

Progressive Nonfluent Aphasia and Subsequent Aphasic Dementia Associated with Atypical Progressive Supranuclear Palsy Pathology

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Key Words

Progressive nonfluent aphasia · Apraxia of speech · Primary progressive aphasia · Progressive supranuclear palsy

Abstract

We describe a right-handed man who developed progressive nonfluent aphasia and apraxia of speech beginning at age 71. By age 74 he had behavioral changes, aphasic dementia, as well as mild parkinsonism; extraocular movements were normal except for mild limitation of upgaze. Serial neuropsychometric testing and single photon emission computed tomography (SPECT) scans showed progressive changes reflecting left>right cerebral hemisphere dysfunction. Neuropathologic examination revealed findings characteristic of progressive supranuclear palsy (PSP) except that the cortical pathology was more widespread than is typical of PSP. We conclude that the clinical manifestations in this case were more similar to the syndrome of progressive nonfluent aphasia with subsequent aphasic dementia and mild parkinsonism, rather than those of PSP. Hence, PSP can present clinically as an atypical dementing syndrome dominated by progressive aphasia/apraxia of speech.

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Introduction

The classic clinical features of progressive supranuclear palsy (PSP) are progressive parkinsonism, supranuclear gaze palsy, and gait impairment [1]. Although dementia was noted in the original description of PSP [2], and more recent reports document the presence of dementia in PSP [3], dementia typically evolves after the more typical clinical features appear. There are a few reports of PSP presenting as a focal or asymmetric cortical degeneration syndrome such as the progressive asymmetric rigidity and apraxia syndrome (typical of corticobasal degeneration) [4, 5], and a progressive aphasia syndrome associated with PSP has been reported [6], but detailed descriptions of such cases are lacking.

The progressive nonfluent aphasia (PNA) syndrome is characterized by the insidious onset and progressive course of nonfluent spontaneous speech, often with oral apraxia, impaired repetition, and preservation of word meaning [7]. Severe amnesia and perceptuo spatial dysfunction are absent on neuropsychological testing, and neuroimaging studies typically demonstrate asymmetric findings maximally affecting the dominant hemisphere [7]. Parkinsonism can evolve late in the disorder. Although disorders with prominent tau inclusions and non-specific histopathology can underlie the PNA syndrome

[8], PSP has not yet been specifically reported. We report herein the serial clinical, neuropsychological, and radiological data on a case with the PNFA and subsequent aphasic dementia associated with atypical PSP pathology.

Methods

Clinical Evaluations

All speech/language and neurologic clinical data were reviewed and summarized.

Neuropsychological Assessments

All data from two sessions of neuropsychological testing were tabulated and analyzed. Testing included assessments of global cognitive functioning (M Mattis Dementia Rating Scale [9]), intellectual functioning (Wechsler Adult Intelligence Scale-Revised (WAIS-R) [10]), attention/concentration (Trail Making Test [11], Stroop Neurological Screening Test [12]), language functioning (Boston Naming Test [13], Multilingual Aphasia Examination Token [14], Controlled Oral Word Association Test [14]), learning and memory (Wechsler Memory Scale-Revised (WMS-R)[15], Rey Auditory Verbal Learning Test [16]), and visuoconstructive skills (Bender Gestalt figures [17]). For the WAIS-R and WMS-R scores, 100 represents the mean, 15 points above and below 100 represents one standard deviation above (i.e., 115) and below (i.e., 85) the mean, and 30 points above and below 100 represents two standard deviations above (i.e., 130) and below (i.e., 70) the mean. For all other scores, the raw scores and percentile levels for each score were determined. The percentile levels were either derived from norms published with the test, or derived from the Mayo Older American Normative Studies (MOANS) norms [18-20].

Neuroimaging Examinations

Magnetic resonance imaging (MRI) was performed using a GE scanner at 1.5 Tesla, and images of the brain were obtained in the sagittal, axial, and coronal planes. Single photon emission computed tomography (SPECT) was performed using HMPAO as tracer, and images of the brain were obtained in the sagittal, axial, and coronal planes.

