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Progression to Corticobasal Syndrome: A longitudinal study of patients with nonfluent primary progressive aphasia and primary progressive apraxia of speech

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Abstract

Background and objectives: Nonfluent variant primary progressive aphasia (nfvPPA) and primary progressive apraxia of speech (PPAOS) can be precursors to corticobasal syndrome (CBS). Details on their progression remain unclear. We aimed to examine the clinical and neuroimaging evolution of nfvPPA and PPAOS into CBS.

Methods: We conducted a retrospective longitudinal study in 140 nfvPPA or PPAOS patients and applied the consensus criteria for possible and probable CBS for every visit, evaluating limb rigidity, akinesia, limb dystonia, myoclonus, ideomotor apraxia, alien limb phenomenon, and nonverbal oral apraxia (NVOA). Given the association of NVOA with AOS, we also modified the CBS criteria by excluding NVOA and assigned every patient to either a progressors or non-progressors group. We evaluated the frequency of every CBS feature by year from disease onset and assessed grey and white matter volume loss using SPM12.

Results: Asymmetric akinesia, NVOA, and limb apraxia were the most common CBS features that developed, while limb dystonia, myoclonus, and alien limb were rare. Eighty-two patients progressed to possible CBS; only four to probable CBS. nfvPPA and PPAOS had a similar proportion of progressors, although nfvPPA progressed to CBS earlier (p-value = 0.046), driven by an early appearance of limb apraxia (p-value = 0.0041). The non-progressors and progressors both showed premotor/motor cortex involvement at baseline, with spread into prefrontal cortex over time.

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Discussion: An important proportion of patients with nfvPPA and PPAOS progress to possible CBS, while they rarely develop features of probable CBS even after long follow-up.

Keywords

Primary Progressive apraxia of speech; nonfluent/agrammatic variant primary progressive aphasia; nonverbal oral apraxia; Corticobasal syndrome

Introduction

Primary progressive apraxia of speech (PPAOS) is a motor speech disorder with insidious onset in which patients present with apraxia of speech (AOS) as the only initial symptom resulting from focal atrophy of the premotor cortex [1]. The main characteristics of AOS are the presence of segmentation within and between words and sound substitutions and distortions [2]. The rate of progression of AOS and the emergence of additional impairments varies among PPAOS individuals [3]. While some will deteriorate and develop new symptoms (such as agrammatism, extrapyramidal signs including bradykinesia and rigidity, oculomotor impairment, and limb apraxia), others remain with an isolated speech disorder [1, 2, 4].

In contrast, patients with the nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) present with agrammatism with or without features of AOS at onset and tend to show more significant atrophy in Broca's area compared to patients with PPAOS [5, 6]. Worsening language impairment and the onset of additional deficits outside of the language and speech domains are also common in these patients [7]. Among the different variants of PPA, nfvPPA is the most commonly associated with motor symptoms and extrapyramidal signs [8]. In fact, it has been shown that both nfvPPA and PPAOS can evolve into different parkinsonian syndromes, including progressive supranuclear palsy (PSP) and less frequently corticobasal syndrome (CBS) [4, 8–11], suggesting that nfvPPA and PPAOS might be precursors to these neurodegenerative disorders [2, 12].

Few studies have addressed the progression of patients with nfvPPA and PPAOS into CBS, even though it has been shown that speech and language disorders are often the first signs in patients who die with corticobasal degeneration (CBD) pathology [12]. Two levels of diagnostic certainty have been defined in the CBS consensus criteria [13]. Probable CBS requires the insidious onset and gradual progression of at least two of a) asymmetric limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus, plus two of d) orobuccal or limb apraxia, e) cortical sensory deficit, or f) alien limb phenomenon. The criteria for possible CBS requires the presence of only one of a) limb rigidity or akinesia, b) limb dystonia, or c) limb myoclonus, plus one of d) orobuccal or limb apraxia, e) cortical sensory deficit, or f) alien limb phenomenon, which can be symmetric [13].

Over the past decade, we have followed a large cohort of patients with nfvPPA and PPAOS and have observed the development of CBS features in many patients. We, therefore, aimed to examine the clinical evolution of nfvPPA and PPAOS into possible and probable CBS and examine differences in the rate of progression between patients with both diagnoses. Previous studies showed that up to 70% of patients with PPAOS [14] and 50% of patients

with nfvPPA [15] developed CBS. Thus, we hypothesized that more than 50% of patients with nfvPPA and PPAOS would evolve into CBS but show different rates of evolution into the CBS syndrome because of their anatomical and pathological distinctiveness [5, 16]. We also aimed to assess the neuroanatomical underpinnings of the progression to CBS, with the hypothesis that progression to CBS would be associated with the development of frontoparietal and basal ganglia atrophy, given that these regions are typically affected in CBS [17] [18].

Methods

Study Design:

We conducted a retrospective longitudinal study in a cohort of patients with nfvPPA and PPAOS and evaluated their clinical progression to possible or probable CBS.

Setting and Participants:

We identified all patients who were recruited into NIH-funded speech/language focused grants at Mayo Clinic, Rochester, who met criteria for PPAOS [19] or nfvPPA [6] and had undergone at least one research visit which included detailed neurological and speech/language evaluations (140 patients and 329 visits) and a volumetric head MRI. All patients were recruited by the Neurodegenerative Research Group (NRG) between July 6th, 2010, and May 18th, 2023. We excluded patients who met criteria for any other neurodegenerative disease, including PSP [20] and CBS [13], at first visit, as well as those who presented with non-speech and language impairment. Identical follow-up evaluations were performed on a yearly basis. The cohort completed a median number of 2 visits (range: 1– 12 visits).

Clinical Assessments:

At each visit, the neurological assessment included tests of general cognition, executive function, and neuropsychiatric features, including the Montreal Cognitive Assessment (MoCA) [21], Frontal Behavioral Inventory (FBI) [22], and Neuropsychiatric Inventory Questionnaire (NPI-Q) [23], respectively. The Movement Disorders Society Sponsored revision of the Unified Parkinson's Disease Rating Scale Part II was used to assess disability, and the part III (MDS-UPDRS III) [24] was used to assess Parkinsonism. The limb apraxia subset of the Western Aphasia Battery (WAB) [25] was used to evaluate apraxia. The Progressive Supranuclear Palsy Rating Scale (PSPRS) [26] and the Progressive Supranuclear Palsy Saccadic Impairment Scale (PSIS) [27] were also completed.

Apolipoprotein E (ApoE) was measured using a modified version of single-day ApoE method [28]. In addition, 136 patients were tested for the three most common FTLD mutations: MAPT. GRN and C9ORF72.

