REVIEW ARTICLE

Primary Progressive Aphasia and Stroke Aphasia

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ABSTRACT

PURPOSE OF REVIEW: **This article summarizes the clinical and anatomic features of the three named variants of primary progressive aphasia (PPA): semantic variant PPA, nonfluent/agrammatic variant PPA, and logopenic variant PPA. Three stroke aphasia syndromes that resemble the PPA variants (Broca aphasia, Wernicke aphasia, and conduction aphasia) are also presented.**

RECENT FINDINGS: **Semantic variant PPA and Wernicke aphasia are characterized by fluent speech with naming and comprehension difficulty; these syndromes are associated with disease in different portions of the left temporal lobe. Patients with nonfluent/agrammatic variant PPA or Broca aphasia have nonfluent speech with grammatical difficulty; these syndromes are associated with disease centered in the left inferior frontal lobe. Patients with logopenic variant PPA or conduction aphasia have difficulty with repetition and word finding in conversational speech; these syndromes are associated with disease in the left inferior parietal lobe. While PPA and stroke aphasias resemble one another, this article also presents their distinguishing features.**

SUMMARY: **Primary progressive and stroke aphasia syndromes interrupt the left perisylvian language network, resulting in identifiable aphasic syndromes.**

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INTRODUCTION

Aphasia is a central disorder of language comprehension and expression that cannot be attributed to a peripheral sensory deficit (such as reduced auditory acuity) and is not due to a peripheral motor disorder (such as weakness of the muscles of articulation) that may mimic aphasia. Aphasia is associated with disease that affects the language network in the brain. Many different impairments can result in aphasia. This article focuses on primary progressive aphasia (PPA) and stroke aphasia but does not consider systemic disorders or psychiatric disorders, conditions such as head trauma or surgical interventions (eg, for neoplasms or hemorrhage following ruptured aneurysms), or transient changes in neurologic functioning that can disturb language functioning (eg, seizures or inflammation).

PPA refers to a group of focal neurodegenerative syndromes primarily affecting language. *Primary* refers to the absence of obvious structural abnormalities, including the absence of stroke, space-occupying lesion, or head trauma; *progressive* refers to the gradual worsening of the language deficit over several years.

In 1892, Arnold Pick described a woman with a social disorder involving disinhibition and poor insight.[1] Her speech gradually worsened, and she eventually became mute. In 1893, Paul Serieux described a patient with isolated language decline consisting of worsening speech fluency but relatively preserved memory and social and visuospatial functioning.[2] M. Marsel Mesulam reported a series of patients whom he characterized as having slowly progressive aphasia.[3] A positron emission tomography (PET) scan of brain functioning in one of these cases revealed reduced glucose metabolism in the left hemisphere.[4]

A diagnosis of PPA requires that the language impairment is the primary cognitive deficit and that it is progressive in nature.[5,6] Language difficulty should be the primary impairment for 1 to 2 years, with minimal memory, visuospatial, executive, or social difficulty during the early course of the disease, thereby eliminating other neurodegenerative conditions, such as typical amnestic Alzheimer disease (AD), in which memory difficulty can be accompanied at times by disproportionate impairment of language. The average age of onset tends to be in the late fifties, although a wide range of onset age is reported, and we are only beginning to learn about the factors contributing to this substantial variability.[7] Survival is about 7 years, although estimates of prognosis vary widely.[8,9] The underlying neuropathology of PPA is heterogeneous and largely corresponds to forms of frontotemporal lobar degeneration (FTLD); however, at least 20% of all patients with PPA may have a nonamnestic clinical presentation of AD due to plaque and tangle pathology, as revealed at autopsy.[10] Specific clinical syndromes of PPA have some predictive value for underlying molecular pathology (as discussed later in this article), but these associations are not absolute, posing a significant impediment for the development of disease-modifying therapies based only on clinical presentation.[11]

Stroke is another major cause of aphasia. The manifestations of aphasia due to stroke appear suddenly, not gradually as in PPA. As in PPA, several different forms of stroke aphasia exist, and these are determined in large part by damage to a portion of the language network where perfusion has been interrupted. The specific language deficits that are seen in stroke aphasia overlap only in part with those associated with PPA. This may be partially because stroke aphasia and PPA often affect different portions of the language network. Moreover, a stroke indiscriminately damages both gray matter regions of the brain that contain neurons and nearby white matter regions that contain projections that integrate several gray matter regions into a functional unit. Unlike PPA, in which white matter disease is typically the result of wallerian degeneration associated with disease in gray matter portions of the language network, the white matter tracts damaged in stroke may be *en passant* fibers that happen to be near the area of ischemia but connect brain regions unrelated to the language network. Because of the indiscriminate damage caused by a stroke, it can be difficult to parcel out the relative contribution of gray matter processing regions and white matter projections in a stroke-induced language disorder. Defining the gray matter regions and white matter regions contributing to a language disorder in a neurodegenerative condition causing a progressive aphasia is relatively easier

because the physical damage is more selective compared to that seen following a stroke and involves a gray matter and white matter network more specifically related to language.

