Original Article

Primary progressive aphasia: A comparative study of progressive nonfluent aphasia and semantic dementia

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Primary progressive aphasia (PPA), a degenerative disorder, is often misdiagnosed as Alzheimer's disease. Its subtypes, semantic dementia (SD), and progressive nonfluent aphasia (PNFA), are often difficult to differentiate from each other. Our objective was to highlight the differences in the language profiles of patients with SD and PNFA. To bring out these differences, we report two patients with PPA, one with SD and the other with PNFA. They were administered the Western aphasia battery (WAB) and a semantic battery, which assesses semantic memory. The profiles of language impairment on the WAB indicated that the patient with PNFA had syntactic errors in expressive speech but relatively preserved semantics and comprehension, whereas the patient with SD had preserved syntax but made semantic errors in expressive speech, and had impaired comprehension. There were differences in their performance on the semantic battery too. The patient with SD made relatively less errors on confrontation naming, although on the pointing task he failed to point to those line drawings, which he was unable to name on confrontation. In contrast, the finding of the PNFA patient was the reverse of this. Supplementing conventional neuropsychological tests with formal tests for assessment of language functions is useful in the early diagnosis of PPA. The performance of PPA patients on a detailed assessment of language that includes use of formal tests such as the semantic battery helps to differentiate PNFA from SD.

Key Words: Dementia, language, neuropsychology, primary progressive aphasia, semantic

Frontotemporal lobar degeneration has three major clinical syndromes – the frontal variant of frontotemporal dementia with prominent behavioral changes, and semantic dementia (SD), and progressive nonfluent aphasia (PNFA) [the two forms of primary progressive aphasia (PPA)] with prominent language dysfunction.[1]

In its early stages, the 'naming (language) impairment' of PPA is often mistaken for 'knowing (memory) impairment' and diagnosed as Alzheimer's disease (AD). Likewise, early PNFA is difficult to differentiate from SD.[1],[2] We are aware of only one reported case of PPA from India.[3] Our experience of 4 years in a memory clinic suggests that PPA is under/misdiagnosed as AD.[4]

This report presents the detailed evaluation of a PNFA and a SD patient comparing and contrasting their language profiles and highlights the key diagnostic features.

Material and Methods

Case 1 with SD and Case 2 with PNFA were right-handed, native Malayalam speakers, underwent routine clinical, biochemical, neuroimaging, neuropsychological [including Weschler's memory scale,[5] Addenbrooke's cognitive examination (ACE),[6] Reitan's trail making[7]] and language [Western aphasia battery (WAB)[8]] evaluations. Tests were administered in Malayalam. Semantic memory was tested using a battery which was a modification of an earlier version.[9] It included the following tests.

1) Attribute identification: Names of four objects/items are provided as verbal stimuli. One of them differs from the rest on a particular semantic character. The participant is asked to tell the odd-item (e.g., 'car' is the odd-item in an array of furniture names – 'chair, bed, almirah, car'). Almirah is a commonly used word for cupboard in India. In case of incorrect or no response, the names are provided as visual stimuli on a card and the subject asked to point to the correct response. Verbal response attracts full and pointing half credit.
2) Naming to description: A set of semantic features, which taken together, are characteristic of a particular item/object, is read aloud. The participant has to tell the name of the item/object (e.g., for the description, 'a household appliance, which works on electricity and keeps things cold', the correct response is 'fridge', or 'freezer' or 'refrigerator'). In case of incorrect or no response, the correct answer with two semantically related distracters is read aloud

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from a card (e.g., 'fan', 'fridge,' and 'almirah') and the subject has to choose the appropriate response. Spontaneous response attracts full and forced-choice half credit.

3) Verification of semantic attributes: A statement attributing a semantic feature to an item/object is read aloud. The participant is asked if the statement is correct [(verbally 'yes' or 'no') or nod of their head] (e.g., for the statement 'Birds fly using their wings,' the response is 'yes').
4) Sentence completion: An incomplete sentence (with a blank) is read aloud. A word describing a semantic attribute of the subject in the sentence fits the blank. The participant is asked to tell the most appropriate word to fill-in the blank (e.g., for the sentence 'The crow is _____ in color', the correct response is 'black').
5) Confrontation naming: The subject is shown line drawings of many objects/items, one at a time, and is asked to tell the correct name for each.
6) Picture pointing: Many cards, each with a line drawing of an item/object with no two cards alike, are presented as an array of either 10 or 15 cards at a time. The items/objects in each array are semantically/structurally/functionally related to serve as distracters for the target item. The examiner says aloud the name of the target item/object in the array and asks the participant to point to it.

The composite score on the first four tests is used to assess the attribute awareness.