Additionally, all patients underwent a detailed speech/language evaluation where the following battery of tests was administered: the Token test [29], the Boston Naming test (BNT) [30], the Motor Speech Disorder Severity Scale (MSD) [31], the Apraxia of Speech Rating Scale (ASRS) [32] and the Nonverbal oral apraxia scale [33]. Performance on the picture description task, the narrative writing subset of the WAB [25], and observations

during general conversation were used to assess for agrammatism and AOS as previously described [14]. Patients received an initial diagnosis of PPAOS [19] or nfvPPA [6]. In addition, patients with AOS were subclassified into prosodic and phonetic subtypes based on their speech characteristics during spontaneous conversation and structured speech tasks [5, 34]. Patients were considered phonetic AOS if distorted sound substitutions, deletions, or additions were the predominant features [34]. Those with lengthened inter-segment durations between syllables or words as predominant features were considered prosodic AOS [34]. If the characteristics of either of these subtypes were too mild, too severe, or equal, patients were considered to have mixed AOS [34].

Evaluation of CBS features:

We applied the 2013 consensus criteria for CBS at each visit [13]. Specifically, we assessed each patient for the presence of the following CBS features: limb rigidity, akinesia, limb dystonia, limb myoclonus, orobuccal apraxia, limb apraxia, and alien limb phenomena at each visit. These features were always recorded in a standard manner as present or absent. We extracted the limb rigidity and akinesia scores on items 3.3 to 3.8 of the MDS-UPDRS III and compared hemisphere data to determine symmetry.

We assessed the performance in 90 healthy controls (ages 44.5–84.7) for limb rigidity and limb akinesia scores on the MDS-UPDRS III (item 3.3 for rigidity and items 3.4 to 3.8 for akinesia). We determined the cutpoint at the 97^{th} percentile in the 90 healthy controls. The cutpoint was a score of 0/20 for the five rigidity items (neck, right upper extremity, left upper extremity, right lower extremity, and left lower extremity) and a score of ≤ 2/40 points for the five akinesia items (right and left finger tapping, hand movements, pronation-supination of hand movements, toe tapping, and leg agility). With this analysis, we established a cutpoint of > 0 points for limb rigidity (i.e., >0 is abnormal) and 2 points for akinesia (i.e., >2 is abnormal) to define abnormality for these two tasks. Patients met criteria A for probable CBS if they had asymmetric limb rigidity or akinesia (i.e., the score on the left or the right side is > the score on the other side). If either was present but in a symmetric pattern, the patient met criteria A for possible CBS.

Criteria B and C for possible and probable CBS require the presence of limb dystonia and myoclonus, respectively. We reviewed the neurological medical records documented by a movement disorders and behavioral neurology expert (KAJ or HB) to determine whether either of these features was present. We observed that a significant proportion of the patients had poly mini-myoclonus; hence, we also included this symptom in our analysis as a separate feature.

Criteria D requires the presence of orobuccal or limb apraxia. For orobuccal apraxia, we used a cutpoint of 29 on the Nonverbal Oral Apraxia (NVOA) scale [33]. For limb apraxia, we used the limb apraxia subscore of the WAB, excluding items that accounted for facial apraxia; a score of less than 42 out of 45 was considered indicative of limb apraxia. Given that NVOA is a common finding in patients with AOS and is also seen in lvPPA and even in svPPA, we do not think it is a feature specific to CBS [3, 33]. Hence, we calculated a Modified D criteria that only included limb apraxia and ignored NVOA.

Finally, for criteria F, we reviewed neurological assessment records for the presence of alien limb phenomenon. We did not assess criteria E (cortical sensory deficit) since we did not record this information in a standardized manner and could not be certain if the absence of this feature was due to it being truly absent or just not documented.

We evaluated the progression to possible and probable CBS at every visit according to the features described above. A patient was considered as possible CBS if they met any of criteria A, B, or C, plus one of criteria D or F, and as probable CBS if they met 2 of criteria A, B, C plus criteria D and F. Additionally, we substituted criteria D for the modified criteria D and again classified patients as meeting the modified probable CBS or modified possible CBS diagnosis. We classified patients as progressors if they met the criteria for either modified possible or modified probable CBS during their follow-up and non-progressors if they did not.

Neuroimaging Analysis:

All patients underwent a standardized 3T MRI protocol at each visit that included a magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted sequence. Voxel-based morphometry in SPM12 was used to assess patterns of grey and white matter volume loss in the non-progressors and progressors that had serial visits compared to a group of age and gender-matched controls (n=16). The controls consisted of six women with a median age at scan of 68 years, MoCA of 27 (range 25–30), and Hoehn and Yahr of 0 (range 0–0). Patterns of volume loss were assessed at the baseline and follow-up visits. The follow-up visit for the progressors was selected as the first visit where they met criteria for possible CBS. The follow-up visit for the non-progressors was selected to match the progressors in terms of scan interval (median scan interval of 2 years for both groups). MPRAGE scans were normalized to the Mayo Clinic Adult Lifespan Template (MCALT), segmented using unified segmentation and MCALT priors, modulated, and smoothed at 8mm full width at half maximum for analysis. Multiple regression analysis was performed in SPM12 to compare groups with age and sex included as covariates, and results assessed at $p<0.05$ corrected for multiple comparisons using the family wise error (FWE) correction and at $p<0.001$ uncorrected.

Genetic screening—All patients who consented to blood samples and had DNA extracted were screened for causative mutations in the most common genes associated with frontotemporal lobar degeneration (FTLD). Sanger sequencing was performed on microtubule associated protein, tau (MAPT), progranulin (GRN) and TAR DNA binding protein (TARDBP). The chromosome 9 open reading frame 72 (C9ORF72) gene was screened by repeat-primed PCR assay.

Statistical Analysis:

The baseline characteristics of patients were summarized and analyzed for each group (CBS progressors and non-progressors). Continuous variables are reported as median (interquartile range), and discrete variables as frequency (percentage). Differences between groups were evaluated using the Kruskal-Wallis test for non-normally distributed continuous variables and the Chi-squared test for categorical variables.

We employed an inverted Kaplan-Meier survival analysis to investigate the cumulative probability of achieving possible CBS status over time for patients diagnosed as PPAOS vs. nfvPPA at baseline. Possible CBS status was defined as the earliest recorded visit at which a patient was considered to meet criteria for possible CBS. Time was defined as time in years from patient reported symptom onset to CBS status. Patients who did not have a visit where they met criteria for possible CBS were censored at their last recorded visit. Following the Kaplan-Meier analysis, the features used to determine possible CBS criteria were explored to see if one feature contributed to the difference in time to meeting possible CBS criteria between nfvPPA and PPAOS. Given the rarity of limb dystonia, myoclonus, and alien limb, we found that Asymmetric akinesia/NVOA and Limb Apraxia were the only features needed to determine CBS possible status for every patient in this sample. The methodology was repeated separately for both limb rigidity/akinesia and limb apraxia (first instance from onset, censored at last visit).

Following the Kaplan-Meier analysis, features of possible CBS criteria were explored to determine if one feature was contributing to the difference in time to meeting possible CBS criteria between nfvPPA and PPAOS. We found that limb rigidity/akinesia and limb apraxia were the only features needed to determine possible CBS status for every patient in this sample, given that they were always observed prior to or in tandem with the other features that determine possible CBS status. The methodology applied to possible CBS status (first instance from onset, censored at last visit) was applied separately for both limb rigidity/akinesia and limb apraxia. Inverted Kaplan Meier curves and corresponding log-rank tests were conducted for both features.