This article focuses on the three subtypes of PPA, one with fluent speech, one with nonfluent speech, and one with a mixed form of aphasic speech. The anatomic distribution of disease in the progressive aphasias is illustrated in FIGURE 4-1.[12] These are compared with three similar forms of stroke aphasia, one fluent, one nonfluent, and one with mixed fluency (TABLE 4-1).

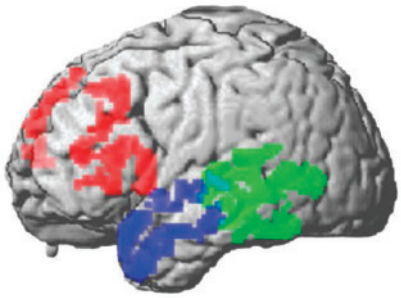

FIGURE 4-1
Anatomy of primary progressive aphasia. The anatomic distribution of gray matter atrophy associated with each of the three forms of primary progressive aphasia is shown, based on MRI scans of cohorts of patients meeting published criteria for these disorders: semantic variant primary progressive aphasia (*blue*); nonfluent/agrammatic primary progressive aphasia (*red*); logopenic variant primary progressive aphasia (green).
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The first form of PPA is known as *semantic variant PPA* (also called *semantic dementia*). This is a fluent form of aphasia associated with a disorder of naming and a deficit of word and object meaning. A somewhat similar form of stroke aphasia is known as *Wernicke aphasia*. This is also a fluent form of aphasia with impaired naming and word meaning. Despite superficial similarities, the language characteristics of semantic variant PPA and Wernicke aphasia have several notable differences. For example, Wernicke aphasia tends to affect word meaning much more than object meaning and is associated with a repetition deficit, while patients with semantic variant PPA often display a distinctive impairment in reading known as *surface dyslexia*.

A second variant of PPA is known as *nonfluent/agrammatic variant PPA*, also called *progressive nonfluent aphasia*. This nonfluent form of PPA is associated with slowed, effortful speech and an impairment of grammatical processing. Although several forms of nonfluent stroke aphasia exist, this article focuses on Broca aphasia, which also includes disorders of effortful speech and grammatical processing. While the stroke and progressive forms of nonfluent aphasia are both most notable for their nonfluent speech, as noted later in the article, some subtle distinctions exist: nonfluent/agrammatic PPA may include a deficit of speech sound articulation known as apraxia of speech, while Broca aphasia is associated with impaired repetition.

Finally, it has been recognized that many patients with PPA are not easily classified as having semantic variant PPA or nonfluent/agrammatic PPA, thus the logopenic variant of PPA has recently been added to the PPAs. This syndrome is characterized by significant word-finding difficulty in conversational speech and an impairment of auditory-verbal short-term memory, resulting in profound repetition difficulty. The analogous syndrome in classic stroke aphasia is conduction aphasia, resulting in relatively isolated repetition difficulties. Again, while logopenic variant PPA and conduction aphasia display mixed fluency associated with impaired repetition, subtle distinctions between these syndromes exist: logopenic variant PPA has more prominent lexical retrieval difficulties,

KEY POINTS

- **Aphasia is a central disorder of language comprehension and expression that cannot be attributed to a peripheral sensory deficit (such as reduced auditory acuity) and is not due to a peripheral motor disorder (such as weakness of the muscles of articulation) that may mimic aphasia.**
- **Primary progressive aphasia refers to a group of focal neurodegenerative syndromes primarily affecting language.**
- **The diagnosis of primary progressive aphasia requires that the language impairment is the primary cognitive deficit and that it is progressive in nature.**
- **The manifestations of aphasia due to stroke appear suddenly, not gradually as in primary progressive aphasia.**

TABLE 4-1 Characteristics of Progressive and Stroke Forms of Aphasia

	Fluent Aphasia		Nonfluent Aphasia		Mixed	
	Semantic Variant Primary Progressive Aphasia	Wernicke Aphasia	Nonfluent/ Agrammatic Variant Primary Progressive Aphasia	Broca Aphasia	Logopenic Variant Primary Progressive Aphasia	Conduction Aphasia
Speech features						
Fluent speech	Yes	Yes	No	No	Yes/No[a]	Yes/No[a]
Speech errors	Lexical	Lexical	Phonemic	Phonemic	Phonemic more than lexical	Phonemic
Apraxia of speech	No	No	Yes	No	No	No
Naming deficits	Yes	Yes	Yes	Yes	Yes	Yes
Comprehension features						
Single word deficits	Yes	Yes	No	No	No	No
Object deficits	Yes	No	No	No	No	No
Grammar deficits	No	No	Yes	Yes	No	No
Other						
Oral reading and writing deficits	Surface dyslexia and dysgraphia	No	Agrammatic	Agrammatic	No	No
Repetition deficits	No	Yes	No	Yes	Yes	Yes
Core anatomy	Anterior and ventral left temporal	Posterior-superior left temporal	Left inferior frontal	Left inferior frontal	Left inferior parietal and posterior temporal	Left inferior parietal
Clinicopathologic correlations	FTLD-TDP>FTLD-Tau>AD	Vascular	FTLD-Tau>AD> FTLD-TDP	Vascular	AD> FTLD-Tau>FTLD-TDP	Vascular

AD = Alzheimer disease; FTLD-Tau = frontotemporal lobar degeneration with tau pathology; FTLD-TDP = frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43) pathology.