Neuropathologic Examination

The brain was fixed in 10% neutral formalin and examined for hemorrhage and cerebral cortical atrophy. Sections were obtained from superior/medial frontal gyrus, superior/medial temporal gyrus, inferior parietal lobule, parahippocampal gyrus/entorhinal cortex, thalamus, caudate, putamen, pallidum, midbrain, pons, medulla. Sections were then stained with hematoxylin-eosin (H-E) and modified Bielschowsky's silver. Using the peroxidase-antiperoxidase or the avidin-biotin complex method, representative sections were immunostained using antisera directed toward tau, amyloid, ubiquitin, and phosphorylated neurofilament. The topographic distribution and severity of histopathology was then determined.

Results

Antemortem Findings

A right-handed man with no family history of a neurodegenerative disorder developed subtle apraxia of speech and language impairment at age 71. His language difficulties were manifested initially by anomia, paragrammatic errors, and verbal hesitancy. There was mild facial masking on examination at age 72 but no abnormal extraocular movement or limb findings. Formal speech-language assessment revealed poorly sequenced speech alternating motion rates (AMRs), infrequent vowel distortions, and subtle articulatory substitutions suggesting subtle apraxia of speech, as well as subtle groping behavior when performing nonverbal oral movements suggesting subtle nonverbal oral apraxia. In addition to his apraxic characteristics, conversational language contained some paragrammatic errors and his narratives were slowly produced. Sentence repetition, confrontational picture naming, sentence comprehension, and paragraph comprehension were normal. Word definitions were brief and unelaborated. Proverb explanations demonstrated some appreciation of the abstract concept but were very awkwardly and inadequately expressed. He printed his own name and dictated words and sentences adequately, but his own generated sentence was awkward ('I am want to get at the speech difficulty'). Neuropsychometric testing showed impairment in cognitive flexibility, verbal learning, verbal memory, receptive and expressive language, and visual memory (table 1), although the memory deficits were relatively mild compared to expressive language deficits. Magnetic resonance imaging (MRI) showed mild left temporal lobe atrophy (not shown). Single photon emission computed tomography (SPECT) demonstrated left temporal > parietal cortical abnormalities (fig. 1).

By age 74 he was exhibiting odd behaviors and intermittent agitation, yet he drove a car without apparent difficulties, used a computer, and managed his finances reasonably well. Memory had declined some. He tended to express less emotion and was apathetic. On examination he had apraxia of speech, nonverbal oral apraxia, non-fluent aphasia, mild facial masking and mild limitation of upgaze. Downgaze was preserved, and rigidity, tremor, bradykinesia, and postural instability were all absent. On the Three Words-Three Shapes Test [21], he copied all six items accurately, but on immediate incidental recall, he could only reproduce two of the shapes partially. After one study trial, he reproduced two shapes well and one partially, and one word well. After the second trial, he

Table 1. Neuropsychometric performance^a

	Age 72	Age 74
<i>Global Functioning</i>		
Mattis Dementia Rating Scale ^c		
Attention	35	
I & P	31	
Construction	6	
Conceptual	35	
Memory	18	
Total	125 (5)	
<i>Intellectual Functioning</i>		
Wechsler Adult Intelligence Scale-Revised ^b		
Verbal IQ	99	
Performance IQ	97	81
Full Scale IQ	99	
Verbal Comprehension Factor	97	
Freedom from Distractibility Factor	106	
Perceptual Organization Factor	97	80
<i>Attention/Concentration</i>		
Trail Making Test ^c		
A, s	67 (6–10)	118 (<1)
B, s	127 (29–40)	240 (1)
SNST ^c		
Interference Task	57 (41)	
<i>Language Functioning</i>		
Boston Naming Test ^c	53 (35)	49 (5)
MAE Naming ^c		42 (5)
MLAE Token ^c	36 (2)	CNP
COWAT (CFL) ^c	14 (<1)	10 (<1)
<i>Learning and Memory</i>		
Wechsler Memory Scale-Revised ^b		
Verbal Memory Index	93	
Visual Memory Index	97	72
General Memory Index	92	
Attention/Concentration Index	95	
Logical Memory ^c		
Immediate	18 (19–28)	
Delay	15 (29–40)	
% retention	83 (60–71)	
Visual Reproductions ^c		
Immediate	34 (72–81)	17 (2)
Delay	0 (<1)	7 (3–5)
% retention	0 (<1)	41 (6–10)
Auditory Verbal Learning Test ^c		
Trial 5	6	4
Delay	2 (6–10)	3 (11–18)
% retention	33 (6–10)	75 (60–71)
<i>Visuoconstruction and Visuospatial Skills</i>		
Bender Gestalt Figures	Slightly Distorted	Slightly Distorted