Standard Protocol Approvals, Registrations, and Patient consents:

The study was approved by the Mayo Clinic Institutional Review Board 09–008772, 12–008988, 16–001703, 17–002468, 17–010087, and all participants consented to enrollment into the study through written informed consent.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

The demographic and clinical features of the cohort are shown in Table 1. Of the 140 patients, 86 (61%) progressed to possible or probable CBS, while the remainder did not meet the criteria for CBS during their follow-up. The progressors had a greater number of visits and a longer time from onset to last visit, although there was no difference in years from onset to first visit. A greater proportion of patients had a baseline diagnosis of nfvPPA compared to PPAOS, although the diagnosis breakdown did not differ between progressors and non-progressors. There were no differences between the type of AOS and progression to CBS. Percentages of patients with different types of AOS who progressed to CBS were not different. Figure 1 shows the characteristics of the follow-up completed by patients and the time they reached possible CBS by their baseline diagnosis.

Baseline neurological and speech and language evaluations:

Table 2 details the performance and differences for each measure by group. Baseline evaluation showed no difference in overall cognitive impairment on the MoCA or behavioral changes on the Frontal Behavioral Inventory. CBS progressors performed significantly worse on the MDS-UPDRS III test, WAB apraxia, PSP-rating scale, and NVOA scores. No differences were observed in the severity of aphasia or apraxia of speech.

Of 136 patients screened for causative FTLD mutations, four patients showed genetic variations. Three variations were identified in the GRN gene (c.1A>C, p.Met1; c.709–2A>G, p.Ala237fs; c.1009C>T, p.Gln337*) and can be considered pathogenic. The variant observed in the TARDBP gene (c.941G>C, p.Gly314Ala) is of uncertain significance.

Twenty-five percent of the patients became dependent on the activities of daily living at a median of 5.2 years, as assessed on their UPDRS II scores. A more significant proportion of progressors (36,8%) lost independence by their last visit compared to those who did not progress (6.2%), $p<0.001$.

CBS features by years since onset:

Eighty-one percent of the patients developed at least one CBS feature, excluding NVOA. The frequency of rigidity and akinesia gradually increased, and performance on the NVOA and WAB apraxia scores worsened with a longer time from onset (Table 3). Conversely, limb dystonia and myoclonus were rare and did not increase in frequency, even at longer times from onset. The frequency of rigidity increased significantly after four years from onset when it was present in almost 60% of patients; however, it was less frequently an asymmetric finding with a slight increase 11 years from onset when it reached 57%. Asymmetric akinesia was more frequent, especially after the third year from initial symptom onset, when it was as high as 56%, and its frequency increased to 75% nine years from onset. Although rare, limb dystonia appeared in the third year of the disease, but its frequency only rose to 12.5% by year nine. Myoclonus was present earlier (in the second year from onset) and almost reached 20% by year ten. Although not a criterion, mini-myoclonus appeared in the first year from onset and was more common than myoclonus for most of the disease course (except for year ten).

The median NVOA score became abnormal (<29) four years from onset, with scores dramatically declining with disease progression. The lowest median score was 0, which occurred 12 years from onset. 79% of patients developed NVOA. Abnormal WAB apraxia scores were first observed three years from onset; however, they did not show a steep decline until nine years from onset. Limb apraxia was present in 70% of the patients. The most frequently met criterion at every time point was Criteria D. Modified Criteria D was less common but still increased throughout the disease course. Alien limb phenomenon reached its highest frequency of just 8.5% four years from onset.

Progression to Probable or Possible CBS

More than a third of the patients did not progress to possible or probable CBS during follow-up (Table 3). Of the patients that did progress (61.4%), 97% progressed to possible

CBS. When using the modified criteria, we found that no patients had progressed during the first year of the disease and that progression occurred slowly. More than half of the patients progressed to modified possible CBS by year 8. Only nine additional patients progressed to possible CBS after year 8. In contrast, only four patients met criteria for probable CBS during follow-up. Three of these four patients had progressed by year 4 of the disease, and it did not differ whether we excluded or included NVOA as a criterion. Thirty-seven patients in the progressor group also developed abnormal eye movements by their last follow-up, evidenced by PSIS scores greater or equal to two.

Patients with nfvPPA progressed to CBS around a year earlier than patients with PPAOS (Figure 2). Criteria A and modified criteria D were the main determinants for this progression. Limb rigidity/akinesia demonstrated no difference in inverted survival curves between nfvPPA and PPAOS (p-value = 0.84). However, limb apraxia appeared around 2.5 years earlier in patients with nfvPPA. It demonstrated clear separation in inverted survival curves and a significant difference in the log-rank test (p-value = 0.0041) (Figure 3). This suggests that limb apraxia defines the difference in the progression pattern among both groups.

Neuroimaging findings

Patterns of grey and white matter loss at baseline and follow-up for the CBS progressors and non-progressors are shown in Figure 4. At baseline, non-progressors and progressors showed grey and white matter loss in the premotor and motor cortices and in the body of the corpus callosum compared to controls. On direct comparison, the progressors showed greater loss, particularly white matter loss, predominantly in the parietal lobe, compared to the non-progressors. At follow-up, both groups showed noticeable spread in patterns of volume loss, with greater involvement of the premotor and motor cortex, body of the corpus callosum, and prefrontal cortex. The progressors also showed spread into the parietal lobes. On direct comparison, the progressors showed greater grey and white matter volume loss in the parietal lobes, sensorimotor cortex, and premotor cortex compared to the non-progressors. After correction for multiple comparisons, white matter loss in the premotor cortex and body of the corpus callosum survived correction for multiple comparisons (FWE $p<0.05$) in both groups compared to controls at follow-up, with grey matter loss in the premotor cortex also surviving correction in the progressors.

Discussion

We examined the development of CBS in a cohort of patients with nfvPPA and PPAOS. Our findings showed that 81% of nfvPPA and PPAOS patients developed at least one CBS feature; however, some features were more common and appeared at different time points of the disease. Only a small proportion (2.8%) of patients progressed to probable CBS. The progression to CBS occurred earlier in patients with nfvPPA compared to those with PPAOS and was due to the earlier appearance of limb apraxia.

In our cohort, the most common CBS features that patients developed were akinesia and limb apraxia. We found that rigidity was absent during the first year of disease, but it increased progressively, with almost 60% of the patients exhibiting it by the fourth year.

Asymmetric rigidity was less common, and it only exceeded a frequency of 50% by the eleventh year. On the other hand, akinesia was present even during the first year. Its frequency increased rapidly, with over 50% of the patients developing it by the third year of the disease, and it was present in all the patients who were followed for more than 12 years. Asymmetric akinesia was less common; however, it was present during the first year in some patients, and its frequency remained above 50% at each year of disease duration.