Table 1: The scores of the semantic dementia (SD) and progressive nonfluent aphasia (PNFA) patients on semantic battery and the Western aphasia battery (WAB)

Test	Maximum score	Case 1 (SD)	Case 2 (PNFA)
Semantic battery			
Confrontation naming	55	32 (58%)	7 (13%)
Picture pointing	55	34 (62%)	53 (96%)
Attribute identification	9	3	4.5
Naming to description	9	3	7
Verification of attributes	9	6	9
Sentence completion	18	8	0
WAB			
Fluency	10	8	3
Information content	10	6	5
Yes/no	60	48	60
Auditory word recognition	60	54	58
Sequential commands	80	16	66
Repetition	100	100 (100%)	100 (100%)
Object naming	60	55	36
Word fluency	20	4	4
Sentence completion	10	6	0
Responsive speech	10	10	6
Reading comprehension	40	2	18
Reading performing	10	4	10
Reading aloud	10	10	10
Matching tasks	30	30	30
Spontaneous writing	62.5	18	2
Writing to dictation	27.5	23.5	22.5
Copy writing	10	10	8
WAB diagnosis		TC sensory	TC motor

TC: transcortical

Case 1

A 65-year-old man with 11 years of formal education, presented with 1-year history of fluent speech, empty in content and containing incorrect names for objects (e.g., asking for a 'brush' instead of a 'towel,' asking for potatoes when pointing to onions). His memory was relatively preserved though insight was poor. There was no significant medical, psychiatric or family history. Examination was unremarkable.

On the WAB his speech was fluent but lacked content. Auditory comprehension of sequential commands was impaired, repetition was preserved and confrontation naming for real objects better than generative naming [Table 1]. Reading aloud, matching, and copy writing was preserved but reading comprehension and spontaneous writing impaired (he wrote 'the goat is flying a kite'). On the semantic battery, he was poor on the attribute identification. Naming to description was impaired even with cues (e.g., in response to the stimulus 'it is a household appliance, which works on electricity and keeps things cool,' he repeated the statement and when given the options of 'fan,' 'fridge,' and 'almirah,' he chose 'almirah'). He performed better on verification of attributes and sentence completion. Most errors on confrontation naming were either *category co-ordinate errors* [saying the name of an item belonging to the same semantic category as the target – e.g., '*hippo*' for '*bear,*' '*pigeon*' for '*parrot*' (43%)], or attribute *errors* [describing a particular feature or demonstrating the use of the target item instead of naming it – e.g., for '*corn*' he said '*it has small seeds, and you roast it*' (17%)]. On picture pointing he failed on those cards, which he was unable to name on confrontation.

Case 2

A 79-year-old Physics professor, presented with progressive word finding and naming difficulty of 2-year duration. He had no other cognitive or neurological complaints and remained status quo at 30 months into the illness. He continues to read newspapers and books in both Malayalam and English. Examination was unrevealing except for clumsiness while performing tasks using the right hand.

On the WAB his speech was nonfluent consisting of single word utterances or with few content words [Table 1]. For, e.g., 'Tree, house car..., Then...' His comprehension was impaired only for the most complex commands. On confrontation he spontaneously named nine objects and with phonemic cues the remaining. His generative naming was poor. He was able to read aloud and perform matching tasks but made errors on complex reading-comprehension task. Copy writing and writing to dictation was essentially normal though spontaneous writing was impaired.

On attribute identification he could not verbally respond but pointed correctly when the names were presented on a card and read aloud. On naming to description he named correctly five out of nine items spontaneously and the remaining on forced choice (e.g., when provided with cues of 'fan,' 'fridge,' and 'almirah' he chose 'fridge' for the statement 'it is a house-

Table 2: The comparative results on the verbal and nonverbal neuropsychological tests of the semantic dementia (SD) and progressive nonfluent aphasia (PNFA) patients

Test	Maximum score	Controls	Case 1 (SD)	Case 2 (PNFA)
HADS				
Anxiety			0	3
Depression			11	7
Verbal				
Orientation	10	7.8 ± 0.7	6	4
ACE calculation	5	4.7 ± 0.8	2	2
ACE registration	24	16.3 ± 3.2	13	13
ACE recall	10	5.3 ± 1.9	0	0
ACE LF		8.1 ± 3.3	4	2
ACE CF		10.2 ± 3.9	3	3
ACE CN	12	8.5 ± 2.4	7	4
ACE repetition	5	4.9 ± 0.1	4	5
ACE reading	2	1	2	1
WMS-LM immediate	47	18.3 ± 6.7	1	0
WMS-LM delayed	47	15.8 ± 6.2	0	0
Nonverbal				
ACE comprehension	8	8	6	8
ACE construction	5	3.6 ± 1.5	3	0
WMSR-Designs imm.	41	24.9 ± 5.1	0	1
WMSR-Designs del.	41	20 ± 6.4	0	0
WMSR-DS-F	8	8.7 ± 1.7	4	6
WMSR-DS-B	7	5.6 ± 1.4	2	3
Trail making A errors		0	16	NA
Time (s)		60 ± 20	360	
Trail making B errors		1	NA	NA
Time (s)		205 ± 30	NA	

