Aphasia: The natural history of basic progressive aphasia

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ABSTRACT

Primary Progressive Aphasia (PPA) is split into three archetypal subtypes, each of which is defined by a single aphasia symptom. Although other cognitive, behavioural, and motor domains may become engaged later in their course, little is known about each subtype's progression profile in relation to the other subtypes. 24 patients diagnosed with Semantic Variant (svPPA), 22 with non-fluent variant (nfvPPA), and 18 with Logopenic variant (lvPPA) were collected and followed up for 1–6 years in this longitudinal retrospective cohort study based on new biomarker-supported diagnostic criteria. The severity of symptoms, scores on cognitive tests and neuropsychiatric inventories, and development into another syndrome were all evaluated. Over time, lvPPA developed broader language issues (PPA-extended) and nfvPPA developed mutism, although semantic impairment remained the primary issue in svPPA. Aside from linguistic issues, svPPA acquired significant behavioural issues, whereas lvPPA showed a higher deterioration in cognition. Motor impairments were more prevalent in the nfvPPA group. Furthermore, 65.6 percent of individuals met the clinical criteria for another neurodegenerative condition within 5 years of their clinical beginning (PPA-plus). The clinical features of 14 out of 24 (58 percent) svPPA patients were consistent with behavioural variant frontotemporal dementia, whereas 15/18 (83%) lvPPA patients were consistent with Alzheimer disease dementia. In addition, 12/22 (54%) of the nfvPPA patients advanced to satisfy the diagnostic criteria for corticobasal syndrome and progressive supranuclear palsy. Despite the fact that aphasia is the syndrome's initial and distinguishing feature, our longitudinal findings revealed that PPA is not a language-specific disorder, and that each subtype's course differs significantly in terms of symptom nature and disease duration.

INTRODUCTION

Since Marsel Mesulam first described the clinical condition of Primary Progressive Aphasia (PPA) in six patients in 1982, research has concentrated on characterizing the clinical symptoms, underlying molecular pathologies, and genetic foundation of PPA. The syndrome is currently split into three variants: semantic (svPPA), non-fluent/agrammatic (nfvPPA), and logopenic (lvPPA) (lvPPA). On neuroimaging, SvPPA is associated with loss of word and/or object meaning, decreased confrontation naming, surface dyslexia, as well as anterior temporal atrophy. In the presence of impairment of the left posterior frontal and insular regions, nfvPPA is characterized by effortful speech, limited speech production, and agrammatism. The third syndromic form, lvPPA, causes difficulty identifying words and repeating them, as well as temporoparietal atrophy on the left side of the brain [1]. Although prior research indicates that nfvPPA is the most heritable PPA variant (30–40% with a family history), a more rigorous investigation revealed that a definite autosomal dominant history is uncommon in all PPA subtypes. While svPPA and nfvPPA are linked to the diseases of Frontotemporal Lobar Degeneration (FTLD), lvPPA is linked to the pathologies of Alzheimer's disease [2].

The existing diagnostic criteria are known to not encompass all PPA patients, with one-third to half of PPA syndromes remaining unclassifiable. As a result, Mesulam and colleagues (2014) coined the term "PPA mixed" to describe individuals who have both comprehension and grammar problems, which is frequently due to the pathology of Alzheimer's disease. Several other research, on the other hand, has found that the undeclared group may have more complex linguistic issues. Another difficult issue for clinicians is that patients who initially met all of the diagnostic criteria for one of the PPA subtypes develop additional symptoms both inside and outside the language domain as the disease progresses. Louwersheimer et al. coined the term "PPA extended" to describe cases that initially meet the core criteria of one PPA subtype but then progress to another PPA subtype's characteristic language symptoms, whereas Rogalski and Mesulam (2009) coined the term "PPA + (plus)" to describe the progression into other neurodegenerative syndromes that accompany the PPA diagnosis [3]. To our knowledge, the patterns of the three PPA subtypes' PPA-extended and PPA-plus forms have never been investigated systematically in a well-categorized PPA cohort. So far, the few longitudinal research on PPA has either been published before the current diagnostic criteria were established in 2011 or have focused on a single subtype or cognitive domain. Two previous longitudinal cohort studies, to our knowledge, have adopted the current categorization and focused on the syndrome's whole illness course. Unfortunately, these studies are difficult to evaluate due to a lack of information about the participants' amyloid status and a lack of specific descriptions of symptomatology. Furthermore, there is a lack of an overall perspective of the development profiles, as well as patterns of PPA-extended and PPA-plus versions of the PPA subtypes.