The most frequently met criterion at every time point was Criteria D, which includes both NVOA and limb apraxia. Seventy-nine percent of the patients developed NVOA. We found the most significant decline in NVOA scores occurred in the fourth year, although NVOA was present in many patients from the first year of the disease. As expected, and as we have previously shown[3], NVOA severity worsened as the disease progressed. Conversely, limb apraxia was less frequent, and its evolution was different; it appeared later and did not progress much until nine years from onset. This supports the progression of involvement of association cortical brain areas implicated in programming and planning of speech and oral movements to those involved in programming and planning of limb movements [36]. Both features have the same diagnostic value in the CBS criteria; therefore, the presence of either feature equally increases the risk of possible CBS. Patients with AOS often also have NVOA, which tends to worsen with time, independent of whether or not the patient develops other features of CBS [3, 33]. In the absence of AOS, NVOA may be relevant in the diagnosis of CBS, but in this cohort, it was not a discriminating feature. Hence, we believe that the sole presence of NVOA should not be used to determine progression of the disease into the CBS syndrome. In fact, when we excluded the presence of NVOA and only considered limb apraxia, 58.6 % of patients were considered progressors, compared to 75.1% when NVOA was included.

The high prevalence of parkinsonism and limb apraxia accounted for a number of patients that evolved to meet criteria for possible CBS during follow-up. In fact, 59% of our cohort met criteria for possible CBS during follow-up, with patients most commonly meeting criteria eight years after onset. The consensus criteria for probable CBS are more specific, and we identified only four patients (2.8%) in our large cohort who developed probable CBS. The absence of features such as myoclonus, limb dystonia, and alien limb phenomenon, even in patients followed for a long time after onset, explains why few patients met criteria for probable CBS. It should be mentioned that progression to probable CBS happened in a median of four years following symptom onset. This suggests these patients may be unique and similar to patients with typical CBS. Even after excluding NVOA as a criterion for probable CBS, the same patients were considered probable CBS, suggesting that NVOA was not a distinguishing feature in this set of patients. Furthermore, the evolution of PPAOS and nfvPPA seems to combine features of CBS with impairment of vertical eye movements; hence, the syndromes appear to be evolving into a hybrid Parkinsonian syndrome[37] than a classic CBS, which may explain why only a few evolve into probable classic CBS.

We were also interested in investigating differences in the progression to CBS in patients with a baseline diagnosis of PPAOS versus those with nfvPPA. In cases with nfvPPA and AOS and those with PPAOS, corticobasal degeneration pathology is relatively common [2,

9]. Less is known about how these two syndromes evolve over time [13, 38]. In our cohort, 62% of patients with nfvPPA and 59% of patients with PPAOS progressed to CBS. Yet, we observed interesting differences in their temporal evolution. Patients with nfvPPA developed limb apraxia earlier, which was the determining factor for an earlier progression to possible CBS. A previous study showed that limb apraxia is more common in nfvPPA than in other variants of PPA [39]. Unlike limb apraxia, there was a similar temporal evolution for parkinsonism in both groups. Others have referred to the emergence of parkinsonism in PPA as a PPA-plus syndrome and have shown that the time from onset to development into a PPA-plus syndrome was 35.5 months in patients with nfvPPA [10]. A recent longitudinal study examined the clinical progression in patients with three different variants of PPA, including nfvPPA, and reported that motor symptoms were a unique finding in patients with nfvPPA [8]. It is known that patients with nfvPPA have more parkinsonism than those with other PPA variants [40]. In the same study, extrapyramidal symptoms were present in up to 27% of the patients at the initial visit, and by the third year of disease, 80% of patients with nfvPPA had extrapyramidal symptoms [8]. Our findings are also consistent with previous descriptions in patients with PPAOS, who developed early subtle akinesia and worsening limb apraxia in the absence of limb dystonia late in the disease course, meeting criteria for CBS after almost ten years of disease duration [19, 41, 42]. It is worth acknowledging that the referred studies from our group have overlapping patients. Interestingly, we did not find a difference between the type of AOS (prosodic and phonetic) and the evolution into CBS. We would have expected patients with the phonetic type of AOS to be more likely to evolve into CBS given the association of the phonetic type of AOS and corticobasal degeneration pathology [14]. The fact that there was no difference regarding the evolution into CBS may speak to the poor specificity of the possible CBS criteria. That is, developing possible CBS is not a strong predictor of corticobasal degeneration. One wonders whether phonetic AOS is a stronger predictor of corticobasal degeneration pathology than possible CBS. A study to examine the pathological correlations of these clinical entities could help elucidate this question.

The patients who progressed to CBS showed involvement of a similar network of brain regions as the patients who did not progress to CBS. Both groups showed predominant premotor and motor cortex involvement at baseline, and both progressed over time to show worsening in these regions with significant spread into the prefrontal cortex. However, the progressors showed more severe neurodegeneration in these regions at both baseline and follow-up, suggesting that the evolution into possible CBS may be driven by disease severity rather than involvement of different brain regions or networks. The progressors showed slightly greater involvement of the sensorimotor and parietal lobes compared to the non-progressors, although these differences did not survive correction for multiple comparisons. The absence of evolution into probable CBS in which patients have limb dystonia, alien limb phenomenon, and classic action/stimulus sensitive myoclonus is interesting. These three clinical symptoms are strongly linked to involvement of the sensorimotor, parietal, and basal ganglia regions [43–50]. The parietal lobe and basal ganglia were indeed relatively spared in our patients, which may explain the absence of some of these features. The sensorimotor cortex was involved, which may explain the observation of poly mini-myoclonus in the progressors. The reason for the absence of the classic myoclonus of CBS is unclear.

However, it has been shown to be present when there is evidence of underlying limb dystonia [51]. Hence, it may not be surprising that it was absent in these patients given the absence of limb dystonia.

Based on the PSP criteria, 101 patients in this study would meet criteria for suggestive of PSP-SL [20]. Approximately a quarter of the patients developed vertical oculomotor impairment (slowing or palsy) and would meet criteria for possible PSP-SL. Still, only three patients had falls or postural instability on testing within three years of onset and would be considered probable PSP-SL. These findings are in keeping with our previous study showing that it is rare for patients with speech and language disorders to evolve into the classic PSP syndrome [11]. On the other hand, it appears that those who develop oculomotor impairment are also the ones who developed possible CBS. This mixed PSP and CBS combination of symptoms has been previously referred to as the Parkinson-plus Hybrid Syndrome [37].

One limitation of our study is that the date of symptom onset was self-reported, which may result in a recall bias. In neurodegenerative diseases, the insidious onset hinders an accurate estimate of disease onset. Interestingly, most patients estimated that symptoms started two to four years before their first visit. The possible inaccuracy of this data could account for the higher frequencies of CBS features in the later years of the disease. In addition, not all patients completed serial visits; some were only seen once, and we reported longer follow-ups for progressors. Hence, we must consider the possibility that they will develop CBS in the future, and the true progression rates to CBS are higher than we found. Following up to death would be needed to get the absolute proportion of patients who progress. In addition, we did not include pathological correlations of the cohort, which would be interesting to analyze later in order to discern which pathologies are responsible for the clinical progression or lack of it. Another limitation is that we did not include cortical sensory deficit as one of the CBS features because we lacked a standardized test to record it. Hence, we did not evaluate its frequency and how much it impacts the progression to CBS. We suspect that cortico-sensory deficits, similar to limb dystonia and myoclonus, are a relatively rare occurrence in nfvPPA and PPAOS and hence would not have made much, if any, difference to the results. The generalizability of our findings is based on standardized testing and consensus criteria that were used to assess the patients, objectively.

