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Progressive Supranuclear Palsy Syndrome Presenting as Progressive Nonfluent Aphasia: A Neuropsychological and Neuroimaging Analysis

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Abstract: There is currently considerable interest in the clinical spectrum of progressive nonfluent aphasia (PNFA) and progressive supranuclear palsy (PSP) and the intersection of these two entities. Here, we undertook a detailed prospective clinical, neuropsychological, and neuroimaging analysis of 14 consecutive patients presenting with PNFA to identify cases meeting clinical criteria for PSP. These patients had further detailed assessment of extrapyramidal and oculomotor functions. All patients had high-resolution MR brain volumetry and a cortical thickness analysis was undertaken on the brain images. Four patients presenting with PNFA subsequently developed features of a PSP syndrome, including a typical oculomotor palsy. The neuropsychological profile in these cases was similar to other patients with PNFA, however, with more marked reduction in propositional speech, fewer speech errors, less marked impairment of literacy skills but more severe associated deficits of episodic memory and praxis. These PSP-PNFA cases had less prominent midbrain atrophy but more marked prefrontal atrophy than a comparison group of five patients with pathologically confirmed PSP without PNFA and more prominent midbrain atrophy but less marked perisylvian atrophy than other PNFA cases. In summary, although the PSP-PNFA syndrome overlaps with PNFA without PSP, certain neuropsychological and neuroanatomical differences may help predict the development of a PSP syndrome. © 2010 Movement Disorder Society

Key words: primary progressive aphasia; progressive supranuclear palsy; apraxia of speech

INTRODUCTION

Progressive nonfluent aphasia (PNFA) is a degenerative disorder, which presents with speech production impairment.[1,2] However, although speech impairment dominates the early clinical presentation in PNFA, a parkinsonian disorder often cooccurs as the disease progresses. The overlap of PNFA and corticobasal syndrome (CBS) has been well described,[3,4] but more recently, cases have been reported with a progressive supranuclear palsy (PSP) syndrome.[5–10] The language impairment in these cases is usually a disorder of speech production, which has been described variously as the PNFA subtype of frontotemporal lobar degeneration, progressive apraxia of speech (AOS), primary progressive aphasia, anomia, or aphemia. This variation is probably, at least in part, attributable to the inconsistent terminology that has been used to describe speech production disorders.[11] Patients presenting with a progressive "nonfluent" language disorder may have several distinct kinds of impairment including articulatory deficits (or AOS), agrammatism, reduced speech rate, severe word-finding difficulty, or anomia. According to an emerging consensus, agrammatism and/or AOS are core features of the PNFA syndrome.[1,12] It

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has been proposed that PNFA so defined, and in particular the presence of AOS, predicts tau-positive histopathologies, including PSP.[4,7] In this study, we aimed to investigate prospectively the clinical, neuropsychological, and neuroimaging features of patients presenting with PNFA, who subsequently developed characteristic features of PSP. We compared the clinical and neuroanatomical characteristics of these cases with established cases of PNFA without PSP syndrome and with pathologically confirmed classical PSP (Richardson's syndrome, PSP-RS) cases without speech or language impairment.

METHODS

Clinical Assessment

Fourteen consecutive patients presenting with a clinical syndrome of PNFA to the tertiary Specialist Cognitive Disorders Clinic of the National Hospital for Neurology and Neurosurgery, London, United Kingdom, during a 3-year period were assessed by an experienced cognitive neurologist (JW, JR). As part of this assessment all patients had a structured clinical history, neurological examination, Mini-Mental State Examination[12] and Frontal Assessment Battery.[13] A diagnosis of PNFA was made according to modified Neary criteria.[1,2] Clinical features of a PSP syndrome at presentation or developing subsequently were also recorded[14,15]: we refer to these cases hereafter as "PSP-PNFA" and use "PNFA" to refer to those cases not developing a PSP syndrome. All patients with clinical features of PSP-PNFA were further assessed using the activities of daily living (part II) and motor (part III) components of the Unified Parkinson's Disease Rating Scale (UPDRS). In addition, a video analysis of oculomotor function in these cases was undertaken by a neurologist with experience in degenerative movement disorders (DP) and the severity of any gaze abnormality assessed.[16,17]

Neuropsychological Assessment

A neuropsychological battery with a neurolinguistic focus was administered to all patients and to 14 cognitively normal control subjects (matched for age and gender; Table 1). Background neuropsychological tests comprised a general (nonverbal) intelligence test (Raven's Advanced Progressive Matrices[18]) and tests assessing focal cognitive domains including episodic memory (Camden Pictorial Recognition Memory Test[19]), visuoperceptual skills (the Object Decision subtest of the Visual Object and Space Perception Battery[20]), and executive function (Trail Making Test[21]). Limb apraxia was assessed as part of the clinical examination.