CNP = Could not perform; IQ = intelligence quotient; COWAT = controlled oral word association test; MLAE = multilingual aphasia examination.

Numbers in parentheses represent percentile levels.

^a References for neuropsychometric tests are noted in the text.

^b Percentile levels derived from norms published with the test.

^c Mayo Older American Normative Studies (MOANS) norms were used to determine percentile levels for these tests (see text for references).

reproduced all six items correctly. After a fifteen-minute delay, he reproduced the three shapes well but only one word, and could not recognize the other two words when given a forced choice situation. Speech-language assessment confirmed the existence of marked apraxia of speech and marked nonverbal oral apraxia, as well as mild hypokinetic dysarthria. Verbal comprehension was impaired. His conversational/narrative speech was telegraphic and aposodic. Sentence repetition was poor, color naming and oral spelling were mildly impaired, and number naming was intact. Dictated sentences were spelled correctly but syntactic and semantic errors were present. For example, the phrase 'No ifs, ands, or buts' was written as 'No it, if, or cmts.' His own generated sentence about why he was at the clinic read as, 'How are getting to specify, if the clinic?' Neuropsychometric testing demonstrated progression in the aforementioned cognitive deficits, with additional visuospatial and attentional deficits (table 1). Right hand fine motor speed was also slowed. SPECT scan of the brain showed global left > right cerebral cortical hypoperfusion (fig. 2). His medical records over the subsequent three years did not note any axial or limb rigidity, supranuclear gaze palsy, limb apraxia, alien limb phenomenon, dystonia, cortical sensory loss, or myoclonus. He died at age 77 after experiencing a fall.

Pathologic Findings

Autopsy was performed 12 h after death. The brain weight was 1,425 g. There was subarachnoid hemorrhage over the frontal lobes, and intracerebral hemorrhages involving the parasagittal areas of the anterior frontal lobes. There was no significant cerebral cortical atrophy appreciated on gross and microscopic examination. The lateral ventricles were moderately dilated, left more than right. There was mild loss of pigment in the substantia nigra on gross inspection. Microscopic examination revealed marked amyloid angiopathy in addition to subarachnoid and intraparenchymal hemorrhage (fig. 3). Immunocytochemistry for amyloid, ubiquitin, tau, and neurofilament demonstrated flame-shaped and globose neurofibrillary tangles (NFT) in the cardinal subcortical and brainstem nuclei, as well as tufted astrocytes, coiled bodies in oligodendroglia, and superficial spongiosis and gliosis (fig. 4, table 2). The tau-positive (tau+) pathology was marked in the cerebral cortex, white matter, and subcortical structures. Definitive neurofilament-positive ballooned neurons, neuritic plaques, and Lewy bodies were all absent.