HADS, hospital anxiety and depression scale; ACE, Addenbrooke's cognition examination; LF, letter fluency; CF, category fluency; CN, confrontation naming; WMSR, Weschler's memory scale-revised; LM, logical memory component; imm., immediate; del., delayed; DS-F, digit span-forward; DS-B, digit span-backward; NA, not attempted

hold appliance, which works on electricity and keeps things cool'). His performance was good on verification of attributes but poor on sentence completion. On confrontation naming he got only seven correct making mostly *Attempted response errors* [says 'that... that...' but couldn't verbalize (35%)]. On picture pointing he pointed correctly to all items, including those he was unable to name.

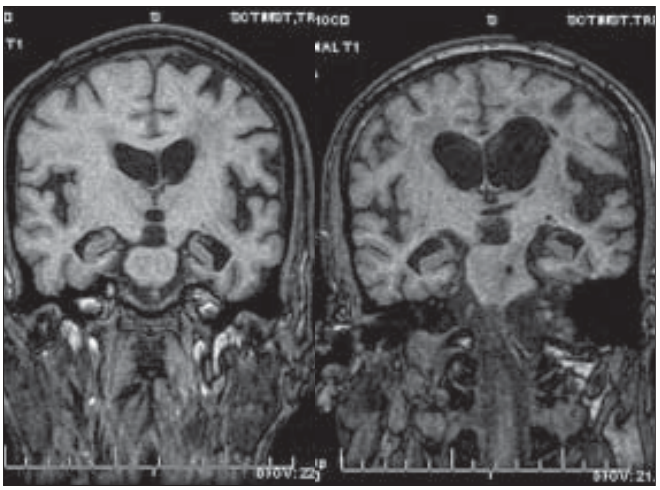

Figure 1: MRI Brain, coronal T1 sections, of the semantic dementia – Case 1 (left panel) and the progressive nonfluent aphasia patient – Case 2 (right panel) showing asymmetrical atrophy involving the left temporal lobe more than the right. The asymmetry is more marked in the patient with progressive nonfluent aphasia

Neuropsychology and imaging results

Scores on verbal and nonverbal tests [Table 2] shows that both patients are more impaired on verbal tests (except for the nonverbal WMS-Designs and trail making). MRI brain of both showed asymmetric cortical atrophy, maximally in the left perisylvian temporal region [Figure 1]. SPECT showed reduced perfusion in the frontal and frontotemporal regions [Figure 2] as commonly found.[10],[11] Both are independent

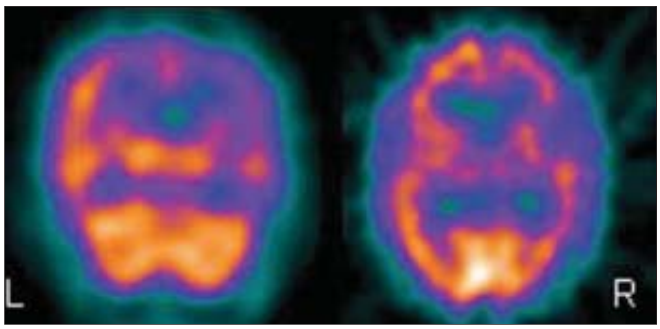

Figure 2: Axial SPECT image of the semantic dementia – Case 1 (left panel) and the progressive nonfluent aphasia patient – Case 2 (right panel) showing reduced perfusion in the left frontotemporal regions

on activities of daily living (ADL), except for the language handicap.

Discussion

Progressive nonfluent aphasia begins with nonfluent aphasia, agrammatism, phonemic paraphasias, or anomia.[12] Supportive features are stuttering or oral apraxia, impaired repetition, alexia, agraphia, early preservation of word meaning and late mutism.[13] Semantic dementia is characterized by fluent, empty spontaneous speech, loss of word meaning, semantic paraphasias, preserved matching, single word repetition, and ability to read and write orthographically regular words.[12] The pathology in PNFA involves the left perisylvian region asymmetrically and in SD the anterolateral temporal lobes, usually bilaterally.[13]

Both our patients presented with naming difficulty with greater impairment on verbal than on nonverbal tests. Poor performance on WMS-Designs, digit span, and the trail making was possibly due to comprehension deficits in SD and motor impairment in PNFA, although a subtle frontal dysfunction often reported in the early stages of PPA,[14],[15] cannot be excluded. These clinical features, in conjunction with the imaging findings, confirm the respective diagnosis of SD and PNFA in our two patients.