The neurolinguistic component of the battery assessed a number of key speech and language functions. Spontaneous speech was analysed from a sample obtained by asking subjects to talk about their last holiday and to describe the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination.[22] This sample was recorded and subsequently transcribed and analysed for the number of words produced per minute, number of speech production (i.e. phonemic or phonetic) errors, and agrammatic (incorrect tense/plural) errors made per minute, and presence and severity of AOS (mild, moderate, or severe). Naming was assessed using the Graded Naming Test,[23] whilst comprehension was evaluated using the Warrington synonyms test for single words[24] and a shortened version of the PALPA55 test for sentences.[25] Repetition of mono- and polysyllabic words and sentences was also tested.[26] Reading was assessed using a 30-item irregular word reading test and the Graded Nonword Reading Test,[27] and spelling was evaluated with the Graded Difficulty Spelling Test.[28] Comparisons between the groups were performed using a linear regression model taking age and gender into account (STATA8, Stata Corp, College Station, TX).

Brain imaging Analysis

All patients and control subjects had volumetric T1-weighted magnetic resonance brain images acquired on a 1.5T GE Signa scanner (General Electric, Milwaukee, WI). Five patients with pathologically confirmed PSP-RS without a PNFA syndrome during life who had been imaged on the same scanner with the same MRI volumetric protocol constituted an additional comparison group. This group comprised four men and one woman with a mean age at scan of 68.9 years (standard deviation 4.0). Estimated mean duration from symptom onset was 4.4 (standard deviation 1.3) years. Image analysis was performed using the MIDAS software package.[29] Scans were outlined using a rapid semi-automated technique, which involves interactive selection of thresholds, followed by a series of erosions and dilations. This yielded a brain region that was separated from surrounding cerebrospinal fluid, skull, and dura. A baseline brain volume was calculated using this region in all subjects. Scans were subsequently transformed into standard space by registration to the Montreal Neurological Institute (MNI) Template.[30] Manual segmentation of the midbrain was conducted

TABLE 1. *Demographic, general neuropsychological, and neurolinguistic data in patients and healthy controls*

	PSP-PNFA*	PNFA without PSP	Controls
No. subjects	4	10	14
Male:female	3:1	7:3	8:6
Age (yr)	71.2 (5.8)	72.0 (7.4)	69.7 (4.7)
Age at onset (yr)	66.0 (6.8)	66.4 (7.9)	NA
Duration from onset of language symptoms (years)	5.2 (2.5)	5.6 (2.1)	NA
MMSE score (/30)	26.5 (2.4)	23.0 (6.2)[a]	29.6 (0.9)
FAB score (/18)	8.3 (3.9)[a]	11.0 (4.2)[a]	17.8 (0.4)
Neuropsychological assessment			
Ravens Advanced Matrices IQ	96.3 (23.2)[a]	94.5 (18.5)[a]	113.6 (9.9)
Camden Pictorial Recognition Memory Test (/30)	27.5 (3.0)[a,b]	29.5 (0.8)	29.6 (0.9)
Trail making test A (scaled score)	2.5 (1.6)[a]	4.0 (2.2)[a]	9.7 (2.8)
Trail making test B (scaled score)	4.2 (2.1)[a]	3.7 (3.2)[a]	9.8 (2.8)
Visuoperceptual skills—VOSP Object Decision (/20)	16.5 (4.5)	16.4 (2.3)	17.1 (2.4)
Limb apraxia (percentage/no. cases)	75%/3	40%/4	0%/0
Digit span forwards	5.0 (1.2)[a]	4.7 (1.3)[a]	7.0 (0.6)
Neurolinguistic assessment			
Words/min[d]	21.0(12.6)[a]	40.3 (18.1)[a]	133.9 (22.9)
Speech production errors/min[d]	0.2 (0.3)	1.5 (1.7)[a]	0.0 (0.0)
Agrammatic errors/min[d]	0.8 (0.1)[a]	0.6 (0.5)[a]	0.0 (0.0)
Apraxia of speech severity (/3)[d]	1.8 (1.0)[a]	1.8 (0.9)[a]	0.0 (0.0)
Naming (/20)	13.5 (9.1)[a]	11.3 (6.4)[a]	19.7 (0.7)
Single word comprehension—Warrington synonyms test (/50)	40.0 (1.4)[a]	38.1 (6.9)[a]	48.6 (1.3)
Sentence comprehension—shortened PALPA 55 test (/24)	20.0 (13.5)[a]	19.2 (4.3)[a]	23.4 (0.9)
Single word repetition (/30)	22.5 (15.0)	22.0 (10.8)[a]	29.8 (0.4)
Sentence repetition (/10)	6.8 (4.6)	5.3 (4.6)[a]	10.0 (0.0)
Reading—irregular word reading test (/30)	20.0 (13.5)	15.2 (8.1)[a]	28.0 (1.8)
Reading—Graded difficulty nonword reading test (/20)	11.3 (8.4)[a]	8.1 (5.7)[a]	19.6 (0.7)
Spelling—Graded difficulty spelling test (/30)	24.7 (3.2)	7.6 (7.8)[a,c]	25.6 (2.8)