The results of this study contribute to the understanding of the clinical characteristics and temporal evolution of patients with nfvPPA and PPAOS. In addition, the clinical relevance of the progression to CBS is related to the loss of independence in the patient’s activities of daily living (ADL), predominantly caused by parkinsonism and apraxia. In fact, we found an association between progression to CBS and ADL dependence. Understanding of the clinical evolution of the disease can help clinicians inform and counsel patients and families about the expected progression of the disease while therapies specifically targeting these neurodegenerative conditions continue to be developed.

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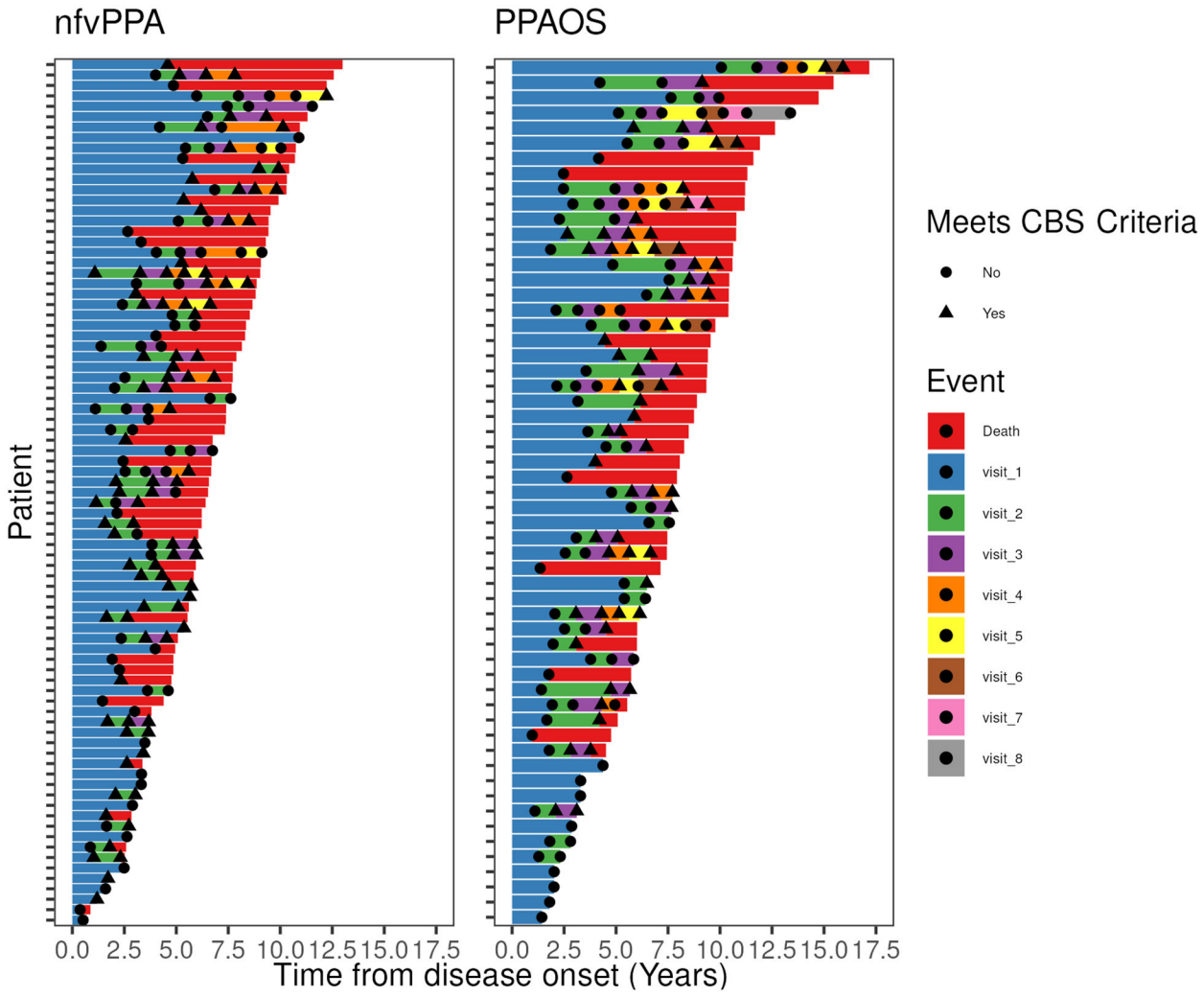

Figure 1.

Longitudinal follow-up of patients by their baseline diagnosis

Swimmer plot depicting the follow-up completed by patients with nfvPPA versus those with PPAOS, and the time at which they meet modified criteria for possible CBS.

