Understanding the Diagnosis of Primary Progressive Aphasia

Becky Khayum, M.S., CCC-SLP
Speech-Language Pathologist
Brain Structure | Each part of the brain has a specific function

- **Hippocampus**: Memory
- **Frontal lobe**: Motor function, problem solving, executive function
- **Temporal lobe**: Language, comprehension
- **Occipital Lobe**: Visual processing
Different conditions can cause injury to the brain regions

- **Traumatic Brain Injury** → Frontal Lobes → Problems with judgement, problem solving, executive function
- **Stroke** → Left Frontotemporal Lobe → Language deficits (aphasia), weakness on right side
- **Neurodegenerative Disease** → Hippocampus → Short term memory loss
- **Neurodegenerative Disease** → Left Frontotemporal Lobe → Language deficits (aphasia)
What is Neurodegenerative Disease?

Neurodegenerative disease is an umbrella term for a variety of protein abnormalities in brain cells that cause them to die.

There are different families of neurodegenerative diseases.

1. Amyloid
   "Alzheimer's Disease"
   - Mixed proteinopathy

2. Tauopathies

3. Synucleinopathies

4. TDP-43 proteinopathies
Where do neurodegenerative diseases occur in the brain?

• The 5 families of protein abnormalities may start in different regions of the brain.

• Initial symptoms will depend upon WHERE the protein abnormalities start in the brain.
<table>
<thead>
<tr>
<th>Neuropathological Diagnosis / Protein Abnormality</th>
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What is a clinical diagnosis?

- A **clinical diagnosis** is a diagnosis that is made by describing the symptoms you are experiencing.

- A "**clinical dementia syndrome**" is a clinical diagnosis caused by neurodegenerative disease.

- There are many different types of clinical dementia syndromes.
Dementia Map | Connecting the dots between protein abnormalities, their symptoms and clinical diagnoses

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<td>Posterior Cortical Atrophy</td>
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Is there a 1:1 correlation between the abnormal protein and clinical dementia syndrome?

- No. Each family of abnormal proteins are associated with a predominant dementia syndrome; however, there is no 1:1 correlation between the abnormal protein family and dementia syndrome.

- This is the case for primary progressive aphasia (PPA).

- PPA may be caused by 3 different families of abnormal proteins.
Primary Progressive Aphasia can be caused by 3 different families of protein abnormalities.

- TDP-43
- Amyloid Plaque + Tauopathies (Alzheimer’s Disease)
- FTLD-Tau

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The Neuropathologic Diagnosis

• The “neuropathological diagnosis” refers to the underlying protein abnormality causing your symptoms. Currently, the neuropathologic diagnosis can only be confirmed at autopsy.

• Researchers are developing tests for patients that look for "biomarkers" - evidence of the type of protein abnormality.
Why is the neuropathologic diagnosis important?

- **Disease modifying treatments** will likely target the type of protein abnormality, NOT the patient’s symptoms.

- Different drugs will likely be needed for different types of protein abnormalities.

- There are currently no disease modifying treatments for neurodegenerative diseases.
What does the word dementia mean?

• Dementia is an **umbrella** term.

• Dementia is also a **clinical term** (describes SYMPTOMS).

• Dementia refers to a **cognitive impairment** (memory, language, behavior) that **gets worse over time**.

• Some ”dementias” are reversible (e.g., medication side effects or vitamin deficiencies).

• Dementia syndromes caused by neurodegenerative disease are **not reversible**.
Are “Alzheimer’s” and “Dementia” the same thing?

• No. Alzheimer’s dementia is one type of dementia syndrome caused by neurodegenerative disease.

• It is the most prevalent type of dementia syndrome (accounts for 60-80% of cases).

• It is the type of dementia syndrome that was first discovered.

• Many people are not aware that there are many different types of dementia syndromes that do NOT involve memory loss.
There is a difference between the terms "Alzheimer's Disease" and "Alzheimer's Dementia"

- **Alzheimer's Disease** refers to the neuropathology (mixed proteinopathy of amyloid and tauopathy)

- **Alzheimer's Dementia** refers to the clinical dementia syndrome that starts in the hippocampus and causes short term memory loss.
Is Primary Progressive Aphasia a type of dementia syndrome?

