Primary Progressive Aphasias and Apraxia of Speech

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ABSTRACT

PURPOSE OF REVIEW: This article reviews two of the primary progressive aphasias (PPAs), disorders characterized by the early and predominant impairment of language, and primary progressive apraxia of speech, a degenerative motor speech disorder that is closely related to PPA. An outline of the history and controversy surrounding how these disorders are classified is provided before the article focuses on each disorder's clinical and imaging features.

RECENT FINDINGS: Over the past decade, the classification of degenerative speech and language disorders has been refined. Clinical, imaging, and pathologic evidence suggests that primary progressive apraxia of speech is a distinct degenerative disorder. Furthermore, multiple lines of evidence have highlighted issues with nonfluent/agrammatic variant PPA, which complicates the diagnosis, prognosis, and study of this disorder. Semantic variant PPA, while not without controversy, remains one of the most well-defined disorders, with good clinicopathologic correlation.

SUMMARY: Accurate classification and diagnosis of these degenerative speech and language disorders is crucial in clinical practice and ongoing research efforts. For nonfluent/agrammatic variant PPA, the authors suggest emphasizing agrammatism as the core inclusion criterion and taking care not to include patients with isolated or predominant apraxia of speech. Isolated apraxia of speech can be the manifestation of a degenerative disease and, based on the different prognosis, should be recognized as distinct from PPA. Finally, it is important to recognize that some patients with semantic dementia, despite sharing the same pathologic associations, may not meet criteria for PPA.

INTRODUCTION

Primary progressive aphasia (PPA) refers to a group of neurodegenerative diseases characterized by early and prominent language impairment occurring in the relative absence of cognitive impairment, behavioral disturbance, or motor symptoms.[1] Although this label was coined in the 1980s and was important in the recognition of PPA as a clinical entity distinct from Alzheimer disease dementia,[2] the concept of progressive language impairment as the initial manifestation of a

TABLE 5-1   **Root Criteria for a Diagnosis of Primary Progressive Aphasia[a]**

Inclusion: Criteria 1–3 Must Be Answered Positively

1 Most prominent clinical feature is difficulty with language

2 These deficits are the principal cause of impaired daily living activities

3 Aphasia should be the most prominent deficit at symptom onset and for the initial phase of the disease

Exclusion: Criteria 1–4 Must Be Answered Negatively for a Primary Progressive Aphasia Diagnosis

1 Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders

2 Cognitive disturbance is better accounted for by a psychiatric diagnosis

3 Prominent initial episodic memory, visual memory, and visuoperceptual impairments

4 Prominent, initial behavioral disturbance

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TABLE 5-2   **Criteria for Variants of Primary Progressive Aphasia[a]**

	Nonfluent/Agrammatic Variant Primary Progressive Aphasia	Logopenic Variant Primary Progressive Aphasia	Semantic Variant Primary Progressive Aphasia
Core features	At least one of the following: Agrammatism in language production Effortful, halting speech with inconsistent speech sound errors (apraxia of speech)	Both of the following core features must be present: Impaired single-word retrieval in spontaneous speech and naming Impaired repetition of sentences and phrases	Both of the following core features must be present: Impaired confrontation naming Impaired single-word comprehension
Supportive features	At least two of the following: Impaired comprehension of syntactically complex sentences Spared single-word comprehension Spared object knowledge	At least three of the following: Speech (phonologic) errors in spontaneous speech and naming Spared single-word comprehension and object knowledge Spared motor speech Absence of frank agrammatism	At least three of the following: Impaired object knowledge, particularly for low-frequency or low-familiarity items Surface dyslexia or dysgraphia Spared repetition Spared speech production (grammar and motor speech)

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degenerative disease dates back to the work of Arnold Pick[3] more than a century ago. The past decade has seen considerable advances in our understanding of the neurobiological mechanisms underlying language and disorders affecting language, with PPA playing an important role in expanding the simplistic models based on stroke and other focal insults.[4] Three canonical variants of PPA are recognized, of which two (nonfluent/agrammatic variant PPA and semantic variant PPA) are classified as frontotemporal dementia syndromes because of their propensity to affect the frontal and temporal lobes and their association with frontotemporal lobar degeneration pathology, while the other (logopenic variant PPA) is most commonly viewed as an atypical variant of Alzheimer disease. For more information on logopenic variant PPA, refer to the article "Early-onset Alzheimer Disease and Its Variants" by Mario F. Mendez, MD, PhD, FAAN,[5] in this issue of *Continuum*.

In parallel to advances in the study of language, much has been learned about the mechanisms underlying speech and the disorders affecting it. Apraxia of speech is one such speech disorder and is thought to result from impaired planning and programming of the movements required for speech production.[6] Since its initial description in the 1960s, it has become increasingly recognized as an important feature of neurodegenerative diseases.[7] Only recently, however, has it been recognized that it may be the initial manifestation of a degenerative disease termed *primary progressive apraxia of speech*.[8]

This article discusses nonfluent/agrammatic variant PPA, semantic variant PPA, and primary progressive apraxia of speech. These disorders are first placed within a broader context by discussing the classification of degenerative speech and language disorders. An understanding of classification schemes is crucial to interpreting the literature, which has important implications for ongoing research (eg, clinical trial enrollment and assessment of external validity) and patient care (eg, treatment decisions and prognostication). Each disorder is then discussed in detail, with unclassified or mixed cases briefly reviewed. A simplified approach to the diagnosis and management of degenerative speech and language disorders is then presented.

CLASSIFICATION AND CONTROVERSY

The most widely accepted current classification scheme and diagnostic criteria for PPA consist of two stages.[1] First, in keeping with PPA being viewed as a distinct clinical disorder targeting language, a root diagnosis of PPA is considered (TABLE 5-1). In simplified terms, this requires that language dysfunction is the primary cause of difficulty in the initial phase of the illness and that no prominent findings (eg, amnesia, behavioral disturbance) indicate that an alternative diagnosis is more likely. Thus, a patient presenting with progressive aphasia accompanied from the start by prominent asymmetric motor impairment would not qualify for a diagnosis of PPA and may instead be diagnosed with corticobasal syndrome. Second, criteria for the three main variants are considered, each with a set of mandatory core features and supportive features (TABLE 5-2). In other words, only patients who have met the root criteria (ie, have aphasia in the absence of more prominent cognitive, behavioral, or motor disturbances) are considered for a subtype diagnosis. Despite many advantages of these new criteria, they have not been without controversy.

In the case of nonfluent/agrammatic variant PPA, the criteria require only one of the core features, which results in an inherent heterogeneity: some patients will have agrammatism and no apraxia of speech, some will have nonagrammatic aphasia and apraxia of speech, and some will have both agrammatism and apraxia of speech. More important, if the two-step process is not followed, patients with isolated apraxia of speech or another motor speech disorder that may mimic it may erroneously be diagnosed with nonfluent/agrammatic variant PPA. This amounts to conflating language and speech function and dysfunction despite distinct underlying neurobiological mechanisms. But while motor speech disorders such as dysarthria and apraxia of speech often co-occur with aphasia, these are clearly not language impairments that would, on their own, qualify a patient for a diagnosis of PPA. Practical implications also exist for patients, given the differences in management and prognosis discussed later in this article.[9,10]

The primary source of confusion and controversy with semantic variant PPA has been its relation to semantic dementia, which predates the description of semantic variant PPA. Semantic dementia, as evidenced by earlier consensus criteria for frontotemporal dementia, was thought to result from disruption of semantic memory in a way that results in deficits regardless of the modality by

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TABLE 5-3	Features of Apraxia of Speech[a]

◆ Slow overall speech rate[b]

◆ Lengthened intersegment durations (between sounds, syllables, words, or phrases; possibly filled, including intrusive schwa)[b]

◆ Increased sound distortions or distorted sound substitutions with increased utterance length or increased syllable/word articulatory complexity

◆ Syllable segmentation within words >1 syllable[b]

◆ Sound distortions[b]

◆ Syllable segmentation across words in phrases/sentences[b]

◆ Audible or visible articulatory groping; speech initiation difficulty; false starts/restarts[c]

◆ Lengthened vowel and/or consonant segments[b]

◆ Distorted sound substitutions

◆ Deliberate, slowly sequenced, segmented and/or distorted (including distorted substitutions) speech sequential motion rates in comparison with speech alternating motion rates[c]

◆ Increased sound distortions or distorted substitutions with increased speech rate

◆ Distorted sound additions (not including intrusive schwa)

◆ Sound or syllable repetition

◆ Sound prolongations (beyond lengthened segments)[c]

◆ Inaccurate (off-target in place or manner) speech alternating motion rates (as in rapid repetition of *puh, puh, puh*)[c]

◆ Reduced words per speech breath group relative to maximum vowel duration

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[a] Modified with permission from Josephs KA, et al, Brain.[8] © 2012 The Authors.
[b] Can also be present in spastic dysarthria.
[c] Can also be present in aphasia.

which it is tested (eg, verbal, nonverbal). In contrast, semantic variant PPA is suspected of resulting from relatively restricted involvement of the verbal aspects of semantic memory. While some researchers have simply replaced the term *semantic dementia* with *semantic variant PPA*, others have continued to draw the distinction between predominantly verbal semantic difficulties versus more widespread semantic difficulties. With disease progression, this distinction becomes less relevant as all aspects of semantic memory are affected, but patients who present with primarily nonverbal semantic deficits (usually from right-sided greater than left-sided involvement) will not meet root criteria for PPA. Therefore, this article discusses semantic dementia more broadly, albeit while focusing on the language-predominant presentation.