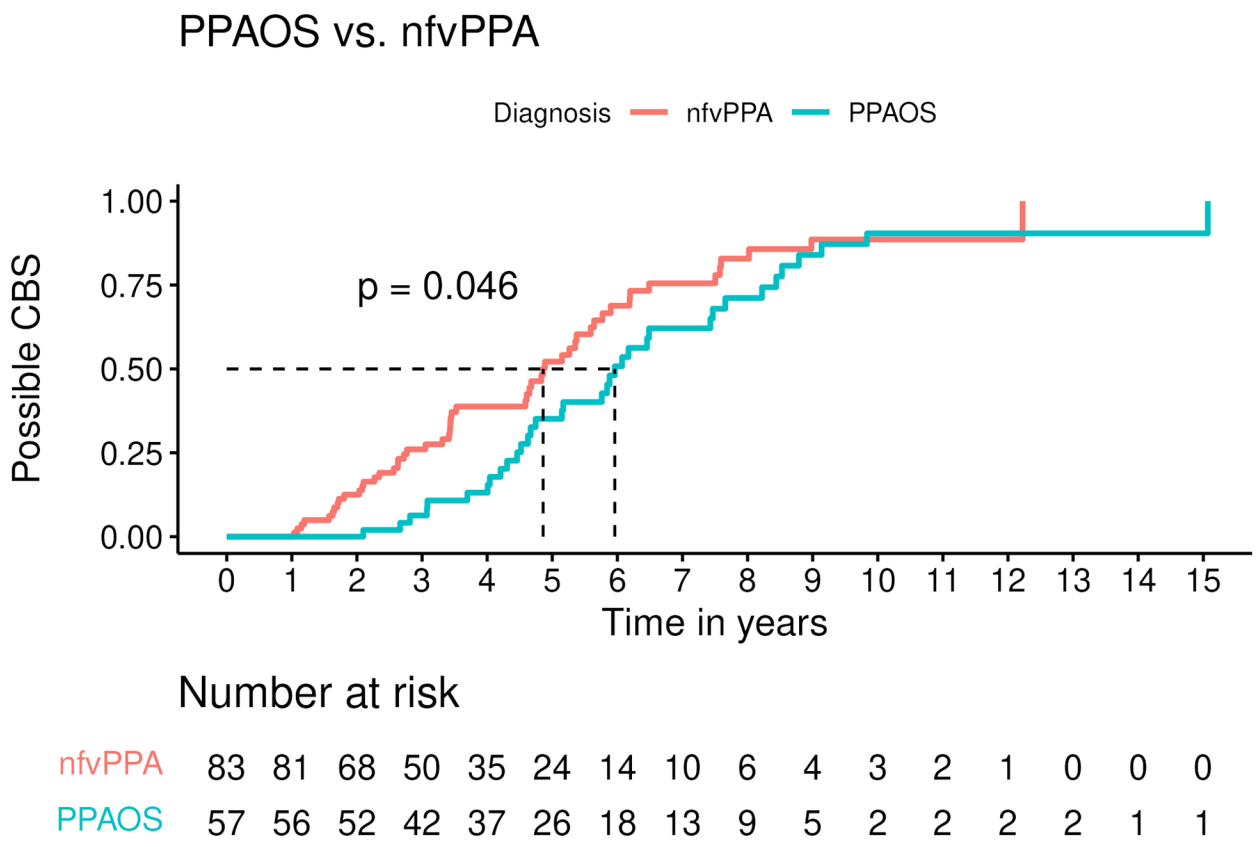

Figure 2.

Probability of patients with nfvPPA/PPAOS progressing to Possible CBS.

Kaplan-Meier curves show the probability of patients with nfvPPA and those with PPAOS progressing to possible CBS using the modified criteria.

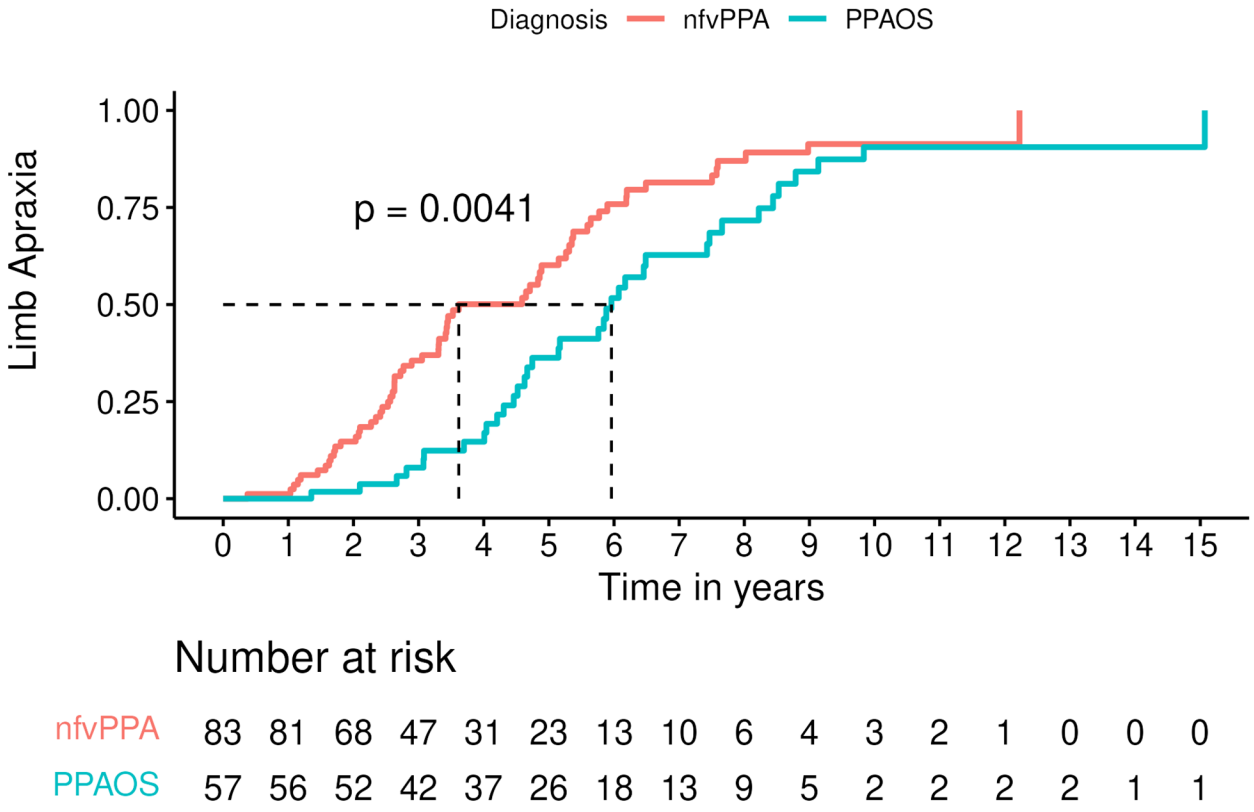

Figure 3.

Probability of patients with nfvPPA/PPAOS developing limb apraxia.

Kaplan-Meier curves show the probability of patients with nfvPPA and those with PPAOS developing limb apraxia, and the difference between both groups. The time of symptom onset was self-reported.

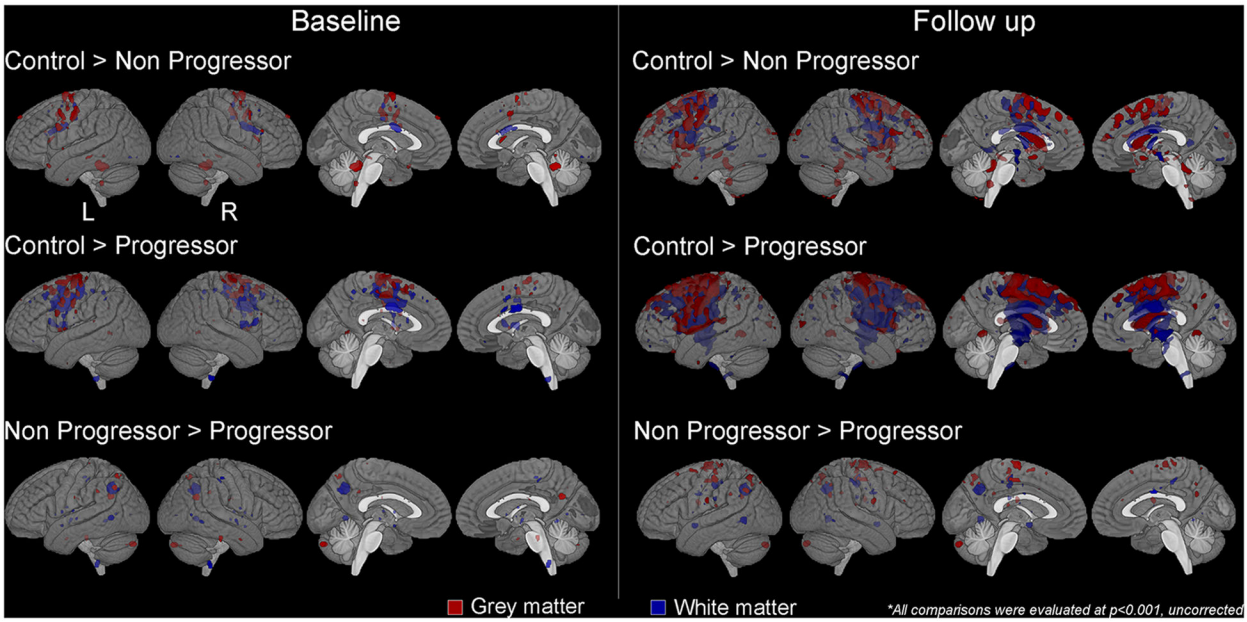

Figure 4:

Voxel-level maps of grey and white matter loss in nfvPPA/PPAOS progressors and non-progressors at baseline and follow-up.