METHODS

Patient selection

Between January 2011 and March 2019, 126 patients who met the current diagnostic criteria for PPA were retrospectively included from the Amsterdam Dementia Cohort [4]. The unclassified individuals (n=14) were removed from the study since the goal was to show the progression pattern of each subgroup. We also eliminated the cases (n=5) that had the clinical profile and neuroimaging markers of right temporal variant frontotemporal dementia on closer inspection. This is significant since right temporal variant frontotemporal dementia has been demonstrated not to be a primary language disorder and to have a distinct development pattern than svPPA. It's worth noting that all of the rtvFTD instances that were excluded were right-handed. In addition, cases in which the patient was not a native Dutch speaker (n=3), had no records of amyloid status (n=1), or had less than a year of clinical follow-up (n=39) were omitted. CSF amyloid beta-42 levels (n=54) or amyloid PET data (n=32) were available for the remaining individuals. Initial neuroimaging (MRI n=62, CT n=2, FDG-PET n=14) met PPA radiological diagnostic criteria. The final selection resulted in a sample of 64 PPA patients, 24 of whom were diagnosed with svPPA, 22 with nfvPPA, and 18 with lvPPA, according to current diagnostic criteria [5].

Statistical analysis

SPSS Statistics, version 24.0 (IBM), and R Studio were used to conduct the analyses (R Core Team, 2018). Chi-square was used to assess differences in categorical variable frequencies between groups (svPPA, nfPPA, and lvPPA), and one-way ANOVA or Kruskal–Wallis analysis was used to compare continuous variables between groups, depending on the distribution of the variables based on the Shapiro–Wilk normality test. The Bonferroni correction was used to correct post hoc comparisons for multiple comparisons. For each individual, Linear Mixed Models (LMM) with a random intercept and slope were used to measure the change in cognitive functioning across time. For each diagnostic group, separate models were run for each cognitive test (dependent) with time (measured on a continuous level) as the independent

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variable. To determine progression into PPA-plus, nonparametric survival analyses were undertaken using Kaplan–Meier estimates Interquartile Range (IQR)] with post hoc Mantel-Cox log-rank testing. The data was thresholded at a corrected p-value of less than 0.05 [6].

RESULTS

In the lvPPA group, the gender distribution was nearly equal. The majority of svPPA subjects, on the other hand, were male, whereas the nfvPPA group was predominantly female. The CDR and IADL scores did not differ across diagnostic groups in terms of age, symptom or follow-up time, or CDR and IADL scores. All svPPA patients tested negative for amyloid, but one (4%) nfvPPA patient and 15 (83%) lvPPA patients tested positive for amyloid. Although a few patients in each group were left-handed, there was no statistical difference in the distribution of handedness (p=0.86) [7]. To determine receptive language dominance in left-handed people, we looked at whether clinical symptoms matched the anatomic distribution of cortical atrophy and clinical presentation. One nfvPPA patient with a hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (C9orf72) gene had a positive family history for FTD, and two lvPPA patients had a positive family history for AD, whereas none of the svPPA patients had a clear autosomal dominant inheritance of any type of dementia. Pathological confirmation had not been obtained in any of the cases. Apart from the C9 or f72 repeat expansion patient, another nfvPPA patient had a pathogenic mutation in the progranulin gene, a missense variant with a modified Goldman score of 2. The most apparent symptoms and comprehensive longitudinal symptom distribution are displayed to determine the distinct clinical profile and progression pattern of each subtype [8].

The three PPA variations' initial clinical profiles

Language issues were the most common concern in all diagnostic categories, as expected, and because our inclusion criteria were based on the current classification system, the types of deficiencies were consistent with the diagnoses. lvPPA individuals reported more general cognitive impairments such as memory deficits (p0.01), executive dysfunction (p0.01), apraxia (p=0.01), and visuospatial problems (p0.01) [9]. They also performed worse on the FAB and VOSP fragmented letters tests, showing executive and visuospatial impairment, though the difference was not statistically significant. Although memory problems were noted more frequently in lvPPA patients, svPPA patients initially performed worse on verbal memory tests. In nfvPPA, motor symptoms were nearly exclusively observed. At the initial visit, extrapyramidal impairments were found in 27% of nfvPPA participants, which was higher than the other groups (p=0.02). Pyramidal symptoms were observed in one nfvPPA individual, but not in the svPPA or lvPPA subjects.