While not the focus of this article, criteria for logopenic variant PPA have also been problematic, primarily because of the overlap with working memory deficits in early-onset Alzheimer disease[11] and the inclusion of impaired repetition as a mandatory criterion.[4,12] Finally, it has become evident that the current criteria result in a large proportion of PPA cases being unclassifiable.[13] Changes have been proposed to address this, but some cases will likely remain unclassifiable.[12,14] Unclassified and unclassifiable PPA are briefly discussed in this article after primary progressive apraxia of speech, nonfluent/agrammatic variant PPA, and semantic variant PPA are discussed.

PRIMARY PROGRESSIVE APRAXIA OF SPEECH

Apraxia of speech can be defined in simple terms as a "neurological speech disorder that reflects an impaired capacity to plan or program sensorimotor commands necessary for directing movements that result in phonetically and prosodically normal speech."[6] This definition also captures the fact that the relative dominance of phonetic impairment (sound level errors, such as distorted substitutions or additions) or prosodic impairment (such as slow rate or segmented speech) is the primary source of heterogeneity in the disorder, although others exist (TABLE 5-3). This has led to the recognition of subtypes of apraxia of speech: phonetic (formerly Type 1), prosodic (formerly Type 2), and mixed (formerly Type 3).[10,15]

As mentioned previously, while several case reports and retrospective studies documented the occurrence of apraxia of speech as the initial manifestation of a degenerative disease,[7,8] prospective characterization of apraxia of speech as the sole manifestation of a neurodegenerative disease occurred within the past decade. Operational definitions for primary progressive apraxia of speech continue to be refined and, much like the criteria for PPA, require that features of other degenerative disorders are not present (TABLE 5-4).

Epidemiology

No studies have formally evaluated the prevalence of primary progressive apraxia of speech, but based on the proportion of patients with primary progressive apraxia of speech included in observational studies relative to disorders for which prevalence has been established, it has been estimated to be approximately 4.4 per 100,000.[16] Age of onset varies considerably, ranging from the late forties to early eighties, although it is older than age 65 in about two-thirds of cases. It appears to affect men and women approximately equally, and no demographic, socioeconomic, or environmental risk factors are known.

Clinical Presentation

Patients typically present with complaints pertaining to articulating words (eg, "I know what I want to say but can't get the words out") or their overall rate of speech (CASE 5-1). It is crucial to ask about writing or typing, as preservation of these forms of communication is often striking despite severe speech impairment. In fact, many patients continue to work and may rely on assistive devices despite having little meaningful speech output, in contrast to PPA, in which these devices are rarely useful. Given the fact that apraxia of speech may occur early in other degenerative diseases, it is crucial to ask the patient and family members about cognitive and other symptoms, such as decline in gross or fine motor skill, changes in gait, and behavioral disturbance. When patients present later in the course of the illness, features of other degenerative disorders may accompany severe apraxia of speech, which tends to remain the predominant symptom. It can be almost impossible to ascertain, after the fact, whether such patients indeed had primary progressive apraxia of speech that evolved into a hybrid syndrome (eg, with features similar or identical to those of corticobasal syndrome or Richardson syndrome) or if the apraxia of speech was merely one of many abnormalities early in the course of the disorder. However, it is worth noting that cases in which apraxia of speech dominates over aphasia appear to have clinical and imaging features that are more like those seen in

TABLE 5-4	Criteria for a Diagnosis of Primary Progressive Apraxia of Speech

Inclusion

◆ Insidious onset and progressive worsening of speech disturbance

◆ Apraxia of speech is the only or dominant speech disturbance at the time of testing

◆ Dysarthria can be present but must be less severe than apraxia of speech

◆ Any evidence of aphasia is considered equivocal

Exclusion

◆ Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders

◆ Cognitive disturbance is better accounted for by a psychiatric diagnosis

◆ Unequivocal evidence for aphasia on detailed language/neuropsychological testing (ie, the patient may meet root criteria for primary progressive aphasia)

◆ Dysarthria deemed to be more severe than apraxia of speech

◆ Prominent initial episodic memory, visual memory, and visuoperceptual impairments (ie, the patient may meet criteria for typical or atypical Alzheimer dementia)

◆ Prominent initial behavioral disturbance (ie, the patient may meet criteria for behavioral variant frontotemporal dementia)

◆ Prominent initial parkinsonism, falls, or eye movement abnormalities (ie, the patient may meet criteria for progressive supranuclear palsy)

◆ Prominent initial ideomotor apraxia, parkinsonism, dystonia, or other asymmetric motor and cognitive features excluding speech/language (ie, the patient may meet criteria for corticobasal syndrome)

◆ Prominent upper and/or lower motor neuron abnormalities (ie, the patient may meet criteria for motor neuron disease)

primary progressive apraxia of speech than, for example, nonfluent/agrammatic variant PPA.[10] Whether these cases should be viewed as a separate entity or a subtype of nonfluent/agrammatic variant PPA has been a source of controversy.

Cognitive Examination

Patients with primary progressive apraxia of speech typically score well within the normal range on bedside cognitive testing and may continue to do so in the later disease stages, provided written responses are allowed.[8,9] On formal neuropsychological testing, patients may score in the impaired range on tests that are dependent on the rate and accuracy of speech, such as lexical or semantic fluency.[8] A discrepancy often exists between tests that allow for written responses compared to tests in which oral responses are required. Similarly, some patients are motorically slow and so may underperform on certain tests, such as the Trail Making Test.[8]

Speech and Language Examination

Referral to a speech and language pathologist is warranted for multiple reasons. First, the referral can be important diagnostically since patients often present when apraxia of speech is mild and difficult to appreciate. Apraxia of speech is also a heterogeneous disorder with features that overlap with dysarthria and aphasia (TABLE 5-3). Spastic and ataxic dysarthria are especially difficult to differentiate from apraxia of speech in some cases. These are, however, not typically accompanied by the trial-and-error articulatory attempts, groping, and distorted substitutions seen in apraxia of speech. When the predominant features are prosodic, rather than articulatory, patients are often diagnosed with a functional speech disorder by inexperienced clinicians. Second, referral allows for more thorough language testing, which is often nontrivial in these patients because of the speech difficulties, necessitating specialized batteries to rule out, or rule in, any concomitant aphasia. Finally, more than any of the aphasia syndromes, apraxia of speech may be amenable to speech therapy.

The most helpful parts of the speech examination are those that demand the production of motorically complex utterances. An adequate sample of conversational or narrative speech should be obtained, which also allows the clinician to assess grammar. It is helpful to obtain a written response to the same question or stimulus for comparison. As for more focused examination of speech mechanisms, assessment of alternating motion rates, sequential motor rates, and repetition of increasingly complex words and sentences are most helpful (TABLE 5-5).[6]

Neurologic Examination

About two-thirds of patients have a coexisting nonverbal oral apraxia, which can be assessed at the bedside by asking patients to perform simple movements such as smacking their lips, clicking their tongue, coughing, or blowing.[17] When present in a patient with a progressive but subtle speech impairment, this nonverbal oral apraxia raises the probability that the patient may have apraxia of speech. Care should be taken to differentiate between apractic errors and errors resulting from comprehension or semantic deficits. In the case of apraxia, patients may show groping, imprecise execution of the correct movement, or complete inability to complete a simple task such as coughing (often to the frustration and disbelief of the patient), whereas deft execution of the incorrect

movement, lack of task engagement, or perseveration suggests nonapractic errors. These may be seen in semantic variant PPA, logopenic variant PPA, and other dementia syndromes.

Subtle parkinsonian signs, such as rigidity with contralateral activation, mildly slowed finger tapping, or reduced spontaneous movements, may be present 2 to 3 years into the illness. Around the same time, mild difficulties with limb praxis can be seen in roughly one-third of participants, typically involving complex transitive instructions (eg, "pretend to start and drive a car").[8]

Neuroimaging

Primary progressive apraxia of speech appears to result from dysfunction of and damage to a distributed set of cortical and subcortical regions that are closely linked to the planning, production, and monitoring of speech, with sparing of language regions such as the inferior frontal gyrus and lateral temporal regions.[8,10,14] Gray and white matter atrophy of the motor, premotor, and

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CASE 5-1

A 70-year-old woman presented with a 5-year history of "stumbling over words" and slowed speech. She had no cognitive symptoms and denied language difficulties, such as with word finding, spelling, reading, following conversations, or putting together a sentence. Over time, her disease progressed to the point that she had minimal intelligible verbal output and relied on written forms of communication. No clear diagnosis had been reached despite several evaluations.