- Yes. Primary Progressive Aphasia is a clinical dementia syndrome caused by neurodegenerative disease.
- Symptoms get worse over time.
- There is no cure.
There are 3 described PPA clinical variants (or subtypes), based on what part of the language region is impacted by the neurodegeneration:

- **Semantic** (PPA-S or svPPA)
- **Nonfluent/Agrammatic** (PPA-G or nfvPPA)
- **Logopenic** (PPA-L or lvPPA)
# PPA Variant: Strengths and Challenges

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<td>• Fluent conversational speech</td>
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<tr>
<td>Agrammatic (PPA-G)</td>
<td>• Single word comprehension&lt;br&gt;• Knowing meaning of words&lt;br&gt;• Using content words in conversation</td>
<td>• Grammatical errors&lt;br&gt;• Abnormal word order&lt;br&gt;• Shorter sentences&lt;br&gt;• May have effortful speech (apraxia – motor programming)</td>
</tr>
<tr>
<td>Logopenic (PPA-L)</td>
<td>• Knowing meaning of words&lt;br&gt;• Circumlocuting (talking around) words&lt;br&gt;• Single word comprehension</td>
<td>• Difficulty finding words&lt;br&gt;• Frequent hesitations&lt;br&gt;• Difficulty with repetition&lt;br&gt;• Poor comprehension of longer sentences</td>
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PPA Variants: Limitations

• People may have symptoms from several different variants.

• Symptoms change over time. People may develop symptoms from multiple variants.

• Important to focus on language strengths and challenges, to develop strategies to help with communication.
Variant and Neuropathology

- There is no 1:1 correlation between PPA variant and the neuropathology.

- Correlation is probabilistic, not deterministic.
  - PPA-S – TDP-43
  - PPA-G – FTLD-tau
  - PPA-L – Alzheimer's Disease neuropathology
Primary Progressive Aphasia Facts

• Dementia syndrome characterized by changes in language, comprehension, reading, and writing that get worse over time.

• First described in 1982 by Dr. Marsel Mesulam.

• PPA is not caused by stroke or traumatic brain injury. It is caused by neurodegenerative disease.

• If early symptoms include other cognitive areas (memory loss, behavioral changes), the diagnosis is not PPA.
Primary Progressive Aphasia Facts

• **Early onset dementia** syndrome (age of onset frequently between 45-64 years, but can occur later in life as well).

• **Less common** than Alzheimer's dementia.

• Impacts women and men **equally**.

• **Insight is often preserved**, resulting in higher rates of anxiety and depression, as compared to Alzheimer's dementia.

• **Frequently misdiagnosed** as depression, psychiatric disorder or Alzheimer's dementia.
What is Frontotemporal Dementia (FTD)?

- FTD is a clinical term.
- **Umbrella term** for dementia syndromes where the neurodegenerative disease starts in the frontotemporal region of the brain.

- There are three main categories of frontotemporal dementia:

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<th>Motor</th>
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<td>Corticobasal Syndrome</td>
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<td>Progressive Supranuclear Palsy</td>
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<td>ALS-FTD</td>
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Frontotemporal Dementia Facts: Genetics

• Most PPA cases are sporadic.

• Small percentage of cases are familial:
  • Some family history of neurodegenerative disease, but no gene mutation identified

• Strong family history of FTD/ALS and gene mutation is identified. Can be inherited (autosomal dominant).
  • Most common gene mutation is progranulin (GRN)
PPA vs. Alzheimer's Dementia Risk Factors

• Alzheimer's: Getting older
• Alzheimer's: Genetic risk factor is ApoE4 allele

• PPA: personal or family history of learning disability (dyslexia)
  • *Selective vulnerability theory – areas of vulnerability in the brain may be prone to neurodegeneration*
Progression of Symptoms

• There is significant individual variability in the progression of language symptoms and emergence of new symptoms.

• There is much research in the area of predicting where and how the disease will progress.

• Life expectancy from the onset of symptoms is also variable: documented cases of 2-20 years.
Treatment - Medications

• There is **no disease-modifying treatment** for PPA.

• For suspected Alzheimer's disease pathology, Alzheimer medications may be recommended by your neurologist.

• There are no medications for suspected FTLD-tau or TDP-43 pathology.

• Medications for depression, anxiety, and sleep may be used to help with symptoms.
Treatment – Non-pharmacological

- **Speech therapy**: find a therapist who uses a personalized, life participation approach to care, with ongoing communication partner training
- **Social Work**: counseling, support, resources
- **Support Groups/Aphasia Groups**: virtual opportunities
- **Noninvasive brain stimulation**: tDCS or TMS
  - Transcranial direct stimulation or transcranial magnetic stimulation
  - Still in clinical trials to determine if this is effective treatment.
References

References