Progression to PPA-extended

During the disease, patients developed numerous cognitive and behavioral impairments as well as motor abnormalities, even though linguistic problems remained prevalent in all subtypes. In terms of language impairments, nfvPPA and lvPPA patients developed various additional language problems throughout the disease that formally satisfied the diagnostic criteria of another PPA condition, which we refer to as "PPA extended." In svPPA, on the other hand, loss of semantic knowledge remained the primary issue, as evidenced by severe declines in naming and semantic memory tests. Although the other language issues of svPPA patients, such as repetition problems and diminished spontaneous speech, were not enough to justify using PPA-extended, they did demonstrate a significant decline in letter fluency with time on the letter fluency test. It's worth noting that none of the svPPA subjects developed mutism, and dysarthria was never observed in svPPA. During follow-up, mutism was seen in 8 patients, 7 of whom had nfvPPA. Repetition, as well as a single word and phrase comprehension, decreased in nfvPPA participants. Furthermore, over time, four of the nfvPPA patients satisfied the diagnostic criteria for svPPA (PPA-extended). During the disease, however, PPA-extended was the most common in the lvPPA group.

Progression to PPA-plus

Apart from a linguistic impairment, all groups experienced an overall cognitive decline over time, especially the svPPA and lvPPA. The MMSE declined significantly in the svPPA and lvPPA groups (p=0.001), but not in the nfvPPA group. At the follow-up visits, lvPPA individuals reported significant memory losses, executive dysfunction, and visuospatial issues, with a larger deterioration on the visual and verbal memory tests (p0.05), FAB (p0.001), digit span backward (p=0.01), and VOSP fragmented letters (p=0.14). However, in the second year of the disease course, svPPA individuals showed a considerable deterioration on verbal memory tests, and about half of the svPPA subjects indicated episodic memory deficiencies (issues remembering recent events). It's worth noting that our retrospective design didn't allow us to separate the role of semantic impairment in episodic memory problems. In comparison to other subtypes, nfvPPA demonstrated a relatively mild progression pattern on cognitive tests; however, they developed apraxia during the disease. Furthermore, executive dysfunction became a common symptom for svPPA and nfvPPA, as well as lvPPA, and all subtypes showed significant declines on the FAB [10].

DISCUSSION

We explored overlapping and distinguishing clinical characteristics, as well as the progression pattern of the three PPA subtypes, in this retrospective longitudinal cohort study to compare the natural history of the three PPA subtypes. Even though aphasia is the first and most prevalent symptom of PPA, our findings revealed that it is a complex clinical condition in which additional cognitive, behavioral, and motor impairments evolve with time. Following diagnosis, each subtype followed a predictable pattern of progression (PPA-extended and PPA-plus). Subjects with nfvPPA developed motor impairment and proceeded into various types of neurodegenerative syndromes such as CBS, PSP, and MND, whereas subjects with svPPA experienced motor impairment and progressed into various forms of neurodegenerative syndromes such as CBS, PSP, and MND. In terms of linguistic issues, nfvPPA and lvPPA patients developed symptoms outside the fundamental criteria over time, whereas svPPA patients did not. On deeper inspection, lvPPA dropped on repetition, understanding, and speech production, while nfvPPA declined on comprehension and repetition, in keeping with prior longitudinal research. The development of phrase comprehension issues, on the other hand, was the most significant change in svPPA across time, as previously observed. Even though svPPA patients scored lower on the letter fluency test, as revealed in a recent longitudinal study, they were more fluent than the other subtypes, and svPPA patients did not have mutism/dysarthria or PPA-extended.

In conclusion, while aphasia is the only and most common symptom of PPA, it does not take long for other symptoms to appear. More critically, it has a subtype-specific progressive pattern. Although svPPA appears to have a more homogeneous language profile, healthcare providers and caregivers should be aware of any behavioral issues that may arise, whereas lvPPA should be expected to have global cognitive decline and broad language problems due to underlying Alzheimer's disease pathology. Patients with nfvPPA may be least impacted in the behavioral and cognitive domains at first but may proceed to other neurodegenerative diseases, notably those linked with motor impairment, which can be fatal

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