*One PSP-PNFA case was mute at the time of assessment.
[a]$P < 0.05$ disease group worse than controls,
[b]$P < 0.05$ PSP-PNFA worse than PNFA without PSP.
[c]$P < 0.05$ PNFA without PSP worse than PSP-PNFA.
[d]Assessed using a spontaneous speech analysis of a description of the patient's last holiday and the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination.

PSP, progressive supranuclear palsy; PNFA, progressive nonfluent aphasia; NA, not applicable; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; VOSP, Visual Object and Space Perception Battery.

to determine the midbrain volume using a previously described protocol.[31] In brief, two orthogonal views were used to define a superior cutoff (upper border of the midbrain tegmentum in the mid-sagittal slice), an inferior border at the superior border of the pons in the mid sagittal slice, and anterior and posterior borders defined by the brain tissue/cerebrospinal fluid boundary (interpeduncular cistern anteriorly and including the quadrigeminal plate). Brain and midbrain volumes were expressed as a percentage of the total intracranial volume.

Cortical reconstruction and thickness estimation was performed with the Freesurfer image analysis suite[32,33] as previously described.[34] A vertex-by-vertex analysis using a general linear model was performed to examine differences in cortical thickness between the disease groups and the control group. Cortical thickness, C, was modelled as a function of group, controlling for age and gender by including them as nuisance covariates. $C = \beta_1$ PSP-A + β_2 PNFA without PSP + β_3 PSP-RS + β_4 controls + β_5 age + β_6 gender + μ + ϵ (where μ is a constant and ϵ is error). Contrasts of interest between the estimates of the group parameters were assessed using two-tailed *t* tests. Maps showing statistically significant differences between the groups were generated and, for the comparison with controls, corrected for multiple comparisons by thresholding the images of *t* statistics to control the False Discovery Rate (FDR) at a 0.05 significance level.

Literature Review

To assess the present series in relation to previously reported cases of PSP with PNFA, we conducted a search of the published literature using the MEDLINE internet database (www.ncbi.nlm.nih.gov/sites/entrez/) and the keywords "PSP," "progressive supranuclear palsy," "gaze palsy," "PNFA," "FTLD," "PPA," "apraxia of speech," "progressive aphasia," and "aphasia," in isolation and in combination. For all articles identified, the clinical details of all cases with pathological confirmation were abstracted. Age at

TABLE 2. *Brain volumetric data in patients, controls, and pathologically confirmed group of patients with classical PSP*

	PSP-PNFA (n = 4)	PNFA without PSP (n = 10)	PSP-RS (n = 5)	Controls (n = 14)
Brain volume (% TIV)	65.2 (5.9)	62.1 (4.9)[a]	65.4 (4.1)	69.4 (4.2)
Midbrain volume (% TIV)	4.2 (0.5)[a,b]	5.2 (1.0)	3.1 (0.5)[a,c,d]	5.3 (0.6)

