

Primary Progressive Aphasia

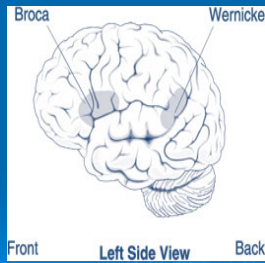
Melanie Shulman, MD

Associate Director, Cognitive and Behavioral Neurology
Pearl Barlow Center for Memory Evaluation and Treatment

Assistant Director, NYU Alzheimer Disease Center Clinical Core
NYU Langone Medical Center, Center of Excellence on Brain Aging

What is aphasia?

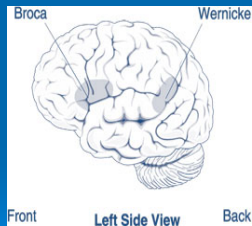
- Aphasia is a disorder that results from damage to portions of the brain that are responsible for language
- In the vast majority of people, these are areas on the left side of the brain
- The disorder impairs the expression and understanding of language as well as reading and writing



What types of aphasia are there?

NON-FLUENT (Broca-type)
Typically resulting from damage to the frontal lobe
People with Broca-type aphasias speak in short phrases, requiring great effort. They often leave out small words such as "and" "the" "is".
Often these patients understand speech quite well, often aware of their difficulties, and become easily frustrated.

FLUENT (Wernicke-type)
Typically resulting from damage to the temporal lobe
People with Wernicke-type aphasias speak in long sentences that have no meaning, add unnecessary words, create made-up words.
Often these patients have great difficulty understanding speech and are unaware of their mistakes.



What causes aphasia?

SUDDEN ONSET

Stroke

Traumatic brain injury

Infection

SLOW ONSET

Neurodegenerative disease
(Primary Progressive Aphasia)

Tumor

Infection

Primary Progressive Aphasia

The diagnosis is made in any patient in whom language impairment (*aphasia*) caused by a neurodegenerative disease (*progressive*) constitutes the most important aspect of the clinical picture (*primary*).

Time criterion of 2 years

- Language disorders can be heterogeneous at onset, but by definition, must remain isolated for **≥ 2 years** with relative preservation of activities of daily living (ADL) and other cognitive functions (→ effectively ruling out CJD which is usually more rapid and amnesic-AD primarily affecting memory)

Varied language patterns in PPA

- These language disorders are heterogeneous
- Some are fluent, others not
- Some with comprehension deficits, others not
- They often do not fit the classical patterns of aphasia established from the stroke literature

Three clinical subtypes of PPA

- **Agrammatic/dysfluent** (NON-FLUENT)
 - Also known as Progressive Nonfluent Aphasia (PFNA)
 - Characterized by impairments of syntax and fluency but preserved word comprehension
- **Semantic** (FLUENT)
 - characterized by poor word comprehension but preserved syntax and fluency
- **Logopenic** (COMBINATION)
 - Characterized by interruptions of fluency due to frequent word-finding pauses but relatively intact syntax and word comprehension



B John Gifford was the kind of person who would go off sailing in his yacht the 'Neva' around the island of Scorbua whenever there were signs of chaos at work. He had a thorough knowledge of this area as he had grown up there in his childhood, and this was how he always sought relaxation from the busy routine of the office life at Bergess, Challice & Co. He would sit on deck sipping his champagne, as the breeze tangled his normally immaculately combed hair. Gradually his business worries would recede. Dressed in his old, baggy sweater, decrepit suede boots and with his stubby beard he felt quite the part of an ancient mariner.

Examples of spontaneous speech in the progressive aphasia

> Progressive nonfluent aphasia

The sea ... er ... er ... er ... um ... a man in a soup ... no suit ... with a panner (*pointing at paddle*) falling out of the boat. Er ... nice stand ... no sand next to the sea and the boy making a nice h. h. house ... houses. Another (*long pause*) m. m. m. man ... a big men ... no man ... and little g. g. g. girl p. p.p. playing. The two skygurls (*points to seagulls*). Water round castle ...

> Semantic dementia (fluent)

That's the father, playing with his son, that thing (*points to ball*) ... hitting the thing in the air. (*Pointing to boy falling out of boat*) He's in the garden isn't he, playing that game again. I hope he doesn't fall down. Looks as if he's wobbling. (*Pointing to sandcastle*) I'm not quite sure. That's the water there, coming right up to there, and that stays there and he's working, he's pressing that down, isn't he? He's working it. He's moving it down there because that's the equivalent of that, and that goes there ... both sides. I've seen something like that somewhere else.