On examination, she scored 26/30 on the Montreal Cognitive Assessment (MoCA). No abnormalities were seen on bedside testing of frontal lobe function, limb praxis, or higher-order visual processing. Her speech output was slow and segmented, with frequent distortions and groping, consistent with severe apraxia of speech (VIDEO 5-1, *links.lww. com/CONT/A263*). She had no difficulty naming, reading, writing, or following instructions, although poor intelligibility complicated testing. When allowed to respond in writing, she performed well. She had no evidence for agrammatism on written picture description, review of emails, or dedicated testing with the Northwestern Anagram Test (a test of grammar). She was slightly bradykinetic on motor testing but had normal extraocular movements and no postural instability or gait changes. Neuropsychological testing was normal accounting for slowed and distorted speech, which negatively impacted tests of verbal and semantic fluency, and slightly slowed performance on the Trail Making Test. A clinical diagnosis of primary progressive apraxia of speech was made.

Brain MRI did not reveal atrophy beyond that expected for her age (FIGURE 5-1A). A fludeoxyglucose positron emission tomography (FDG-PET) scan was performed and revealed hypometabolism of the supplementary and premotor areas bilaterally, with no involvement of inferior frontal (Broca) or posterior temporal (Wernicke) areas (FIGURE 5-1B).

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supplementary motor areas bilaterally has been reported at a group level, but it is worth noting that this may be hard to appreciate, and fairly asymmetric, on the individual level. Subcortical structures, including the striatum and midbrain, may also be involved. Although hypometabolism on fludeoxyglucose positron emission tomography (FDG-PET) typically occurs in these same areas, abnormalities may be more noticeable on the individual level using this modality compared to MRI (FIGURE 5-2). With progression, patients with primary progressive apraxia of speech often show midbrain atrophy, in contrast to nonfluent/agrammatic variant PPA without apraxia of speech.[10]

Genetics
While case reports exist of known genetic mutations presenting with prominent and early apraxia of speech, the majority of these patients had coexisting behavioral, motor, cognitive, or language impairment. A 2015 evaluation of a large, prospectively recruited cohort of patients with primary progressive
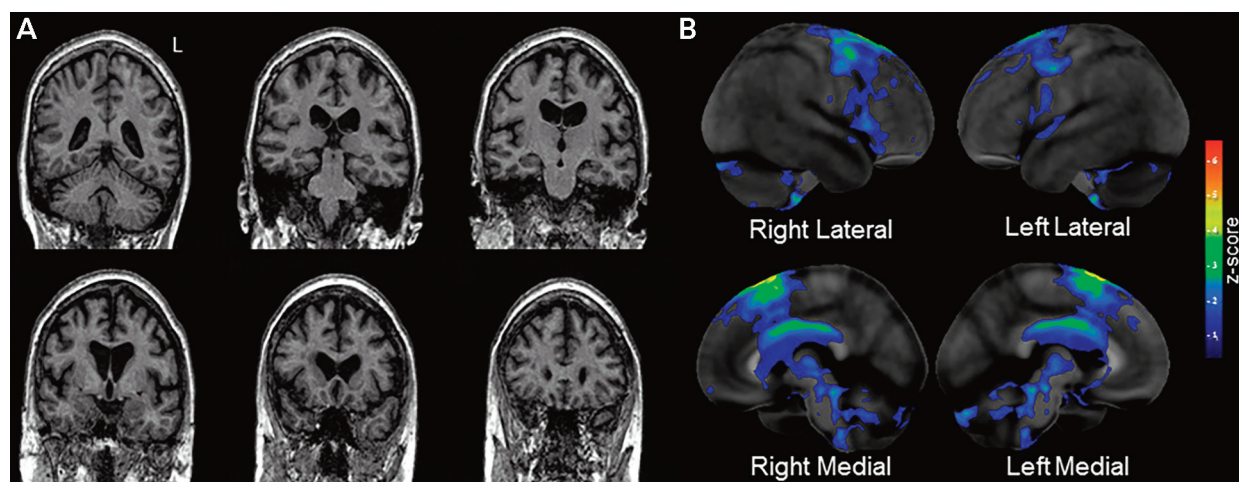

FIGURE 5-1
MRI and fludeoxyglucose positron emission tomography (FDG-PET) findings of the patient in CASE 5-1. *A,* Coronal T1-weighted MRI shows a relative lack of atrophy. *B,* The stereotactic surface projection *z*-score map of the patient's FDG-PET shows focal hypometabolism of the supplementary motor and dorsolateral premotor areas. (*Black/dark blue* represent normal uptake; *green/yellow/red* represent worsening degrees of hypometabolism.)

This case highlights several characteristic features of primary progressive apraxia of speech. This patient's problems were primarily phonetic, which tend to be easier to appreciate than predominantly prosodic symptoms. Despite being 5 years into the illness, her only difficulty was with speech. In fact, she found an electronic communicative device incredibly helpful, which greatly aided her independence. However, if her speech problem had not been recognized, she may have been diagnosed with aphasia because of impaired verbal responses. The subtle parkinsonism was expected at this stage. The very restricted involvement on FDG-PET was consistent with her isolated motor speech disorder.

COMMENT

apraxia of speech and PPA did not document any mutations in the three genes most commonly associated with frontotemporal lobar degeneration pathology (*MAPT*, *GRN*, *C9orf72*) in patients with primary progressive apraxia of speech.[18] While one in four patients reported a family history of neurodegenerative disease, a history of multiple affected first-degree relatives was found in only 5%, with the majority of cases occurring after 60 years of age. As such, a diagnosis of primary progressive apraxia of speech appears to confer a relatively low risk of an underlying genetic mutation compared to other disorders associated with tau, especially in comparison to behavioral variant frontotemporal dementia (bvFTD).

Prognosis

All patients with primary progressive apraxia of speech appear to develop parkinsonian signs, usually with axial greater than appendicular rigidity, and all patients develop worsening of their apraxia of speech.[9] Approximately 40% of patients develop a progressive supranuclear palsy (PSP)/corticobasal syndrome–like disorder, which has been termed *progressive supranuclear palsy–apraxia of speech*, approximately 5 years into their illness. This is characterized by slowing of saccades or frank supranuclear gaze palsy, ideomotor apraxia that may be asymmetric, falls, and a frontal lobe syndrome of neuropsychological impairment. Dysphagia, urinary incontinence, dysarthria (spastic more than hypokinetic), and aphasia with agrammatism are often accompanying features in these patients. In the remaining 60% of patients, worsening apraxia of speech remains the primary issue, although mild cognitive impairment and aphasia may be present. It does not appear that aphasia worsens to the point of overtaking apraxia of speech unless accompanied by more general cognitive and motor decline, at which point patients may be most appropriately labeled as having an alternative clinical diagnosis (eg, PSP or corticobasal syndrome).

Neuropathology

The overwhelming majority of autopsied cases of primary progressive apraxia of speech reported in the literature were found to have an underlying 4-repeat tauopathy, with corticobasal degeneration pathology being the most common.

TABLE 5-5	Helpful Aspects of the Bedside Speech and Language Examination

Obtained as Part of Language Examination

◆ Conversational or narrative speech sample

◆ Conversational or narrative writing sample

◆ Sentence repetition

Focused Speech Examination

◆ Speech alternating motion rates (rapid repetition of *puh*, *tuh*, and *kuh* sounds individually)

◆ Speech sequential motion rates (rapid repetition of *puh-tuh-kuh* sequence)

◆ Repetition of graded-in-complexity words (eg, *cat*, *catnip*, *catapult*, *catastrophe*, *specific*, with each word repeated 3 times)
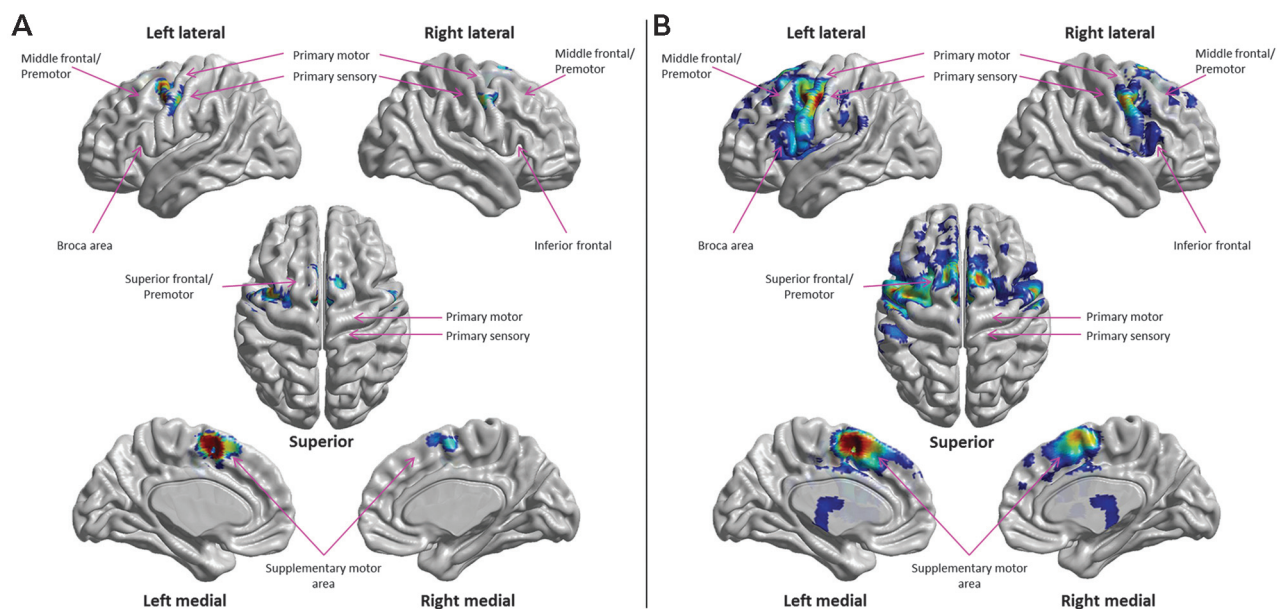
◆ Nonverbal oral praxis assessment

FIGURE 5-2
Surface projections of typical patterns of hypometabolism in primary progressive apraxia of speech (*A*) and dominant apraxia of speech with coexisting agrammatic aphasia (*B*).