[a] $P < 0.05$ disease group smaller than controls.
[b] $P < 0.05$ PSP-PNFA smaller than PNFA without PSP.
[c] $P < 0.05$ PSP (RS) smaller than PSP-PNFA.
[d] $P < 0.05$ PSP (RS) smaller than PNFA without PSP.
PSP, progressive supranuclear palsy; PNFA, progressive nonfluent aphasia; RS, Richardson's syndrome.

onset, disease duration, and age at death were recorded, as well as clinical features at presentation and later in the disease course. Whether the cases would meet current research criteria for a diagnosis of PSP[15] was also recorded.

RESULTS

Clinical Features

Four of 14 patients presenting with PNFA exhibited clinical features of PSP. Each of these patients had initially developed speech production impairment and, only later in the disease course, developed features of PSP. Over the same time period, two other patients with PNFA developed features of a CBS.[35] The group of PSP-PNFA cases and the group of other PNFA cases were comparable in terms of age, gender, and clinical disease duration (Table 1). In these cases, the mean time from onset of language symptoms to development of features of PSP was 4.9 years (range 3.0–8.5 years) for gaze palsy and 4.0 years (range 1.0–8.0 years) for falls. The patients with PSP-PNFA had mean (standard deviation) scores of 20.0 (6.3) for UPDRS part II and 30.5 (15.8) for UPDRS part III compared with the scores for the five patients, with pathologically proven PSP of 18.0 (7.2) for part II and 17.2 (7.2) for part III. The four PSP-PNFA subjects had clear supranuclear abnormalities of their eye movements with slow and hypometric vertical and horizontal saccades of similar severity to the cases with pathologically proven PSP.

Neuropsychological Assessment

The pattern of neuropsychological and neurolinguistic deficits exhibited by patients with PSP-PNFA was similar to other PNFA patients (Table 1). On the general neuropsychological assessment (Table 1) relative to healthy controls, both groups had impaired executive function and reduced digit span but intact visuoperceptual skills. The PSP-PNFA group had mildly impaired performance on a recognition memory task and a higher incidence of limb apraxia than the other PNFA cases. On the detailed neurolinguistic assessment (Table 1), spontaneous speech analysis was broadly similar in both disease groups. PSP-PNFA and PNFA cases showed similar mean severity of AOS and number of agrammatic errors. However, the mean overall speech rate (words/minute) was substantially (though nonsignificantly) lower in the PSP-PNFA group than in the other PNFA cases, whereas speech production errors were significantly more frequent than healthy controls, only in the PNFA group. Relative to healthy controls, performance on comprehension, repetition, and reading tasks was impaired in the PNFA group but not in the PSP-PNFA group, however, the performance of the two disease groups did not differ significantly. Spelling was significantly more impaired in the PNFA group than the PSP-PNFA group.

Brain Imaging Analysis

Mean total brain volume as a percentage of intracranial volume was significantly smaller than controls, only in the PNFA group. Mean midbrain volume was smaller than controls in the PSP-PNFA and PSP-RS groups. Mean midbrain volume in the PSP-PNFA group was significantly smaller than the PNFA group but significantly larger than the PSP-RS group (Table 2).

Cortical thickness maps showed a characteristic pattern of predominantly left hemispheric atrophy in the PNFA group compared with the control group, with most significant thinning of inferior frontal and superior temporal cortices (Fig. 1A). The PSP-PNFA group had significant cortical thinning, mainly in the left inferior and superior frontal lobe (Fig. 1B). There were no significant areas of cortical thinning in the PSP-RS group compared with controls. There were no significant differences in cortical thickness between any of the disease groups when compared directly and corrected for multiple comparisons. Uncorrected significance maps and percentage thickness difference maps between groups are shown in Figure 2: cortical thick-