> Alzheimer's disease ('logopenic aphasia')

A beach scene ... playing on the beach. A pier ... (*pause*) and a building on the pier and a row of beach (*pause*) things. (*long pause*) In the middle ground, a father and child playing with a large ball on the ... (*pause*). On the left, erm ... a rower has overbalanced next to the beach really ... and is falling out over the (*pause*) side of the erm. (*pause*) rowing boat. In the foreground is a youngster building some (*pause*) sandcastles.

PPAs break the aphasia fluent/nonfluent "rule-book"

- > The dysarthria, almost universally present in Broca's non-fluent aphasia due to CVA, is rarely present
- > The comprehension deficits, the hallmark of Wernicke's fluent aphasia due to CVA, are relatively mild
- > *Logopenia*, or, intermittent dysfluency, is common in PPA (whereby the patient is fluent when engaged in conversational "small talk," but markedly nonfluent when responding to directed questioning)
- > In some patients, the ability to write language may be less impaired than the ability to speak (rarely the case due to CVA)

Natural history of PPA

Prognosis of PPA is largely unknown with only a few patient series reported

Best study thus far from *Neurology* 2005 (Rhun et al 65: 887-891) following 49 patients over 10 years who presented with PPA as their initial symptom

Results:

Median age of onset 62 years

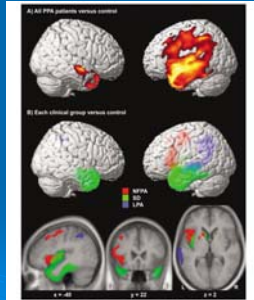
Impairments of activities of daily living developed a median of 6-7 (range of 2-12) years post onset in > 50% of patients

75% of patients eventually met criteria for frontotemporal dementia (FTD)

Overall, the researchers found that in PPA autonomy is maintained until late in the disease, but survival is no longer than in other dementias

Neuroimaging

- A wide network of brain regions including the whole L perisylvian region, L anterior temporal lobes bilaterally (L>R), and basal ganglia bilaterally were found to be atrophied in all PPA pts.
- NFPA (red) inferior frontal and insular atrophy
- SD (green) anterior temporal atrophy
- Logopenic (blue) L posterior temporal cortex and inferior parietal lobule



Neuropathology

- Atrophy tends to be mostly in the perisylvian region in the agrammatic/ dysfluent and logopenic variants but extends into anterior and medial temporal cortex in the semantic variant.
- 60-70% of PPA patients demonstrate FTLN subtypes, and approximately 20% demonstrate the typical plaques and tangles of AD

Neuropathology

- The FTLN pathology may include focal neuronal loss, gliosis, tauopathy, ubiquinopathy with TDP-43 proteinopathy (known as FTLN-U), and superficial vacuolation.
- Unknown: In the PPA-AD cases, why does the plaque/tangle pathology, known to cause the greatest initial neuronal loss in entorhinal and hippocampal areas, seemingly effect other distinct brain regions, accounting for the "aphasia without amnesia" pattern.

Genetics

- In non-familial cases, the agrammatic/ dysfluent variant (PNFA) seems more closely associated with tauopathy whereas the semantic variant may be more closely associated with FTLN-U.
- Most cases of PPA are sporadic, but familial cases have also been linked to FTLN-U pathology and mutations in the progranulin gene.
- In contrast to the sporadic cases, the familial cases display an association of FTLN-U pathology with the agrammatic/dysfluent rather than the semantic variant of PPA.

Genetics

- In some of the progranulin mutation families, affected members display phenotypical homogeneity for PPA; whereas, in others, some members have PPA and other the behavioral variant of FTD.
- The frequency of learning disabilities, especially dyslexia, is higher in PPA families than in controls or typical AD.
- The cellular mechanisms that make the same mutation lead to bv-FTD and others manifest PPA is unknown – but the possibility exists that, in some patients, selective vulnerability of the language network might be genetically determined.

Treatments – not very encouraging so far

- Small controlled trial with bromocriptine was negative
- Memantine versus placebo trial nearing completion
- Anecdotal reports with cholinesterase inhibitors are mainly negative (one small study showed a marginal benefit with galantamine)
- Some selected patients with PPA benefit from speech therapy

Approaches to speech therapy treatment

1. Focused directly on the language skills that are impaired, i.e. word retrieval skills
2. Provide augmentative/alternative communication strategies of devices, i.e. use of a communication notebook, use of gestures, use of drawing