Isolated case reports of patients with a primary progressive apraxia of speech–like syndrome but with underlying Pick disease (3-repeat tau) or even nontau have been reported, but whether these patients truly had isolated apraxia of speech at onset is unclear.

NONFLUENT/AGRAMMATIC VARIANT PRIMARY PROGRESSIVE APHASIA

Nonfluent/agrammatic variant PPA may be the most heterogeneous of PPA subtypes, in large part because of variable interpretations of the criteria. First, patients with isolated apraxia of speech may be included if the root PPA criteria are not applied. Even more uncertainty exists when it comes to cases in which apraxia of speech is the predominant source of impairment but unequivocal evidence for aphasia is present. Impaired grammar, despite the name of the disorder, is also not required by the criteria. Some have argued that this should be a core feature,[12,14] whereas others have proclaimed that neither agrammatism nor apraxia of speech is present in the majority of cases.[19] This may seem confusing at first but results from emphasis being placed on a loss of fluency and telegraphic verbal output rather than grammar. Variable interpretations of fluency have also plagued this disorder, with some interpreting the frequent word-finding pauses seen in PPA as a loss of fluency and others viewing fluency as synonymous with rate and accuracy of speech. However, if neither agrammatism nor apraxia of speech is present, the differentiation between this and logopenic variant PPA becomes very difficult (TABLE 5-2). It is no surprise that this variant has the weakest association with any one neuropathologic entity.

This article focuses on cases in which agrammatism is present. In the authors' opinion, PPA cases that appear nonfluent but without agrammatism are best labeled unclassified, assuming they do not meet criteria for logopenic variant PPA, as discussed later in this article. Even with this prerequisite, some heterogeneity still exists, resulting from the presence/absence of apraxia of

speech. Given the importance of apraxia of speech from a diagnostic and therapeutic standpoint, the authors view nonfluent/agrammatic variant PPA as consisting of two subgroups: those with apraxia of speech and agrammatic aphasia, which is by far the most common, and those with agrammatic aphasia in the absence of apraxia of speech. Where such data exist, this article highlights clinical and imaging features with reference to these two subgroups.

Epidemiology

Based on the relative proportion of cases included in clinical and autopsy series, the prevalence of nonfluent/agrammatic variant PPA has been estimated to be 0.5 to 3.9 per 100,000 people.[20] Although the age of onset varies greatly, including patients diagnosed in their eighties, the average age of onset appears to be around 60. Men and women appear to be at equal risk and, although no socioeconomic, demographic, or environmental risk factors have been validated, a higher proportion of patients with degenerative speech and language disorders

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CASE 5-2

A 68-year-old woman presented with a 2-year history of word-finding difficulty, reduced verbal output, and word choice errors. Specifically, her family noticed frequent reversal of *yes* and *no* and shorter sentences overall, at times with words left out. She had no cognitive or motor complaints, which was corroborated by her family.

On examination, she scored 24/30 on the Montreal Cognitive Assessment (MoCA), primarily losing points on language subtests. Bedside testing of frontal lobe function was normal. She was moderately aphasic, with impaired comprehension of complex instructions, reduced category and action fluency, agrammatic verbal and written output, and impaired performance on the Northwestern Anagram Test (a test of grammar) (VIDEO 5-2, *links.lww.com/CONT/A264*). Minimal abnormalities were noted on repetition and naming, and she had no loss of word or object knowledge. During conversational speech and verbal portions of the language examination, she had a normal rate and prosody and no distorted substitutions or articulatory errors. On dedicated motor speech examination, vowel prolongation did not reveal any phonatory or resonance abnormalities, and her speech sequential and alternating motion rates were both normal. In other words, she showed no features to suggest apraxia of speech or dysarthria. She had no evidence of ideomotor apraxia and no parkinsonism, extraocular movement abnormalities, or changes in her gait. The rest of her examination was normal. A clinical diagnosis of nonfluent/agrammatic variant primary progressive aphasia (PPA) was made.

Her MRI showed left frontal periopercular and insular atrophy (FIGURE 5-3A). A fludeoxyglucose positron emission tomography (FDG-PET) scan was performed and revealed hypometabolism of the inferior frontal and medial prefrontal regions on the left (FIGURE 5-3B).

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appear to be teachers than is seen in Alzheimer disease or the population in general.[21] The majority of nonfluent/agrammatic variant PPA cases have coexisting apraxia of speech, with estimates ranging from 56% to 86%, depending largely on whether cases in which apraxia of speech dominates over aphasia are included despite not meeting core PPA criteria.[10,14,22]

Clinical Presentation

While some patients or informants may volunteer examples of impaired grammar or syntax (eg, "sometimes I drop words" or "he uses words out of order"), focused questioning is often necessary to reveal early problems. In general, it is difficult to obtain a history of impaired comprehension of grammatically complex sentences, and thus, the focus is usually on language output. Serial samples of written language, such as emails or letters, may reveal issues before they are evident in verbal output. Patients and family members may notice reversal of binary terms, such as *yes* and *no* or *him* and *her* (CASE 5-2).
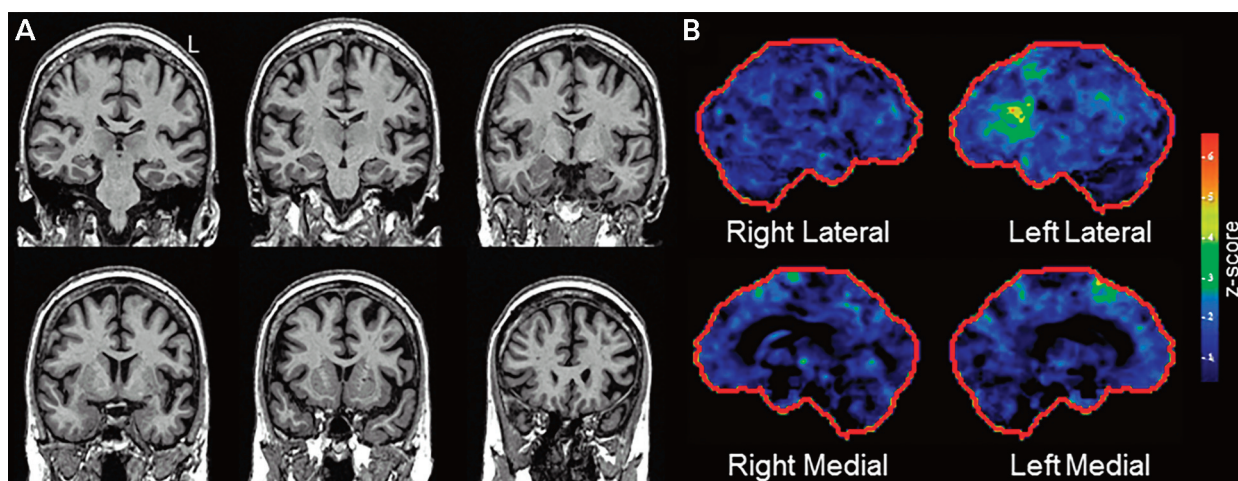

FIGURE 5-3
Imaging of the patient in CASE 5-2. *A,* Coronal T1-weighted MRI shows medial and lateral prefrontal, insular, and inferior frontal atrophy on the left. *B,* The stereotactic surface projection *z*-score map of the patient's fludeoxyglucose positron emission tomography (FDG-PET) scan shows focal hypometabolism involving the left inferior frontal and medial prefrontal regions. (*Black/dark blue* represent normal uptake; *green/yellow/red* represent worsening degrees of hypometabolism.)

COMMENT

This patient had no apraxia of speech, illustrating one end of the nonfluent/agrammatic variant PPA spectrum. Many patients with nonfluent/agrammatic variant PPA will have some apraxia of speech, just as many patients with predominant apraxia of speech will have some agrammatism. It is easy to classify patients with only one of these disorders and much harder when both are present to about the same degree. Also note, in contrast to CASE 5-1, hypometabolism here is present anterior to the supplementary motor area, in keeping with the lack of apraxia of speech in this case, and clear involvement of the inferior frontal region is seen, in keeping with her agrammatism.

If apraxia of speech is present, the initial symptoms may overlap with those discussed for primary progressive apraxia of speech. As mentioned previously, the diagnostic classification of cases in which the dominant feature is apraxia of speech but clear agrammatism is present is controversial. If the root PPA criteria were applied strictly, these cases would not qualify for a diagnosis of PPA as speech, rather than language, is the primary cause of clinical impairment. Furthermore, cross-sectional clinical and imaging studies have documented differences between "dominant apraxia of speech" and "dominant aphasia" cases.[10,14] However, longitudinal data and autopsy-confirmed studies are lacking, and, as such, most research programs have continued to include cases in which apraxia of speech dominates in the nonfluent/agrammatic variant PPA category.[1,23] In the authors' experience, cases of nonfluent/agrammatic variant PPA with apraxia of speech have a different disease course than "pure" agrammatic cases, but it is less clear whether dominant apraxia of speech cases evolve differently from dominant agrammatic cases.