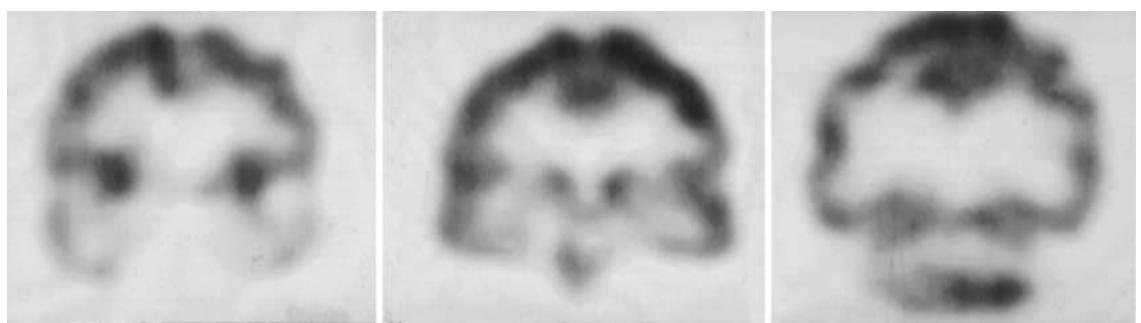


Fig. 1. Coronal single photon emission computed tomography (SPECT) images of the brain at age 72 demonstrates hypoperfusion in the left temporal > frontal > parietal cortex.



Fig. 2. Coronal SPECT images of the brain at age 74 demonstrates global left > right cerebral cortical hypoperfusion.

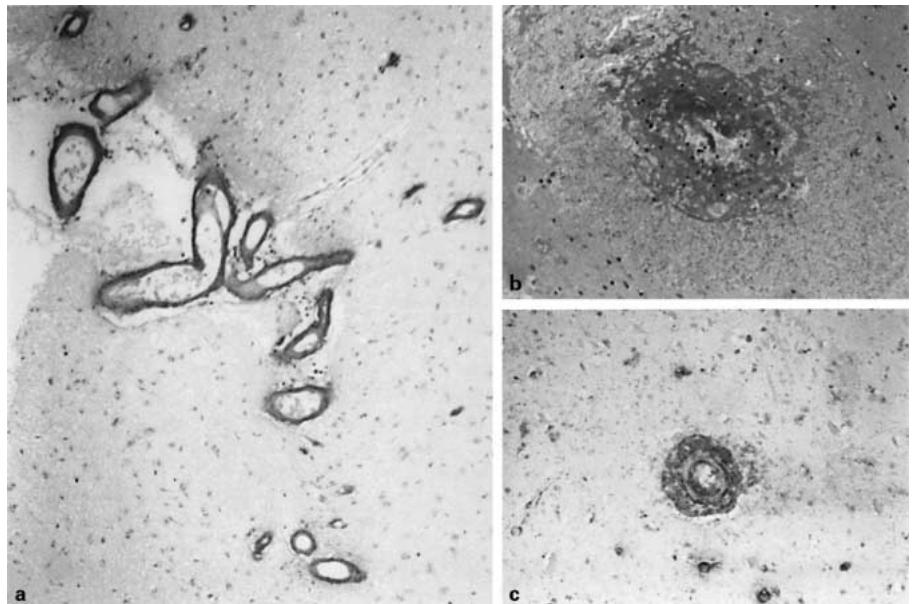


Fig. 3. a Amyloid angiopathy (Aβ42 immunostain); b fresh parenchymal hemorrhage, perivascular; c adjacent section to b immunostained for Aβ42.