All comparisons were evaluated at p<0.001, uncorrected.

Table 1.

Demographic and Clinical characteristics

	Total Cohort (N=140)	Non progressors (N=54)	CBS progressors (N=86)	p-value
Sex (male)	67 (47.9%)	28 (51.9%)	39 (45.3%)	0.453[1]
Race (White)	134 (95.7%)	51 (94.4%)	83 (96.5%)	0.425[1]
Right Handedness	126 (90.6%)	47 (88.7%)	79 (91.9%)	0.504[1]
Years of education	16.0 (13.0, 18.0)	16.0 (12.0, 18.0)	16.0 (13.0, 17.5)	0.742[2]
Family History of neurodegenerative disease	29 (29.6%)	11 (28.2%)	18 (30.5%)	0.807[1]
ApoE e4	30 (23.6%)	10 (22.2%)	20 (24.4%)	0.783[1]
Baseline diagnosis				0.720[1]
nfvPPA	83 (59.3%)	31 (57.4%)	52 (60.5%)	
PPAOS	57 (40.7%)	23 (42.6%)	34 (39.5%)	
AOS type				0.574[1]
Mixed	31 (24.6%)	10 (21.3%)	21 (26.6%)	
Phonetic	49 (38.9%)	21 (44.7%)	28 (35.4%)	
Prosodic	46 (36.5%)	16 (34.0%)	30 (38.0%)	
Age at onset	67.1 (59.0, 71.8)	64.7 (58.8, 69.8)	67.9 (60.2, 72.8)	0.140[2]
Number of visits	2.0 (1.0, 8.0)	1.0 (1.0, 8.0)	3.0 (1.0, 7.0)	< 0.001[2]
Years from onset to first visit	3.0 (2.0, 4.7)	2.9 (1.9, 4.0)	3.1 (2.1, 4.9)	0.401[2]
Years from onset to last visit	4.7 (2.9, 6.7)	3.3 (2.3, 4.9)	5.8 (4.0, 7.5)	< 0.001[2]
PSP- variant				<0.001[1]
Suggestive of PSP-SL	101	52 (96.3%)	49 (57.0%)	
Possible PSP-SL	36	2 (3.7%)	34 (39.5%)	
Probable PSP-RS	3	0 (0.0%)	3 (3.5%)	
TIV Baseline		1.6 (1.4, 1.6)	1.6 (1.4,1.7)	0.30
Dependent on ADLs at last visit	25%	6.2%	36.8%	<0.001

Data shown as a number (%), median (IQR), number of visits are shown as median (range).

[1] Pearson's Chi-squared test,

[2] Kruskal-Wallis rank sum test.

Abbreviations: nfvPPA, nonfluent/agrammatic variant of primary progressive aphasia; PPAOS, Primary progressive apraxia of speech; AOS+, Apraxia of speech plus syndrome; AOS, apraxia of speech; NVOA, Nonverbal oral apraxia; PSP-SL, progressive supranuclear palsy speech-language; PSP-RS, progressive supranuclear palsy-Richardson syndrome; TIV, total intracranial volume; ADL, activities of daily living.

Suggestive of PSP-SL = presence of agrammatic aphasia and/or apraxia of speech only

Possible PSP-SL = presence of agrammatic aphasia and/or apraxia of speech plus oculomotor impairment

Probable PSP-RS = falls or postural instability on testing within 3 years of onset + oculomotor impairment

Table 2.

Neurological and speech and language tests at first visit

	Total Cohort (N=140)	Non progressors (N=54)	CBS progressors (N=86)	p-value[1]
MoCA (/30)	25.0 (22.0, 27.5)	25.0 (23.0, 27.8)	24.0 (21.0, 27.0)	0.373
FBI (/72)	11.0 (6.0, 17.0)	10.0 (6.0, 14.0)	11.5 (6.8, 18.0)	0.273
MDS-UPDRS III (/132)	11.0 (5.0, 18.0)	6.0 (4.0, 10.0)	14.0 (9.0, 21.0)	< 0.001
WAB apraxia (/60)	57.0 (53.0, 59.0)	58.0 (55.2, 59.8)	56.0 (51.0, 58.0)	0.001
PSPRS (/100)	9.5 (5.0, 17.0)	6.5 (3.8, 10.0)	12.5 (7.2, 20.0)	0.001
PSIS (/5)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.5 (0.0, 1.0)	0.094
WAB-Aphasia Quotient (/100)	94.5 (85.0, 97.5)	95.0 (88.0, 98.2)	94.3 (84.4, 96.9)	0.458
Letter fluency	15.0 (8.2, 23.0)	17.0 (10.0, 22.8)	14.0 (8.0, 23.0)	0.225
BNT (/15)	14.0 (12.0, 15.0)	14.0 (12.0, 15.0)	13.0 (12.0, 15.0)	0.896
Token test (/20)	19.0 (15.0, 21.0)	19.0 (16.0, 21.0)	19.0 (14.0, 20.0)	0.466
MSD severity scale rating (/10)	6.0 (5.0, 8.0)	7.0 (6.0, 8.0)	6.0 (5.0, 7.0)	0.121
ASRS (/64)	18.0 (11.5, 25.0)	15.5 (8.2, 23.2)	19.0 (13.0, 26.5)	0.155
NVOA (/32)	28.0 (19.8, 31.0)	29.0 (24.0, 31.8)	27.0 (17.2, 30.0)	0.022

[1] Kruskal-Wallis rank sum test. Data shown as median (1^{st} and 3^{rd} quartiles).

Abbreviations: MoCA, Montreal Cognitive Assessment Battery; FBI, Frontal Behavioral Inventory; MDS-UPDRS III, Movement Disorder Society Sponsored revision of the Unified Parkinson's Disease; WAB, Western Aphasia Battery revised; PSPRS, Progressive Supranuclear Palsy rating scale; PSIS, Progressive Supranuclear Palsy Saccadic Impairment Scale; BNT, Boston Naming test; MSD Motor speech disorder severity scale; ASRS, apraxia of speech rating scale; NVOA, Nonverbal oral apraxia.

Table 3.