It is not uncommon for family members to mention that the patient has become quieter or less talkative, and during the interview it can be very difficult to get more than a few words from the patient in response to questions. However, it is important to note that a lack of spontaneous verbal output or the reliance on short answers does not imply impaired grammar or syntax. Abulia can be seen in many neurodegenerative diseases and may be limited to speech early in some cases. This may represent a distinct entity, which some have argued should be recognized as a subtype of PPA reminiscent of Luria's dynamic aphasia,[24] but in the authors' opinion, these patients should not be diagnosed with nonfluent/agrammatic variant PPA unless unequivocal evidence for agrammatism is present. Psychomotor slowing is common, and symptoms pertaining to fine motor movements (eg, writing) or motoric slowing in general (eg, slowed gait) may be present.

Speech and Language Examination

Examining for apraxia of speech is similar to the examination described for primary progressive apraxia of speech. It is important to establish if apraxia of speech is present and how severe it is, since that may limit the rest of the examination. When assessing language ability, it is important to bear in mind that aphasia typically involves all aspects of language to varying degrees, and thus the PPA classification depends on the relative impairment. Naming and word-finding difficulties are common to all PPA variants,[25] although patients with nonfluent/agrammatic variant PPA should recognize the target word if provided. Typically, patients with nonfluent/agrammatic variant PPA are not significantly impaired on testing of repetition, word meaning, semantic association, or writing and reading of irregularly spelled words. However, with sufficiently challenging tests, some impairment in these areas may be revealed. These should be overshadowed by impairments in grammar and syntax for this diagnosis to be considered. That being said, assessing grammatical ability can be challenging, and no single test appears to have optimal sensitivity. It is crucial to obtain a good sample of conversational speech, such as asking patients to explain their occupation or a sport. For example, when asked to explain baseball, one patient responded: "Uh...baseball...it's a...you have...there's three strikes and you're out. Uh...pitchers line up against batters. They throw...they throw the strikes. Uh...the score...uh...the...first base...second base, shortstop is a...third base and there's fielders. Right field, left field, center field, and left field."

It is also helpful to review samples of written language, such as emails, as they frequently contain errors involving word order or functional morphemes (eg, incorrect use of suffixes meant to convey verbal inflections or plurality or omission of conjunctions), in addition to spelling errors seen in all PPA variants. Verbal picture description is revealing in some patients, although it is important to specify that full sentences are expected. Written language output may be more sensitive, and obtaining a written picture description is advised (FIGURE 5-4). Referral to a speech and language pathologist is advised for more detailed testing and discussion of treatment options. Tests focused more explicitly on grammar, such as the Northwestern Anagram Test, can be considered.[26]

Cognitive Examination

Patients with nonfluent/agrammatic variant PPA often score in the abnormal range on screening tests such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA). Reduced spontaneous verbal output coupled with agrammatism can also complicate cognitive testing, along with psychomotor slowing and apraxia of speech, if present. Patients may show mild evidence of frontal lobe dysfunction in the form of perseveration, impulsivity, and attentional deficits. On neuropsychological testing, patients may be impaired on problem-solving tasks and typically struggle with encoding more than recall on episodic memory tasks.[27] Action or verbal fluency appears to be more impaired than letter or category fluency. Poor planning during visuospatial tasks may be seen.

Neurologic Examination

The rest of the neurologic examination is typically unrevealing, although mild ideomotor apraxia and parkinsonism are possible. Increased reflexes or the emergence of pathologic reflexes (eg, Babinski sign or frontal release signs) may be seen. If neurologic abnormalities are found asymmetrically, it suggests that corticobasal syndrome may develop over time. Although rare, some patients present with nonfluent/agrammatic variant PPA and develop a pyramidal
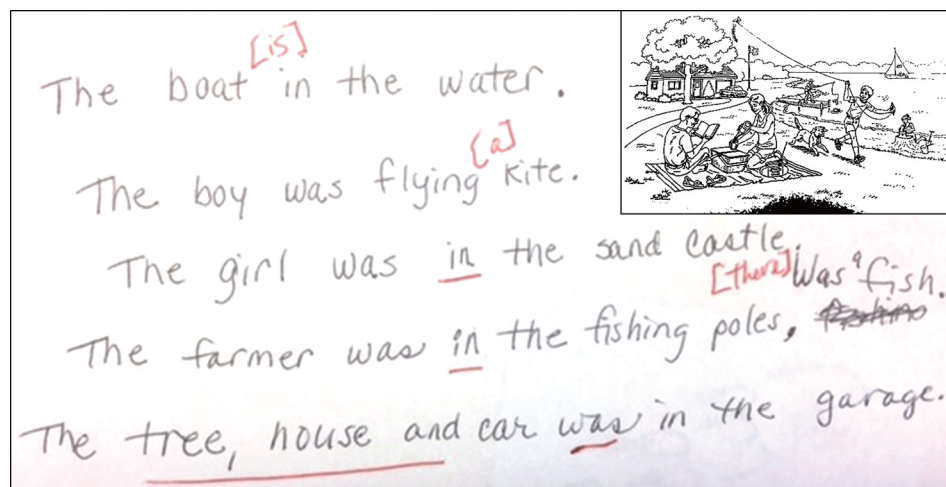

FIGURE 5-4
Example of agrammatism in written picture description.

syndrome, such as amyotrophic lateral sclerosis; therefore, close examination for fasciculations and atrophy is warranted.

Neuroimaging

The anterior portions of the language network appear to be most vulnerable in nonfluent/agrammatic variant PPA. The dominant inferior frontal lobe, including Broca areas 44 and 45, is almost always involved. Other dominant anterior opercular and perisylvian areas are often involved, including the anterior insula and superior temporal gyrus. When apraxia of speech is present, the dorsolateral premotor cortex, motor cortex proper, and supplementary motor areas may be involved (**FIGURE 5-5**).

Genetics

Although up to one-third of patients with PPA may report a family history of neurodegenerative disease, mutations are rarer than those seen in bvFTD.[18,20] Cases with features of nonfluent/agrammatic variant PPA have been reported as resulting from mutations in each of the three main frontotemporal lobar degeneration genes (*MAPT*, *GRN*, and *C9orf72*), although at least some of these had associated behavioral, cognitive, or motor symptoms early in the disease course.[28] Prospectively recruited PPA cohorts suggest mutations are a rare cause of sporadic nonfluent/agrammatic variant PPA.[20]

Prognosis

The heterogeneity inherent in nonfluent/agrammatic variant PPA and variable interpretations of the criteria have complicated the study of the prognosis and natural history of the disorder. Patients may progress along several different
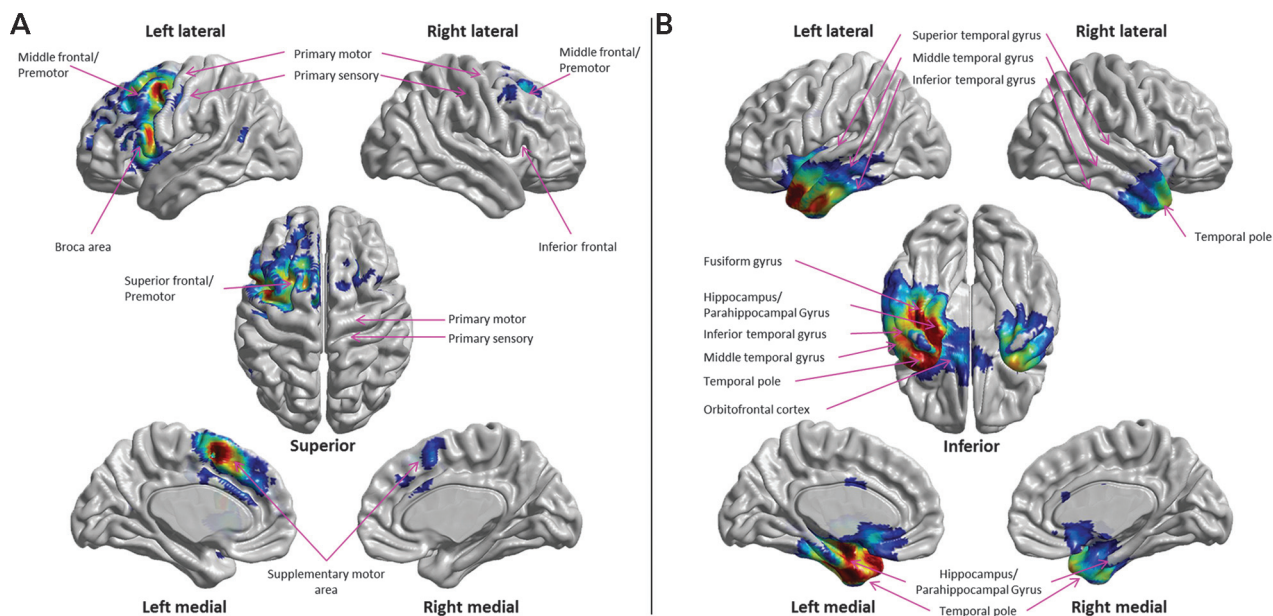

FIGURE 5-5

Surface projections of typical patterns of hypometabolism in nonfluent/agrammatic variant primary progressive aphasia (**A**) and semantic variant primary progressive aphasia (**B**).

trajectories. Some develop more behavioral abnormalities and may later meet criteria for bvFTD. These patients may be more at risk of coexisting motor neuron disease. Others develop features of corticobasal syndrome or PSP. This appears to be more common in those with apraxia of speech, and the relative prominence of articulatory or prosodic difficulty may be predictive of the rate of worsening aphasia or parkinsonism, respectively.[29] Median survival appears to be around 7 years,[20] although this varies greatly, at least in part because of the variety of underlying pathologic processes. In the authors' experience, cases of nonfluent/agrammatic variant PPA without apraxia of speech have a less favorable prognosis.