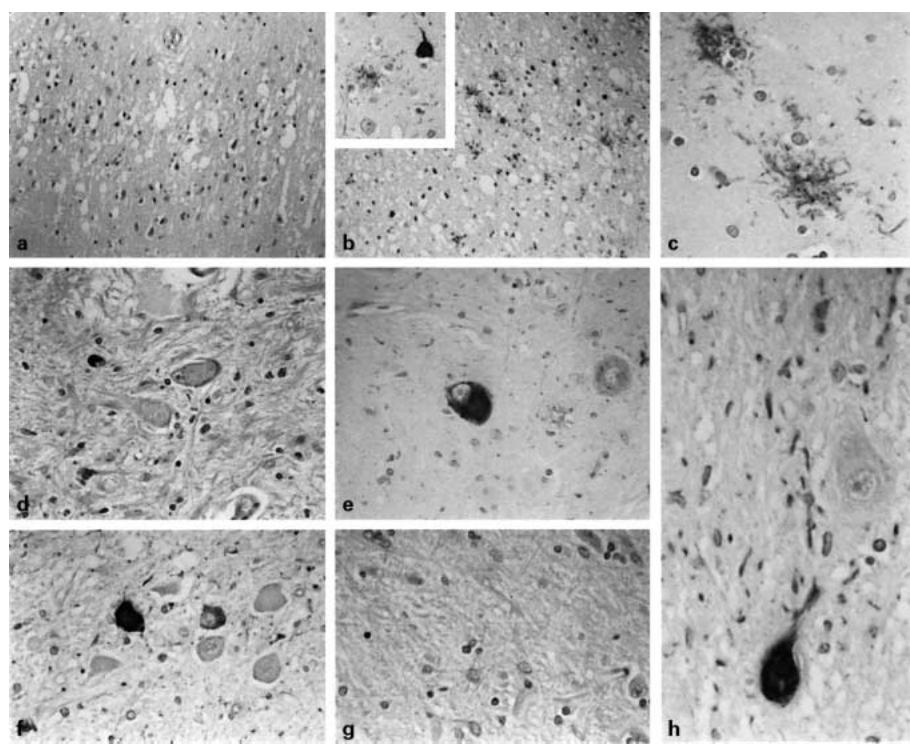


Fig. 4. a Superficial spongiosis in frontal cortex (H&E); b tufted astrocytes and neurofibrillary tangles (NFT) in frontal cortex (higher magnification, inset) (tau immunostain); c tufted astrocytes (tau immunostain); d substantia nigra neuronal loss, gliosis and NFT; e substantia nigra NFT (tau immunostain); f pontine base NFT (tau immunostain); g subthalamic nucleus neuronal loss and gliosis; h cerebellar dentate nucleus NFT (tau immunostain)

Table 2. Distribution of tau + lesions

Region	NFT	Coiled bodies	Tau + astrocytes	Tau + threads
Temporal cortex	+	+	+	+
Frontal and parietal cortices	++	++++	++++	++++ (gray and white matter)
Caudate/putamen	++	+++	+++	+++
Globus pallidus	+	++	+	+
Basal nucleus	++	-	-	-
Hypothalamus	+	+	+	++
Ventral thalamus	++	++	+	++
Thalamic fasciculus	-	++++	-	++++
Red nucleus	+	++	+	++
Substantia nigra	++	++	+	++
Oculomotor nucleus	++	+	+	+++
Tectal plate	+	+++	++	++
Locus ceruleus	++	+	+	+
Pontine tegmentum	++	++	-	++
Raphe nuclei	++	-	-	-
Pontine base	++	+++	-	+++
Medullary tegmentum	++	++	+	++
Inferior olive	+	-	+	++
Dentate nucleus	++	+	-	++
Cerebellar white matter	-	+	-	+

Discussion

A spectrum of clinical syndromes and neurodegenerative disorders must be considered in patients who present with a focal or asymmetric cortical degeneration syndrome [22, 23]. Frontotemporal dementia, progressive nonfluent aphasia, semantic dementia, corticobasal degeneration syndrome, and posterior cortical atrophy all represent syndromes reflecting focal/asymmetric cortical dysfunction. Alzheimer's disease, corticobasal degeneration, and nonspecific neurodegenerative changes (dementia lacking distinctive histopathology) have been reported as the underlying histopathology in each of these syndromes [22, 23]. Pick's disease can present as frontotemporal dementia, progressive nonfluent aphasia, semantic dementia, and corticobasal degeneration syndrome. Progressive supranuclear palsy has been associated with the corticobasal degeneration syndrome [5], and more recently, a progressive aphasia syndrome [6]. Lewy body disease rarely presents as a focal/asymmetric cortical degeneration syndrome. Neuroimaging studies such as MRI and SPECT tend to mirror the topography of dysfunction suggested by the clinical features. No clinical, laboratory, or radiologic findings have yet been identified that accurately predict which specific neurodegenerative disorder underlies any of these syndromes; brain biopsy or autopsy is required to make this determination.