CBS Criteria by years of disease duration

	1	2	3	4	5	6	7	8	9	10	11	12	>12
N visits	4	30	48	47	49	48	34	24	16	16	7	3	3
CBS Features													
Criteria A	2 (50.0%)	16 (53.3%)	24 (50.0%)	32 (68.1%)	29 (59.2%)	28 (58.3%)	22 (64.7%)	14 (58.3%)	12 (75.0%)	10 (62.5%)	5 (71.4%)	2 (66.7%)	2 (66.7%)
Rigidity	0 (0.0%)	14 (46.7%)	17 (35.4%)	28 (59.6%)	27 (55.1%)	27 (56.2%)	18 (52.9%)	11 (45.8%)	10 (62.5%)	12 (75.0%)	4 (57.1%)	1 (33.3%)	2 (66.7%)
Asymmetric Rigidity	0 (0.0%)	11 (36.7%)	15 (31.2%)	17 (36.2%)	18 (36.7%)	17 (35.4%)	10 (29.4%)	8 (33.3%)	7 (43.8%)	4 (25.0%)	4 (57.1%)	0 (0.0%)	1 (33.3%)
Akinesia	3 (75.0%)	14 (46.7%)	27 (56.2%)	34 (72.3%)	32 (65.3%)	38 (79.2%)	28 (82.4%)	18 (75.0%)	14 (87.5%)	15 (93.8%)	4 (57.1%)	3 (100.0%)	3 (100.0%)
Asymmetric Akinesia	2 (50.0%)	16 (53.3%)	27 (56.2%)	32 (68.1%)	28 (57.1%)	26 (54.2%)	22 (64.7%)	13 (54.2%)	12 (75.0%)	9 (56.2%)	4 (57.1%)	2 (66.7%)	2 (66.7%)
Criteria B	0 (0.0%)	0 (0.0%)	2 (4.2%)	4 (8.5%)	5 (10.2%)	4 (8.3%)	0 (0.0%)	0 (0.0%)	2 (12.5%)	1 (6.2%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Criteria C	0 (0.0%)	2 (6.7%)	0 (0.0%)	2 (4.3%)	2 (4.1%)	2 (4.2%)	0 (0.0%)	1 (4.2%)	1 (6.2%)	3 (18.8%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Criteria D	2 (50.0%)	17 (56.7%)	34 (70.8%)	38 (80.9%)	35 (71.4%)	42 (87.5%)	31 (91.2%)	18 (75.0%)	15 (93.8%)	15 (93.8%)	6 (85.7%)	2 (66.7%)	2 (66.7%
NVOA (/32)	29.5 (27.0, 30.5)	29.0 (23.0, 31.8)	29.0 (23.8,31.0)	23.0 (15.2, 29.0)	23.5 (9.0, 29.0)	20.0 (5.0, 27.5)	15.5 (4.8, 23.5)	14.0 (6.5, 26.5)	11.5 (0.8, 17.0)	7.0 (3.5, 12.5)	7.5 (0.2, 23.8)	0.0 (0.0, 16.0)	0.0 (0.0, 16.0)
WABm Score (/45)	43.5 (42.2, 44.0)	43.0 (38.0, 45.0)	41.5 (39.0, 44.0)	41.0 (36.5, 44.0)	40.0 (34.0, 43.0)	40.0 (36.5, 43.0)	40.0 (33.0, 43.0)	42.0 (40.5, 45.0)	36.5 (31.5, 43.5)	38.5 (28.0, 43.8)	43.0 (37.0, 44.5)	44.0 (43.5, 44.5)	29.0 (25.5, 36.5)
Modified Criteria D [1]	1 (25.0%)	12 (40.0%)	24 (50.0%)	25 (53.2%)	28 (57.1%)	32 (66.7%)	19 (55.9%)	11 (45.8%)	11 (68.8%)	10 (62.5%)	2 (33.3%)	0 (0.0%)	2 (66.7%)
Criteria F	0 (0.0%)	0 (0.0%)	1 (2.1%)	4 (8.5%)	1 (2.0%)	2 (4.2%)	2 (5.9%)	0 (0.0%)	1 (6.2%)	1 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diagnostic Categories [2]													
Non-progressor	139 (99.3%)	127 (90.7%)	108 (77%)	89 (63.6%)	76 (54.2%)	59 (42.1%)	48 (34.3%)	44 (31.4%)	39 (27.9%)	37 (26.4%)	36 (25.7%)	35 (25.0%)	35 (25.0%)
Possible CBS	1	12	19	17	13	17	11	4	4	2	1	1	0
	(0.7%)	(8.6%)	13.6%)	12.1%)	7.9%)	12.1%)	(7.9%)	(2.9%)	(2.9%)	(1.4%)	(0.7%)	(0.7%)	(0.0%)
	0.7%)	(9.3%)	(22.9%)	(35.0%)	(42.9%)	(55.0%)	(62.9%)	(65.8%)	(68.7%)	(70.1%)	(70.8%)	(71.5%)	(71.5%)
Probable CBS	0	0	1	2	0	0	0	0	1	0	0	0	0

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	1	2	3	4	5	6	7	8	9	10	11	12	>12
	(0.0%)	(0.0%)	(0.7%)	(1.4%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.7%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)
	(0.0%)	(0.0%)	(0.7%)	(2.1%)	(2.1%)	(2.1%)	(2.1%)	(2.1%)	(2.8%)	(2.8%)	(2.8%)	(2.8%)	(2.8%)
Modified Diagnosis													
Non-progressor	140 (100%)	131 (93.6%)	117 (83.6%)	106 (75.7%)	91 (65.0%)	77 (55.0%)	70 (50.0%)	64 (45.7%)	58 (41.4%)	56 (40.0%)	56 (40.0%)	56 (40.0%)	54 (38.6%)
Mod. Possible CBS	0	9	13	9	15	14	7	6	5	2	0	0	2
	(0.0%)	(6.4%)	(9.3%)	(6.4%)	(10.7%)	(10.0%)	(5.0%)	(4.3%)	(3.5%)	(1.4%)	(0.0%)	(0.0%)	(1.4%)
	(0.0%)	(6.4%)	(15.7%)	(22.1%)	(32.8%)	(42.9%)	(47.9%)	(52.1%)	(55.7%)	(57.1%)	(57.1%)	(57.1%)	(58.6%)
Mod Probable CBS	0	0	1	2	0	0	0	0	1	0	0	0	0
	(0.0%)	(0.0%)	(0.7%)	(1.4%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.7%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)
	(0.0%)	(0.0%)	(0.7%)	(2.1%)	(2.1%)	(2.1%)	(2.1%)	(2.1%)	(2.8%)	(2.8%)	(2.8%)	(2.8%)	(2.8%)

Criteria A: limb rigidity or akinesia; Criteria B: limb dystonia; Criteria C: limb myoclonus; Criteria D: orobuccal or limb apraxia, Criteria F: alien limb phenomenon; NVOA, Nonverbal oral apraxia; WABm; Western Aphasia Battery Revised modified. The relative frequencies (%) of symptoms by year were calculated over the number of patients seen on that year.

[1]Modified Criteria D: Presence of limb apraxia. Not considering nonverbal oral apraxia. For modified diagnoses, modified criteria D was used.

[2]The diagnosis was calculated as a percentage of the total cohort (n=140), for categories different than non-progressors a relative and cumulative frequency are shown. Each patient was only counted once, the first time he or she met criteria for possible or probable CBS. The non-progressors were defined as the number of patients out of the total cohort, who did not meet criteria for possible or probable CBS at a given year.

[*]<1% missing data.