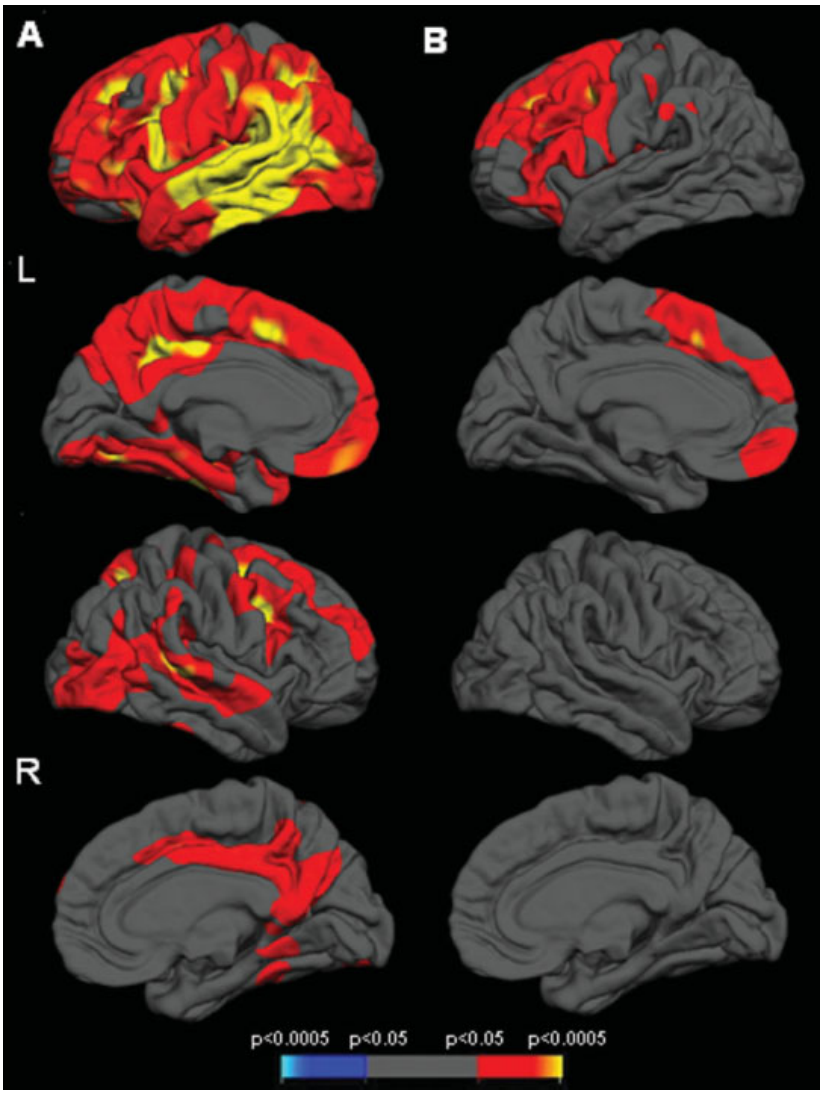

FIG. 1. Cortical thickness maps showing patterns of cortical thinning in disease groups (yellow/red) compared with controls (blue): (**A**) PNFA without PSP and (**B**) PSP-PNFA. No significant areas of thinning were seen in a comparison of PSP-RS and controls. Left hemisphere is shown above, right hemisphere below; for each hemisphere, the top panels are lateral views, and the bottom panels medial views. Coloured bar represents FDR corrected *P* values.

ness was reduced in bilateral prefrontal areas in PSP-PNFA compared to PNFA (blue areas in Fig. 2A); in a more extensive network of predominantly left-sided and mainly prefrontal areas in PSP-PNFA versus PSP-RS (blue areas in Fig. 2B); and in superior and mid-temporal, and posterior peri-Sylvian areas in PNFA versus PSP-PNFA (red/yellow areas in Fig. 2A); there were no significant areas (at an uncorrected level of $P = 0.05$) of cortical thinning in PSP-RS versus PSP-PNFA (Fig. 2B).