Detailed clinicopathologic analyses in single cases can document an association between a syndrome and a disorder that heretofore has not been adequately characterized, which led us to report this case. The early clinical, neuropsychological, and radiologic manifestations in this case are most consistent with the PNFA syndrome [7]. He did not exhibit gait impairment or supranuclear gaze palsy typical of PSP over the initial four years of his illness, and his parkinsonism was very mild. His course was dominated by language deficits with subsequent development of findings suggesting progressive asymmetric cerebral dysfunction. These findings mirrored the widespread topography of the tau+ pathology at autopsy.

Our case did not have typical findings of semantic dementia. Semantic dementia refers to a progressive language disturbance characterized by fluent, empty spontaneous speech with loss of word meaning, poor naming, poor comprehension, and semantic paraphasias [7]. These patients tend to have neuroimaging abnormalities maximally involving the anterior temporal lobe in the dominant cerebral hemisphere. Our patient had nonfluent, apraxic speech with no semantic paraphasic errors. Confrontational naming and comprehension were rela-

tively preserved early in his course, although all aspects of language were subsequently affected. MRI and SPECT scans revealed left temporal lobe abnormalities which later evolved to include the entire left cerebral hemisphere. Thus while some clinical and radiologic features of semantic dementia were present, the preponderance of findings was more consistent with the PNFA syndrome. Primary progressive aphasia refers to a focal language disturbance without evidence of significant dysfunction in another cognitive domain during the initial two years of symptoms [24]. Our patient did fulfill criteria for this syndrome; we chose to use the term 'progressive nonfluent aphasia syndrome' to be consistent with the consensus criteria proposed by Neary et al. [7].

Progressive supranuclear palsy is typically characterized pathologically by globular NFT distributed in the subcortical gray nuclei and brainstem [25]. Tau+ cortical neuronal and glial pathology does occur in PSP, typically in the frontotemporal regions, but such pathology tends to be mild. The pathologic features of CBD are tau+ tufted astrocytes and astrocytic plaques, and coiled bodies in oligodendroglia, which tend to be most frequent in the frontoparietal cortical regions [25]. Achromatic neurons that are phosphorylated neurofilament-positive are also typical of CBD. In this case, while the widespread cortical and white matter abnormalities are more typical of CBD, the topography of NFT, lack of neurofilament-positive achromatic neurons, and minimal astrocytic plaques are more typical of PSP [25]. Hence this case represents PSP on neuropathological grounds, albeit atypical. Widespread cortical and white matter pathology in PSP has been appreciated by others [3, 26].

The amyloid angiopathy may have increased the propensity to hemorrhage, but the insidious onset and progressive course of signs and symptoms, and lack of hemorrhage on neuroimaging studies, indicate that the amyloid angiopathy and hemorrhages found at autopsy were not significant contributors to his symptomatology, at least over the initial four years of his illness.

While the PNFA syndrome has been reported in association with several pathologically-verified cases of CBD [27-29], its association with PSP has not been specifically documented. Perhaps the cases reported by Esmonde et al. are the closest representation of the PNFA syndrome in PSP [6]. They described three patients with 'dynamic aphasia' associated with PSP (two confirmed by autopsy). These patients exhibited difficulties with language output and a pattern of neuropsychological deficits that suggested impaired initiation and search strategies for verbal expression, but no phonologic or articulatory speech er-

rors were present. Semantic memory was mildly impaired, and in two cases constructional praxis and visuospatial orientation was at least moderately impaired. The clinical and neuropsychological findings indicate that the cases of Esmonde et al. have some but clearly not all of the constellation of findings considered typical of the PNFA syndrome. Our patient presented with typical PNFA features which subsequently evolved. Therefore, underlying PSP should be considered in any patient with an atypical dementing syndrome dominated by progressive aphasia/apraxia of speech.

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