On the WAB, spontaneous speech of PNFA patient had dropped function words, and SD patient had meaningless sentences. Comprehension (verbal and reading) was better in PNFA but impaired in SD. Progressive nonfluent aphasia patient could write to dictation while the SD patient could only copy write. The WAB aphasia diagnosis was transcortical motor in PNFA and transcortical sensory in SD, broadly differentiating PNFA from SD.[12] Western aphasia battery could not delineate the nature of semantic memory impairment.

On the semantic battery, although confrontation naming was relatively better in SD, greater impairment on attribute identification, naming to description and pointing demonstrates a greater loss of semantic knowledge that is not only for the names of objects but also for their semantic characteristics. In contrast, although patient with PNFA showed a greater impairment on confrontation naming, a preponderance of attempted response errors, a superior performance on attribute identification and the pointing tasks (pointing correctly to even those line drawings, which he failed to name in both) suggests a relative preservation of semantic knowledge in the presence of an impaired access to the phonological word forms. Preponderance of attribute errors in SD, however suggests, that not all semantic attributes of objects whose names are lost are erased until late stages.

This report illustrates that systematic testing of language and semantic memory and a high index of suspicion can prevent misdiagnosis and aid sub typing of PPA.

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Invited Comments

Primary progressive aphasia (PPA), characterized by deterioration in language for at least 2 years before the onset of other cognitive deficits, has been widely recognized as a distinct clinical entity since Mesulam's description in 1982.[1] However, as well characterized in the article, 'Primary Progressive Aphasia: A Comparative Study of Progressive Nonfluent Aphasia and Semantic Dementia' in this issue, PPA exists in two forms. The first, progressive nonfluent aphasia (PNFA) is often compared to Broca's aphasia, since patients often have effortful articulation, agrammatic sentence pro-

duction, and relatively intact comprehension. Patients with both PNFA and Broca's aphasia due to stroke frequently have more difficulty naming verbs than nouns.[2] Likewise, semantic dementia (SD) is often compared to Wernicke's aphasia, since both are characterized by fluent, grammatical, and well-articulated speech with little content, impaired comprehension, and disproportionate difficulty naming nouns relative to verbs. As demonstrated with voxel-based morphometry, the brain regions affected in PNFA generally lie within the vascular territory typically damaged in Broca's aphasia, the left inferior frontal gyrus and anterior insula.[3] Semantic dementia, like Wernicke's aphasia, often reflects atrophy in the left temporal lobe, although the abnormality is generally more anterior and inferior in SD.

However, there are important differences from the vascular syndromes of Broca's and Wernicke's aphasia. Individuals with PNFA often have relatively spared spelling of both verbs and nouns.[2] Such a pattern is extraordinarily rare in Broca's aphasia. The dissociation between written language (intact) and other aspects of communication – speech articulation, oral naming of verbs, and grammatical sentence production (which are impaired) may provide insights into brain/language relationships. For example, brain regions that are spared in PNFA but damaged in Broca's aphasia after stroke, are good candidates for the neural regions subserving written naming.

In the same vein, there are crucial differences between SD and Wernicke's aphasia. Most notably, patients with SD typically have associative agnosia – impaired access to the meaning of objects – not just the names of objects. They often use objects inappropriately, despite normal visual perception. This deficit has not been described in Wernicke's aphasia caused by unilateral stroke. Identifying areas of the brain that are dysfunction in SD but not in Wernicke's aphasia would provide clues as to the areas responsible for object meaning. To illustrate, SD is generally associated with atrophy in temporal areas that are inferior and anterior to Wernicke's area, and more bilateral. Thus, bilateral inferior and anterior temporal cortex may be crucially involved in accessing the meanings of objects and their associations.

Thus PPA and other focal dementias provide the opportunity to investigate the functions of brain regions that are not often damaged by stroke. However, progress in this domain has been limited, largely because criteria for classification are insufficiently objective and reliable to ensure that investigators worldwide classify patients the same way. For example, the classification of PNFA requires agrammatism and/or impaired articulation for some authors[3] but not others.[4] This dissonance is unsurprising, given that speech 'fluency' is a multidimensional characteristic that encompasses parameters of melody, phrase length, syntax, articulatory agility, and rate of speech. One patient might be fluent along one dimension and nonfluent along another. This problem of classification in nontrivial, since different types of PPA may have different etiologies, but such a clinicopathological relationship has been obscured by different criteria for classification across centers. Studies that carefully describe characteristics of aphasia underlying classification, such as the study in this issue,[5] represent an important first step in forming a set of criteria for distinguishing various types of PPA with high interjudge reliability. Achieving this goal is essential for future multi-center clinical trials of treatment for PPA.

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