Neuropathology

As alluded to previously, nonfluent/agrammatic variant PPA variant lacks the tight clinicopathologic association seen in the other variants. In fact, it appears that the disorder can be associated with 3-repeat tau (Pick disease), 4-repeat tau (corticobasal degeneration or PSP pathology), transactive response DNA-binding protein 43 (TDP-43), and, in cases where agrammatism is not emphasized, even Alzheimer disease.[28] However, the subset of nonfluent/agrammatic variant PPA cases with apraxia of speech is more likely to have underlying 4-repeat tau.[22] Similarly, coexisting motor neuron disease would be predictive of underlying TDP-43 pathology.

SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA/SEMANTIC DEMENTIA

First described more than a century ago,[3] semantic dementia has continued to fascinate behavioral neurologists in the 21st century. Warrington[30] postulated that the syndrome results from a breakdown in semantic memory, the amodal and time-independent knowledge store, in contrast to the episodic memory system, which is involved with recall of specific events or experiences. This has remained the leading hypothesis, as the later stages of the disease are characterized by a severely eroded knowledge base, regardless of the modality used to probe it (eg, verbal versus nonverbal), with relatively spared episodic and autobiographical memory. However, as mentioned previously, most patients do present with language-related symptoms, and these patients usually meet criteria for PPA, thus this subset has been subsumed under the PPA criteria. The authors feel it is important to discuss the approximately 30% or so of patients who do not meet PPA criteria and who often present with predominant right temporal disease.[31] This article uses the term *semantic dementia* to refer to the broader syndrome, including those who do not meet criteria for PPA, and uses *semantic variant PPA* when referring to the subset of patients who present with predominant language difficulty.

Epidemiology

Dedicated prevalence studies in semantic dementia are lacking, but it is estimated that it accounts for one-fourth to one-third of frontotemporal dementia cases.[32,33] Based on frontotemporal dementia prevalence estimates of 10 to 22 per 100,000 people, that would suggest a prevalence of 2.5 to 7.3 per 100,000 for semantic dementia.[32,34]

The average age of onset in semantic dementia appears to be around 60, although it is worth noting that about one-fourth of cases may present after the age of 70.[35] About 70% of cases have predominant left-sided involvement (ie,

would be viewed as semantic variant PPA), while the remaining 30% present with predominant right-sided involvement.[35,36] As mentioned previously, a higher number of teachers is seen among patients with degenerative speech and language disorders, but beyond that, no socioeconomic, demographic, or environmental risk factors for semantic dementia are known.

Clinical Presentation

Most commonly, patients with semantic variant PPA present with language- or memory-based symptoms, such as word-retrieval difficulties or trouble remembering words. Nouns are typically most difficult, which may result in circumlocution (eg, saying *device for moving around* in place of *car*), the use of a more general or category label (eg, *animal* for *dog*), or the use of nonspecific filler words (eg, *thing* or *place*). However, it is not uncommon for patients to be relatively blind to the extent of their impairment. Perhaps more than any of the other syndromes discussed in this article, the diagnosis of semantic dementia often hinges on focused history taking, including from collateral sources, and dedicated bedside cognitive testing. Specifically asking family members about a history of loss of word meaning is crucial and often results in striking examples (such as the patient not knowing what *asparagus* is). The same is true of right-sided semantic dementia, which may present later, typically with associative agnosias such as prosopagnosia (loss of face knowledge and hence recognition). Patients are unlikely to volunteer examples of misidentification of acquaintances or the complete lack of recognition of family members. Yet, when asked, a history of not recognizing a best friend or repeatedly introducing themselves to a brother-in-law may be revealed.

An overlap exists between right-sided semantic dementia and right temporal predominant bvFTD,[37] and, unsurprisingly, patients with right-sided semantic dementia are more likely to have behavioral disturbances than those with semantic variant PPA.[36] That being said, behavioral symptoms are more common in semantic variant PPA than in any of the other PPA variants.[25]

Cognitive Examination

Patients with semantic dementia may struggle on some aspects of general bedside screening tests, especially if they require naming, but early on, most patients perform well. Similarly, most patients do not have evidence of frontal lobe dysfunction. The most helpful tests tend to be those specifically targeted toward semantic dementia. Testing for a breakdown of semantic memory can be broadly split into verbal and nonverbal measures, although most involve some degree of both. Verbal testing, which is most helpful in semantic variant PPA, is discussed later in this article; the focus here is on nonverbal tests, which tend to be more helpful in right-sided semantic dementia.

Testing for prosopagnosia is usually done by showing pictures of celebrities or other famous people and asking the patient to either identify the famous face among distractors or to provide some information to prove that they have correctly recognized the person. This is not a naming test, although patients will likely name the people they recognize. When faces are not recognized, it is often helpful to probe further. For example, if a patient fails to recognize Michael Jordan ("I think he is a movie star or singer"), it can be helpful to ask who, in fact, Michael Jordan is. In more advanced cases, a dense loss of person knowledge is

seen, often accompanied by loss of knowledge about historically important events, such as World War II or the Civil War.

Another helpful set of bedside tests involves matching pictures, sounds, or smells without requiring any explicit verbal response. For example, the patient may be played a sound and shown four pictures to choose from, or the patient may be shown a stimulus picture (eg, a strawberry) and asked to choose the best fit from other pictures (eg, cream, butter, and salt). Many of these tests are possible at the bedside, although formal neuropsychological tests are available that follow the same design. In general, one would expect concepts at the edge of semantic space to be affected first, which translates to a failure to identify less familiar objects and people first.

One important thing to note when reviewing neuropsychological testing on patients with semantic dementia is how pervasive the effect of loss of word knowledge can be. Remembering a word list can be hard if the words are not recognized, for example. In general, patients with semantic dementia have spared episodic memory, but it may require modification of the battery to show this.

Speech and Language Examination

The most prominent feature on language testing in semantic variant PPA is anomia, which is often severe. However, anomia in itself does not differentiate semantic variant PPA from the other subtypes. Instead, loss of word meaning must be demonstrated if it was not evident on history. This can be explored during the naming task by first providing a verbal cue and then providing a list of possible words to choose from for unnamed items. Whereas patients with nonfluent/agrammatic variant PPA or logopenic variant PPA typically benefit greatly from this, patients with semantic variant PPA often fail to choose the correct word from a small list. Further probing can involve asking them what the correct word refers to. For example, one patient could not name a scorpion, did not benefit from a verbal cue, and chose a different word when presented with choices. Asked to define the word *scorpion* she said it was "a plaything for kids." Verbal batteries are available that follow the same design as the nonverbal batteries discussed previously, in which the patient is provided with a word and asked to match it to another related word or to one of a number of pictures.

A supportive, albeit not specific, feature is trouble with reading (surface dyslexia) and writing (surface dysgraphia) of irregularly spelled words such as *yacht*, *colonel*, and *debt* (CASE 5-3 and FIGURE 5-5). These words do not follow the typical lexical-phonetic rules and require the recognition of the entire word to be pronounced or written correctly. Patients may write them phonetically (eg, *det* for *debt*) and regularize them during reading (*co-lo-nel*) (FIGURE 5-7).

Speech, grammar, and repetition are typically spared, and sentence comprehension tends to be better than single-word comprehension since the context may provide sufficient clues as to what is required. Patients with right-sided semantic dementia will likely show mild deficits on language-related semantic memory tests early on, just as patients with semantic variant PPA may show deficits on nonverbal tests, such as recognition of famous faces.

Neurologic Examination

The remaining parts of the neurologic examination are usually unremarkable in semantic dementia. In a small subset of patients, features of motor neuron disease emerge during the illness, so a close motor examination is still warranted.

Ideomotor apraxia, parkinsonism, oculomotor abnormalities, and gait changes should, however, prompt a reevaluation of the diagnosis.

Neuroimaging

Focal anterior temporal pole involvement is characteristic of semantic dementia (FIGURE 5-5).[32] While usually bilateral, with the left side being more involved in semantic variant PPA and the right side more involved in right-sided semantic dementia, some patients have involvement of only one side. This is especially common early in the disease course. Atrophy tends to be more severe and hence

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CASE 5-3

A 68-year-old right-handed man presented with a history of word-retrieval difficulty. According to his wife, the difficulty had been gradually progressing over the past 2 years, although the patient felt it had only been present for 6 months. He felt that he could not "figure out how to answer questions" because he could not "get the words" and that reading was more laborious. His wife noticed that he had become less specific in his language, substituting *device* for many inanimate objects and *friend* for anyone outside his nuclear family. She also brought up examples of common words he did not comprehend, such as *button*.