Summary of Published Literature

A total of 12 cases of PSP presenting with a speech-production disorder from seven separate studies were identified (Table 3: Refs. [5–10,36]). The diagnosis during life in these cases was most commonly recorded as PNFA, nonfluent dysphasia, PPA, or AOS. Ten of the 12 cases were examined at post mortem and 5 classified as having typical PSP pathology. Atypical PSP pathology, or combinations of pathological abnormalities with PSP as the predominant diagnosis, were identified

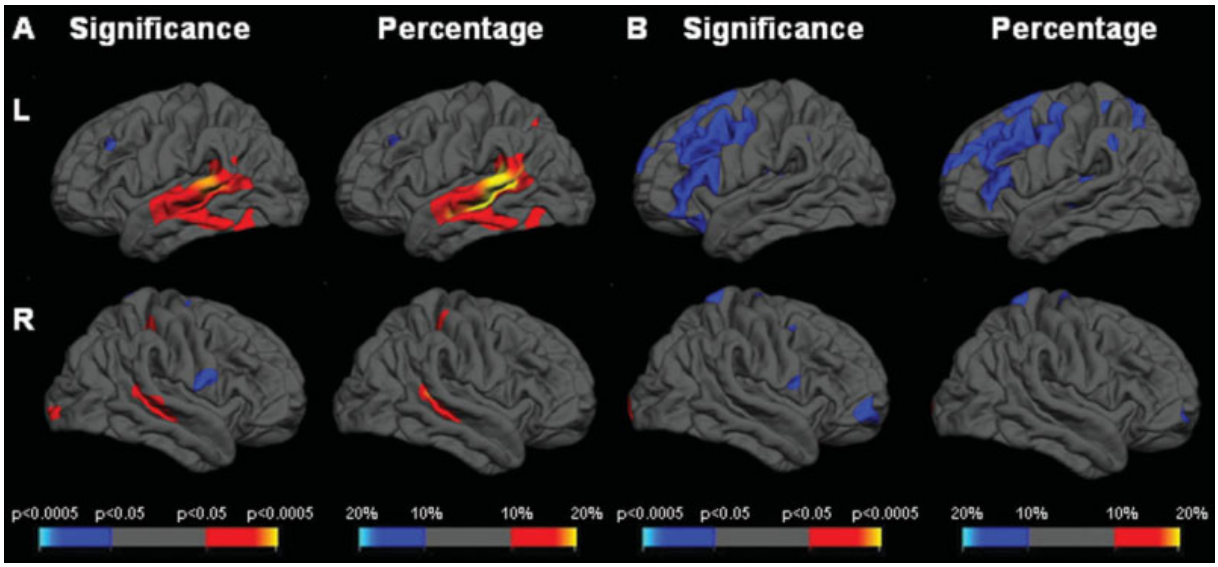

FIG. 2. Cortical thickness maps showing patterns of cortical thinning in disease comparisons: (**A**) PNFA without PSP (yellow/red) versus PSP-PNFA (blue) and (**B**) PSP-PNFA (blue) versus PSP-RS. Left hemisphere is shown above, right hemisphere below with lateral views shown. Left side pictures represent significance maps, with colored bar representing uncorrected *P* values; right side maps represent percentage thinning maps with colored bar representing a percentage value.

in the five remaining cases (Table 3). The clinical features of the four cases presented in this study are included in Table 3 for comparison with the previously presented cases. The age at onset, disease duration and age at death of these cases did not differ significantly from other phenotypes of pathologically proven PSP (PSP-RS, PSP-Parkinsonism or PSP-P, and pure akinesia with gait freezing or PAGF: data from Refs. [37,38]) (Table 4). However, disease duration was closer to the classical PSP phenotype (RS) than to PSP-P or PAGF.

DISCUSSION

Here, we have characterized the syndrome of progressive nonfluent aphasia/AOS with clinical features of PSP. The neuropsychological and neurolinguistic profile of PSP-PNFA is similar to PNFA (Table 1), consistent with the extensively overlapping pattern of cortical atrophy in these two syndromes (Fig. 1). However, the syndromes do differ in certain respects: compared with PNFA, PSP-PNFA is associated with more profound reduction in spontaneous speech and more prominent deficits of praxis and episodic memory, but fewer speech errors and less marked impairment of literacy skills. This pattern of clinical and cognitive deficits in PSP-PNFA is consistent with the relatively greater involvement of prefrontal areas and less marked involvement of perisylvian areas visualized in the cortical thickness analysis of the PSP-PNFA cases. However, it is noteworthy that more severe midbrain atrophy was observed in the PSP-PNFA group than the PNFA-only group: midbrain atrophy here is likely to represent a marker for more extensive involvement of basal ganglia and other subcortical structures in PSP-PNFA. Lesions of subcortical nuclei can themselves give rise to a range of neuropsychological deficits.[39] Furthermore, pathological examination in cases of PSP with progressive aphasia/AOS has demonstrated grey matter atrophy predominantly affecting the superior premotor cortex, spreading to the bank of the precentral gyrus and supplemental motor area and other frontal regions, as well as the caudate nuclei and the globus pallidus.[7] Considering these lines of evidence together, it is, therefore, plausible that a conjunction of cortical and subcortical damage determines the neuropsychological profile in PSP-PNFA.

