the differences in the frequency of NPS between cases and controls are not due to age, sex, education or functional status.

RESULTS

Consistent with the matched case-control design, there was no significant difference between PPA and cognitively normal persons in age ($p = 1.00$), sex ($p = 0.31$) and education ($p= 0.56$). The median (range) age of the PPA group was 70.5 and that of the cognitively normal group was 70.8. The sex distribution was also identical in both groups [(30/55 cases of PPA (54.5%) and 60/110 of the cognitively normal persons (54.5%) were males)]. The median education for both cases and controls was 14 years. There was no difference between cases and controls ($p =0.99$) when education was also dichotomized at 12 years of education (≤ 12 years vs > 12 years of education). As expected, there was a significant difference in median CDR score between PPA and controls ($p<0.001$), it was 0.5 for PPA and “0” for controls. As expected, the median BNT score was 21.5 for PPA where as it was 55 for controls. We chose to use “median” as it is a more robust measure of central tendency than “mean” which is quite sensitive to outliers.

The frequency distribution of NPS is displayed in the Table. The comparison of NPS between PPA cases and controls was made after adjusting for age, sex, education and CDR. The median (range) NPI score for PPA group was 2.0 (0.0-9.0), where as it was 0 (0 to 5) for the cognitively normal group. The most distinguishing features between subjects with PPA and those with controls were apathy ($P<0.001$), agitation ($P=0.003$), anxiety ($P=0.009$), depression ($P<0.001$), appetite change ($P<0.001$), and irritability ($P=0.004$). Delusions, euphoria, and hallucinations were rare or absent in both the PPA and cognitively normal groups. Aberrant motor behavior and disinhibition were present in only PPA subjects. Night-time behaviors were not found to be significantly associated with PPA. Further details of the neuropsychiatric data comparing subjects with PPA and cognitively normal persons are shown in Table.

DISCUSSION

Here we report a case-control study that compared the frequency of neuropsychiatric features of 55 cases of PPA with 110 cognitively normal persons. The neuropsychiatric comparisons were made after adjusting for potential confounders. The matched case-control design ensured that the PPA cases were not different from controls in age, sex and

education. Functional status as measured by CDR was adjusted by analysis. We observed that PPA is associated with depression, apathy, agitation, anxiety, appetite change, and irritability. Symptoms such as hallucinations and delusions were virtually absent in PPA. Night time behavior was not significantly associated with PPA. Our findings are consistent with what had been observed by Banks and Weintraub who were perhaps the first to systematically examine NPS in PPA[13]. They used NPI-Q to measure NPS in PPA (n = 42) then compared it with bvFTD (n = 28). They observed that the two groups differed in both quantity and quality of NPS where in they observed depression, anxiety and irritability in PPA, where as apathy, disinhibition and aberrant motor behavior were more common in the bvFTD group. The investigators further divided the PPA group into early stage (< 5 years) and late stage (≥ 5 years) based on the duration of the illness. They noted that patients with early stage PPA tended to have mood symptoms where as late stage PPA tended to have more symptoms of disinhibition and night-time behaviors; we also did not observe hallucinations, delusions and night-time behaviors to be significant problems in PPA. Our findings are also consistent with depressive symptoms observed by other investigators[1, 12, 19]. In 1982, when Mesulam first reported PPA, four of the six PPA patients showed signs of reactive depression, sadness, and distress after the onset of PPA.[1].

As discussed above, NPS particularly non-psychotic symptoms are associated with PPA. This is a cross-sectional association and this does not meant that it is a cause-effect association. Even though, this study is not designed to examine mechanism of disease, nevertheless, it is important to speculate on potential mechanisms that link PPA with NPS. Since PPA is a predominantly left hemisphere disease, we will briefly examine theories relevant to NPS and hemispheric dysfunction. The reader is referred elsewhere for a comprehensive and authoritative review of the interaction of emotional disorders and neurological diseases[23]. Heilman and colleagues trace the work in the area of emotional experience and mood to Goldstein who as early as 1948 commented on the association between anxious depression and left hemisphere lesions[23]. Studies involving patients with cerebral infarcts indicate that left-sided lesions, particularly the more anteriorly located ones tend to be associated with depression[20]. This has been replicated in other stroke-depression studies as well as in left sided brain injury [21,22]. Heilman suggests that in the normal state, the left side of the brain imparts a positive bias to emotional experience; therefore, in pathological states the normal bias to hedonia is lost and the patient's emotional state becomes negative (dysphoric). In contrast, the right hemisphere imparts a negative bias to emotional experience, so stroke of the right hemisphere is associated with euphoria since the normal negative bias is lost in a pathological state[24]. Additionally, several other theories have also been proposed to explain the laterality of emotional experience and behavior including feedback and central theories. The reader is referred elsewhere for detailed discussion of the pathophysiology of emotional disorders related to hemispheric dysfunction[23].

In summary, this study indicates that NPS particularly non-psychotic symptoms are associated with PPA. To our knowledge, this may be one of the few studies that has systematically examined these associations. However, our findings need to be replicated by a prospective cohort study. Additionally, future studies need to be conducted to examine potential mechanisms linking NPS with PPA. At this point in time, we speculate that NPS is an emotional reaction to language impairment, or NPS is a non-cognitive manifestation of the neurodegenerative process driving both the PPA and NPS.

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Table

Frequency of Neuropsychiatric Features among PPA and Cognitively Normal Participants*

NPI domain	Normal N=110 (%)	PPA N=55 (%)	OR (95% CI)	P-value
Depression/Dysphoria	6 (5.5)	21 (38.2)	12.56 (3.72, 42.4)	<0.001
Night-time Behavior	13 (11.8)	12 (21.8)	2.00 (0.87, 4.61)	0.10
Irritability/Lability	3 (2.7)	10 (18.2)	9.29 (2.02, 42.7)	0.004
Agitation	1 (0.9)	11 (20.0)	22.00 (2.84, 170.4)	0.003
Aberrant Motor Behavior	0 (0.0)	13 (23.6)	N/A	
Disinhibition	0 (0.0)	11 (20.0)	N/A	
Anxiety	1 (0.9)	8 (14.8)	16.00 (2.00, 127.9)	0.009
Appetite/Eating Change	3 (2.7)	14 (25.9)	9.33 (2.68, 32.5)	<0.001
Apathy/Indifference	4 (3.6)	26 (48.1)	24.53 (5.81, 103.6)	<0.001
Euphoria/Elation	0 (0.0)	5 (9.3)	N/A	
Delusions	1 (0.9)	4 (7.4)	8.00 (0.89, 71.6)	0.063
Hallucinations	0 (0.0)	0 (0.0)	N/A	

*Adjusted for age, sex, education (by matched case-control design) and functional status (CDR) by statistical analysis.