On examination, he scored 26/30 on the Mini-Mental State Examination (MMSE) and performed well on bedside tests of frontal lobe function. He was able to recognize famous faces, although he could not name them. He had no speech abnormalities. Detailed language testing (VIDEO 5-3, *links.lww.com/CONT/A265*) revealed marked difficulty with naming, with only moderate improvement after cueing. He did not appear to recognize some objects and had a hard time matching pictures based on their semantic association (eg, matching a bicycle with a bicycle helmet rather than a football or motorcycle helmet). He had difficulty reading irregular words, and his picture description contained numerous nonspecific words such as *device* and *thing*. Grammar, repetition, and sentence comprehension were unaffected. Neuropsychological testing was notable for mild verbal memory impairment but no impairment on testing of visual memory. He was clinically diagnosed with semantic variant primary progressive aphasia.

His brain MRI showed severe medial, inferior, and anterior temporal atrophy on the left (FIGURE 5-6A). A fludeoxyglucose positron emission tomography (FDG-PET) scan was done and demonstrated left anterior temporal hypometabolism, most severe in the temporal pole and amygdala, and orbitofrontal hypometabolism (FIGURE 5-6B).

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easier to appreciate in semantic dementia than in other PPA subtypes. Medial and lateral anterior temporal structures are involved, including the middle and inferior temporal gyri, fusiform gyri, and amygdala, with widening of the collateral sulci. While the Papez circuit is involved in semantic dementia, the mammillary bodies and the body and tail of the hippocampus are typically spared, in keeping with the spared episodic memory seen in the disorder.[38] This may be helpful in differentiating it from other disorders affecting the medial temporal lobe, such as hippocampal sclerosis. FDG-PET is almost always abnormal by the time patients present for evaluation and can be considered in cases in which the diagnosis is unclear.
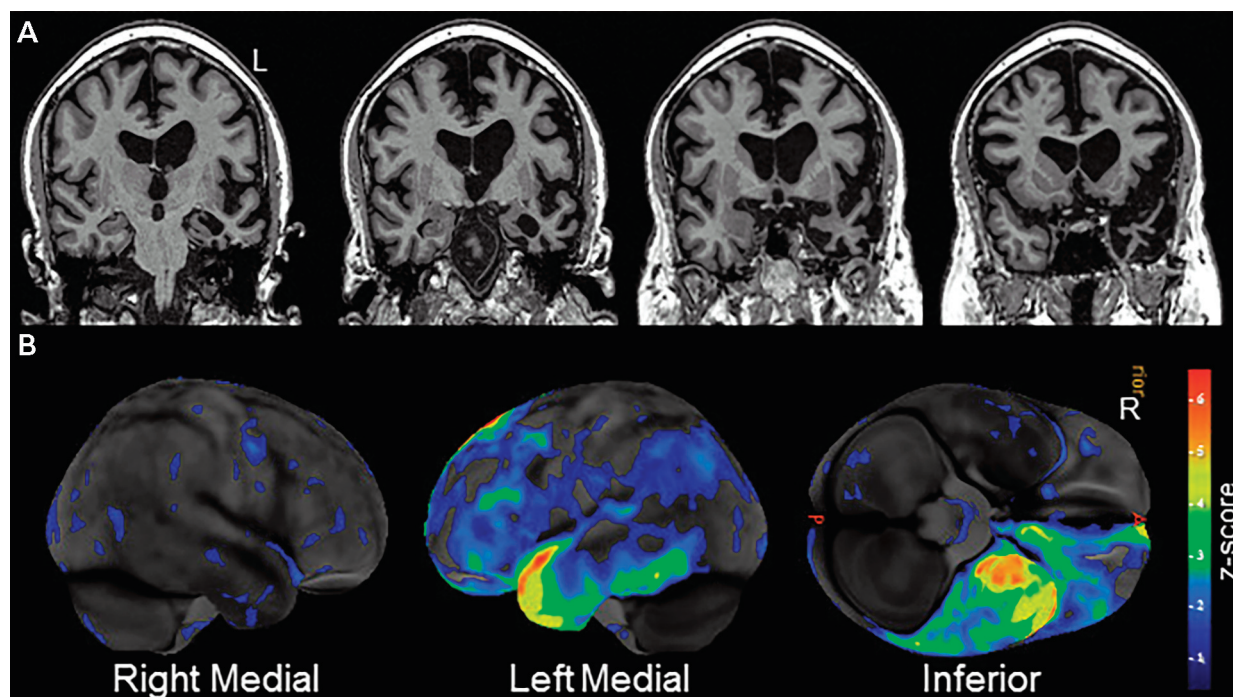

FIGURE 5-6
Imaging of the patient in CASE 5-3. *A*, Coronal T1-weighted MRI shows severe medial, inferior, and anterior temporal atrophy on the left as well as left insular and left frontal atrophy. *B*, The stereotactic surface projection *z*-score map of the patient's fludeoxyglucose positron emission tomography (FDG-PET) scan shows left anterior temporal hypometabolism, most severe in the polar and medial temporal areas, as well as left inferior temporal and orbitofrontal hypometabolism. (*Black/dark blue* represent normal uptake; *green/yellow/red* represent worsening degrees of hypometabolism.)

COMMENT

This case is representative of the left temporal predominant form of semantic dementia (or semantic variant primary progressive aphasia). The patient had no evidence of right temporal involvement on testing (he had no prosopagnosia but rather trouble with naming) or imaging, although he had trouble on semantic association tasks in which a verbal response was not explicitly required, in keeping with a breakdown of semantic memory. The pattern of severe temporal polar atrophy is almost exclusively seen in this disorder.

Yaught	yacht
Guide	guide
Ache	ache
Dept.	debt
knive	knife

bargain	bargain
lapter	laughter
fuisquit	biscuit
machician	magician
curagious	courageous

FIGURE 5-7
Example of surface dysgraphia when writing to dictation.

Prognosis

Median survival is longer than is typically associated with frontotemporal lobar degeneration pathology, on the order of 10 to 13 years.[35] Education, occupation, gender, and age at presentation do not appear to impact survival.[35] Over time, both temporal lobes become severely atrophic and the aforementioned left and right dominant syndromes merge. However, it appears that right-sided cases progress with more orbitofrontal involvement, and hence more behavioral disturbance, than left-sided cases.[36] The small subset of patients with coexisting motor neuron disease naturally have a far shorter disease course.

Genetics

Semantic dementia appears to be the frontotemporal dementia syndrome with the lowest risk of an underlying genetic cause. A history of early-onset dementia in first-degree family members is unusual, and documented cases of genetic mutations associated with semantic dementia are considered rare.[32,35] Despite this rarity, cases of semantic dementia due to mutations in each of the three major frontotemporal dementia genes have been published.

Neuropathology

The majority (>80%) of semantic dementia cases are associated with the accumulation of TDP-43 Type C, making it is one of the frontotemporal dementia syndromes with the highest pathologic predictive value. The remaining cases are due to TDP-43 Type A or Type B, a tauopathy (typically Pick disease), or Alzheimer disease.

MIXED AND UNCLASSIFIED PRIMARY PROGRESSIVE APHASIA

The current consensus criteria for PPA leave a number of cases unclassified.[13,14] However, as with most tools in medicine, criteria have to balance specificity, sensitivity, and practicality, thus some cases will always be unclassifiable.

Some patients do not meet criteria for a PPA subtype because the cases are too mild (eg, cases of isolated anomia). Over time, these patients may progress to meet criteria for semantic variant PPA or logopenic variant PPA, so this is not particularly problematic. Other cases are too severe, rendering them difficult to test and characterize. These cases are likely to remain unclassified. Even so, the presence of certain features (eg, apraxia of speech) may still influence

management and can still be predictive of the underlying pathology. Some cases, however, appear to be unclassifiable throughout the entire disease course (ie, not because they are too mild or too severe). Some of these represent truly mixed cases, meeting major criteria for more than one subtype, and likely have multiple pathologies. For example, the presence of loss of word meaning and apraxia of speech suggests both TDP-43 and 4-repeat tau.[39] Other cases may not be mixed but are distinct enough that some researchers have suggested additional PPA subtypes to capture them (eg, primary progressive speech abulia[24]).

CLINICAL APPROACH TO DEGENERATIVE SPEECH AND LANGUAGE DISORDERS

Given the variable interpretations of the consensus criteria for PPA and the controversy surrounding primary progressive apraxia of speech, the approach to patients will vary significantly from center to center. An approach that is consistent with the discussion of the disorders in this article is outlined in FIGURE 5-8. While it may seem complicated at first, the approach rests on a few simple questions that can be answered with the tests outlined previously. Accurate and consistent classification in the research setting will improve external validity and clinical trial enrollment. It is also important in the clinical setting, given the distinct prognoses discussed previously, the varying degrees of genetic risks between diagnoses, and the different approaches to treating speech and language disorders.