Although subject to ascertainment bias, this study suggests a prevalence of PSP-PNFA of the order of 29% of all cases of PNFA. Although our cases have not been pathologically confirmed, they share a number of clinical and neuroradiological similarities with pathologically proven cases in the PSP spectrum. A review of the presenting clinical features of the 170 cases of pathologically confirmed PSP in the Queen Square Brain Bank database revealed 4 cases with speech or language problems at presentation, although

TABLE 3. *Review of cases from the literature of PSP with progressive aphasia/apraxia of speech in comparison with the four cases presented in this series*

Author; Nomenclature	N	Sex	Age at onset (yr)	Symptoms/signs at onset	Gaze palsy (duration from onset, yr)	Falls (duration from onset, yr)	Duration to death (yr)	Other symptoms and signs during disease course	Pathological diagnosis
Cases in this series; PNFA	4	F	67	Articulatory difficulty: hesitant, effortful speech, confusion between yes and no	+ (3)	+ (3)	NA	Mild limb bradykinesia and rigidity, limb apraxia	NA
		M	73	Speech production impairment with word-finding difficulty and hesitancy	+ (3)	+ (1)	NA	Apathy, depression	NA
		M	65	Articulatory difficulty with effortfulness and word-finding difficulty. Loss of ability to hum or whistle	+ (8.5)	+ (8)	NA	Mild parkinsonian syndrome, with right limb myoclonus and limb apraxia	NA
		M	57	Decreased speech amount with hesitancy and effortfulness in speech production	+ (5)	+ (4)	NA	Limb apraxia	NA
Karnik et al.[8]; PNFA	1	F	62	Apathy, anhedonia, worsening depression, effortful nonfluent speech	–	+ (2)	4	Severe OCD since aged 40 yrs, falls in context of post surgical foot drop	PSP
Josephs et al.[7]; progressive aphasia/AOS[a]	2	F	69	AOS	+ (onset not recorded)	–	9	Limb apraxia, rigidity, and bradykinesia	Atypical PSP
		M	74	AOS	–	–	8	Limb apraxia, rigidity, and bradykinesia	Atypical PSP
Josephs et al.[6]; AOS, PNFA	4	F	77	Naming difficulty and nonfluent speech	+ (2)	+ (3)	5	Mild asymmetric spasticity, axial rigidity	Atypical PSP; hippocampal sclerosis; Braak stage I
		F	53	Articulatory difficulty, AOS, emotional lability	–	–	8	Late obsessional behavior, brisk reflexes	Atypical PSP; Braak stage III
		F	69	Difficulty with pronunciation, confusion between yes/no	+ (4)	–	8	Head tremor, brisk reflexes. Family history of motor neuron disease and dementia	Atypical PSP; Braak stage IV-V; Transitional LB
		M	70	Anomia, hesitancy, paragrammatic errors, AOS	–	–	7	Mild hypomimia, late behavioral problems	Atypical PSP; amyloid angiopathy
Boeve et al.[5]; PNFA	1	M	71	Anomia, AOS	–	+ (5–6)	6	Mild parkinsonism, agitation	Atypical PSP; amyloid angiopathy
Mochizuki et al.[9]; PPA	1	M	64	Difficulty with spontaneous speech on the telephone	–	+ (10)	10	Right upper limb clumsiness, brisk reflexes. Repetitive behavior	PSP
Wakabayashi et al.[10]; PPA	1	M	72	"Aphemia," decreased speech output	–	NR	6	No other early signs. Late right hemisphere (temporal/occipital) stroke	PSP
Perkin et al.[36]; PSP with dysphasia	2	F	57	Speech production difficulties	NR	NR	NA	Right upper limb tremor and rigidity	NA
		F	58	Non-fluent dysphasia	NR	NR	NA	Right upper limb rigidity	NA

[a]Cases not already described in previous publication by the same authors (Josephs et al.[6]).