The first crucial branching point involves establishing whether the patient has a predominantly speech-based or a predominantly language-based disorder. Within speech-based disorders, the next step is establishing whether apraxia of speech is present and, if so, whether it is the only feature or not (TABLE 5-3 and TABLE 5-4). This branch allows for the identification of primary progressive apraxia of speech, cases of apraxia of speech dominating over aphasia, and apraxia of speech embedded within a nonaphasic syndrome.

If language is the primary problem, the next step is to establish whether the core criteria for PPA are met (TABLE 5-1). This allows the differentiation of the PPA syndromes from aphasia embedded within a broader cognitive syndrome, such as dysexecutive Alzheimer disease or other causes of aphasic dementia. Within the PPA branch, the patient is then classified as having a specific subtype (TABLE 5-2), mixed subtype, or unclassified subtype.

The last branch in the approach allows for the inclusion of right temporal predominant semantic dementia cases. It is worth noting that some would simply include these as a PPA. Given the pathologic similarity, this is not a point of major contention.

MANAGEMENT OF SPEECH AND LANGUAGE DISORDERS

No medications have been shown to be beneficial in degenerative apraxia of speech or aphasia, although clinical trials targeting the underlying proteinopathies in these disorders are under way. Medications may play a role in the nonspeech- and nonlanguage-associated features, such as symptomatic management of behavioral disturbances, but the approach here is no different from treating abnormal behaviors in bvFTD.

The lack of pharmacologic options should not dissuade the physician or patient from seeking therapeutic options, however. Speech therapy can be

Is speech the primary problem?

Yes → Is apraxia of speech present?

No (aphasia) → **DAOS[1]**

Yes → Is it isolated apraxia of speech?

Yes → **PPAOS**

No (other) → **Other[2]**

No → **Other[3]**

No → Is language the primary problem?

Yes → Are PPA criteria met?

Yes → Are subtype criteria met?

Yes → **agPPA**

lvPPA

svPPA

No → **Mixed PPA**

No → **PPA-U**

No → **Other[4]**

No → Is loss of semantic memory the primary problem?
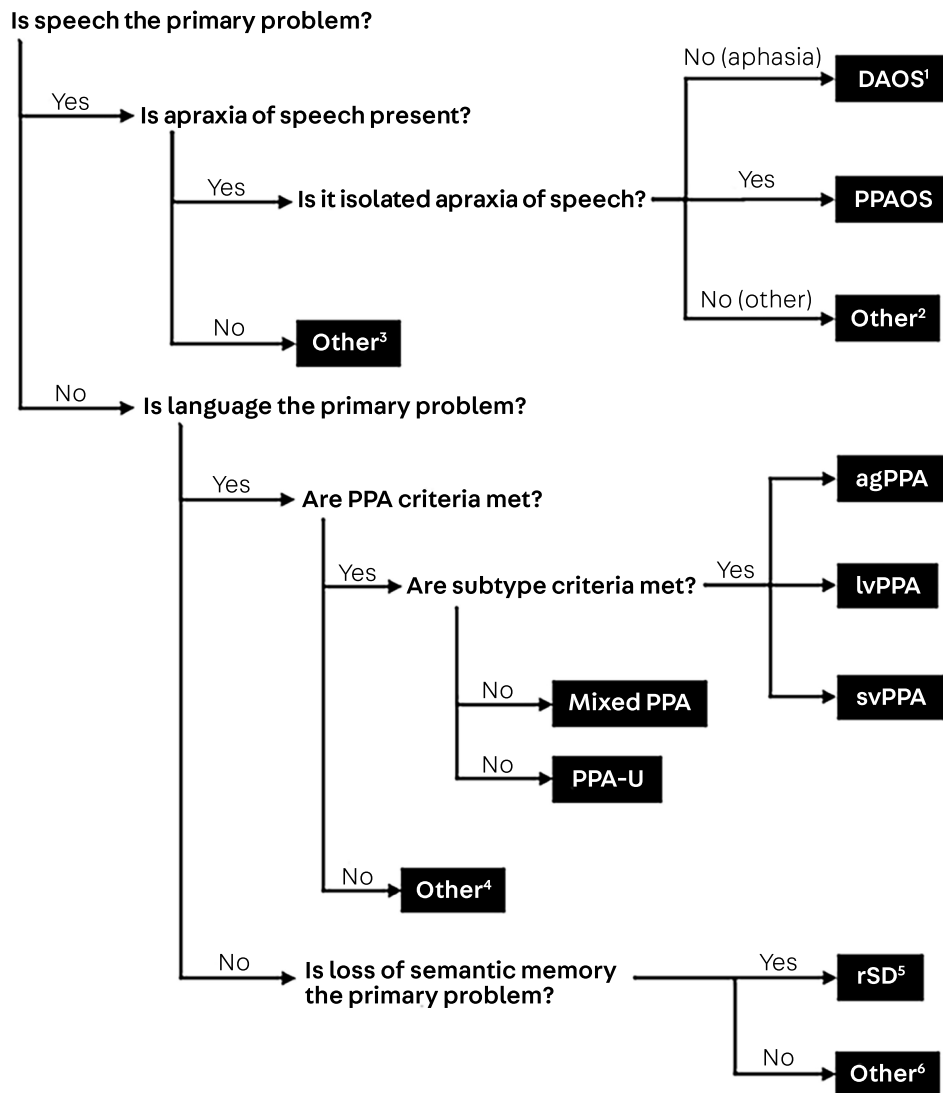
Yes → **rSD[5]**

No → **Other[6]**

FIGURE 5-8

Approach to the patient with a suspected degenerative speech or language disorder.

[1] Note that some would suggest including these patients in the nonfluent/agrammatic variant primary progressive aphasia group, which may be appropriate provided agrammatism is present.

[2] For example, apraxia of speech may be embedded in a corticobasal syndrome phenotype.

[3] For example, progressive spastic-flaccid dysarthria may suggest motor neuron disease.

[4] The patient may have an aphasic dementia due to any number of etiologies, for example.

[5] Note that some would suggest including these patients in the semantic variant primary progressive aphasia group.

[6] Some patients present with language symptoms but, in fact, have visual or working memory dysfunction.

agPPA = nonfluent/agrammatic variant primary progressive aphasia; DAOS = dominant apraxia of speech; lvPPA = logopenic variant primary progressive aphasia; PPA = primary progressive aphasia; PPAOS = primary progressive apraxia of speech; PPA-U = unclassified primary progressive aphasia; rSD = right temporal semantic dementia; svPPA = semantic variant primary progressive aphasia.

particularly helpful in cases of isolated or predominant apraxia of speech, as can assistive communicative devices. Similarly, the associated motor impairment can benefit from occupational and speech therapy. This underscores once more the importance of identifying these disorders. For language impairment, some patients benefit from therapy, while most family members benefit from strategies to maximize communicative effectiveness. As mentioned previously, referral to a speech and language pathologist is highly recommended when a degenerative speech and language disorder is considered.

CONCLUSION

This article has focused on degenerative speech and language disorders that are typically viewed as part of frontotemporal dementia. While considerable controversy remains over the way these disorders are classified, considerable progress has been made in our understanding of them over the past decade. In the approach this article outlines, apraxia of speech is viewed as distinct from aphasia and, when occurring in isolation, is viewed as a distinct degenerative syndrome. The criteria for the two PPA variants discussed (nonfluent/agrammatic and semantic) have significant shortcomings, and the authors advocate for a focus on agrammatism with regard to the nonfluent/agrammatic variant and an expanded view be taken of the semantic variant, incorporating aphasic and nonaphasic presentations within the broader category of semantic dementia. The authors are optimistic that trials of disease-modifying therapies will be expanded to these disorders over the next decade, although these will have to be grounded on consistent and evidence-based classification schemes and improved biomarkers for the underlying pathologies.

VIDEO LEGENDS

VIDEO 5–1
Speech examination in a woman with primary progressive apraxia of speech. Video shows a 70-year-old woman with primary progressive apraxia of speech. Speech alternating motion rates are slow but reasonably accurate. When combining sounds during speech sequential motion rates, a slow rate is required for accurate enunciation. During word repetition, evidence of groping, distortions, and substitutions is seen. This patient had minimal intelligible verbal output during picture description but tested normally on all language measures when written responses were allowed (not shown on video). *links.lww.com/CONT/A270*

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VIDEO 5–2
Language examination in a woman with nonfluent/agrammatic variant primary progressive aphasia. Video shows a 68-year-old woman with nonfluent/agrammatic variant primary progressive aphasia. Agrammatic and telegraphic speech is evident in response to a simple question ("Why are you here?") and during picture description. Specifically, the first sentence in her response is clearly agrammatic: "Well, I not say the words." She also omits *and* and incorrectly uses *is* when she describes the couple as: "The mother dad is picnicking." Also, notice the presumed omission during the final sentence: "The radio is probably music." *links.lww.com/CONT/A271*

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VIDEO 5–3
Language examination in a man with semantic variant primary progressive aphasia. Video shows a 68-year-old man with semantic variant primary progressive aphasia. During picture description the patient uses a nonspecific word in several instances, such as *something* for *wine*, *flower thing* for *kite*, *over there* for *dock*, and *something* for *sand*. When reading irregular words, he regularizes the word in several instances (surface dyslexia). During object naming, he first calls a *screwdriver* a *pen*, and, even after holding it, he cannot name it. He does not benefit from a phonetic cue and appears not to recognize the object. *links.lww.com/CONT/A272*

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