PSP, progressive supranuclear palsy; PPA, primary progressive aphasia; PNFA, progressive nonfluent aphasia; AOS, apraxia of speech; NR, not recorded; NA, not applicable, OCD, obsessive-compulsive disorder.

TABLE 4. *Comparison of age of onset, disease duration, and age at death in the different PSP phenotypes: present PSP-PNFA cases are compared with previous PSP cohorts in Refs. 37 and 38*

	Clinical presentation	Age at onset (yr)	Disease duration (yr)	Age at death (yr)
PSP-PNFA	Difficulty with speech production	64.9 (7.2)	6.7 (2.0)	73.8 (7.0)
PSP-RS	Gaze palsy, axial rigidity, and falls	66.5 (7.4)	6.3 (2.4)	72.8 (7.1)
PSP-P	Asymmetric tremor, late falls, and gaze palsy	63.2 (9.9)	11.7 (4.9)	74.9 (9.3)
PAGF	Gradual onset of freezing of gait	61 (age range 44–78)	13 (age range 5–21)	NR

PSP, progressive supranuclear palsy; PNFA, progressive nonfluent aphasia; RS, Richardson's syndrome; PSP-P, PSP-parkinsonism; PAGF, pure akinesia with gait freezing; NR, not recorded.

no detailed clinical assessments were available on these patients. These retrospective data suggest an approximate prevalence of PSP-PNFA of at least 2% of all pathologically confirmed PSP: this is likely to be an underestimate because of incomplete data recording and ascertainment bias (the majority of cases were recruited and assessed via a specialist movement disorders clinic). Previous work has demonstrated that diseases in the FTLD spectrum may show evolution of the clinical phenotype over the course of the illness: patients may present with a particular syndrome, and subsequently develop features of another syndrome. In one series of 60 patients with FTLD,[40] 22 initially presented with PPA: of these, 9 developed features suggestive of PSP/CBS during the course of the disease, however, none had specific PSP pathology at postmortem. One case presenting as typical PSP clinically developed progressive aphasia as a late manifestation and was found to have histopathological features of PSP. Taken together with the evidence of previous cases of speech-led presentations of pathologically proven PSP (Table 3), it is possible that progressive aphasia is more commonly underpinned by PSP pathology than is widely recognized. On the other hand, a proportion of these cases have "atypical" features histopathologically, and the role of such anomalies in modifying the clinical phenotype has not been defined. There are several potential sources of bias in work of this kind. Patients presenting with progressive aphasia may not undergo comprehensive general neurological examination later in the illness, patients with PNFA in whom clinical features of PSP rapidly supervene may be less frequently included in pathological series of frontotemporal lobar degeneration cases, whereas patients with classical PSP who develop speech or language deficits later in the illness may not have detailed neuropsychological assessment. Conversely, it is unclear what proportion of "typical" PNFA cases may have "subclinical" features of the PSP syndrome: this would entail a detailed (longitudinal) analysis of oculomotor function in all patients presenting with PNFA, which we did not undertake here. These observations further underline the need for detailed longitudinal studies with pathological correlation in patients presenting with PNFA and PSP. It would also be of interest to assess the behavioral and neuropsychiatric features of these cases in more detail: the relatively greater prefrontal and subcortical involvement in PSP-PNFA would predict a greater prominence of abulia or adynamia in these patients compared with other PNFA cases.

Taking these caveats into account, the present study suggests the existence of a fourth clinicoanatomical variant of PSP, in line with previous calls for greater recognition of this syndrome.[4,7] The PSP-PNFA syndrome is of both clinical and neurobiological importance. Clinically, the patient with progressive speech apraxia and early marked impoverishment of propositional speech without prominent speech errors should be observed closely for development of the PSP syndrome. Neurobiologically, such cases suggest that PSP should no longer be regarded as a paradigmatic "subcortical" dementia, rather (analogously with other neurodegenerative disorders, such as dementia with Lewy bodies and corticobasal degeneration) it represents a spectrum of overlapping syndromes that may have a cortical emphasis at presentation.

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