[a] Logopenic variant primary progressive aphasia and conduction aphasia have relatively fluent speech that can by slowed by word-finding difficulty and circumlocutions but lack motor speech or grammatical impairments.

while the quality of repetition impairment in conduction aphasia can have distinct characteristics depending on the precise location of the stroke.

From a clinical perspective, it is important to distinguish between the progressive and stroke forms of aphasia. Moreover, it is valuable to recognize each of the PPA syndromes since they may be markers of a statistically increased risk of a specific form of FTLD pathology,[12–14] and it is valuable clinically to recognize these forms of stroke aphasia since they are often associated with an embolic stroke that may have its origins in the heart.

FLUENT APHASIAS

The fluent aphasias include semantic variant PPA and Wernicke aphasia. The major characteristics shared by these primary progressive and stroke-associated aphasias are the fluent rate of speech paired with impaired comprehension. However, these aphasic syndromes also differ in subtle but important ways.

Clinical Features

Long-term memory for concepts, such as knowledge of objects, actions, and ideas, is represented in semantic memory, and this appears to be compromised in semantic variant PPA. The syndrome of semantic variant PPA was first described by Warrington[15] and Snowden and colleagues.[16] Clinical research consensus criteria for semantic variant PPA focus on two essential features,[17] with reliable and widely accepted recognition of this syndrome.[5,18,19] One major clinical feature is profound confrontation naming difficulty (CASE 4-1).[20,21] Patients are severely impaired at naming pictured objects or using these words in spontaneous speech. Analyses of naming errors suggest that patients with semantic variant PPA may substitute the name of a prototype (eg, calling a camel *horse*) or a more frequent and familiar object that shares many of the same features as the target object (eg, calling a pelican *robin*).[22] They may also substitute a more general, superordinate term when a basic level name of a specific object is difficult (eg, calling a pelican *bird* or *animal*).[23,24] Even superordinate terms become difficult for these patients over time, and the meaningfulness words become increasingly vague as the disease progresses. This interferes substantially with meaningful communication because all objects eventually are called *that* and *thing*.

A second major clinical feature of semantic variant PPA is impaired comprehension of single words.[21] Patients with semantic variant PPA are impaired at understanding basic object level names, such as *camel* or *pelican*. Over time, this may involve difficulty in understanding superordinate terms such as *animal*, paralleling the difficulty in language expression. Because of these impairments, patients with semantic variant PPA may also be impaired in sentence comprehension[25] and sentence expression.[26]

Since the problem in semantic variant PPA appears to affect both comprehension and the expression of single words, the core deficit is thought to involve semantic memory.[21] One hypothesis is that these patients have a deficit for all knowledge represented in semantic memory. This is consistent with Endel Tulving's proposed theory of human memory, which characterizes semantic memory as a single amodal system in which all semantic knowledge is stored.[27] Another possibility involves a distributed model of sensorimotor feature knowledge. This is called the *hub-and-spoke model*,[21] in which most object concepts consist of several features taken from different modalities. Thus, the

KEY POINTS

- It is valuable to recognize each of the primary progressive aphasia syndromes since they may be markers of a statistically increased risk of a specific form of frontotemporal lobar degeneration pathology, and it is valuable clinically to recognize the forms of stroke aphasia since they are often associated with an embolic stroke that may have its origins in the heart.
- Long-term memory for concepts, such as knowledge of objects, actions, and ideas, is represented in semantic memory, and this appears to be compromised in semantic variant primary progressive aphasia.
- One major clinical feature of semantic variant primary progressive aphasia is profound confrontation naming difficulty. Patients are severely impaired at naming pictured objects or using these words in spontaneous speech. A second major clinical feature is impaired comprehension of single words.
- Since the problem in semantic variant primary progressive aphasia appears to affect both the comprehension and expression of single words, the core deficit is thought to involve semantic memory.

CASE 4-1

A 54-year-old right-handed woman presented because she was having difficulty at work. She worked as a lawyer, and her supervising partner told her of increasing complaints from clients about her lack of clear communication. During phone conversations, she used incorrect or imprecise words when discussing facts with her clients. Her assistant also noted that she had difficulty when orally reading and reviewing certain words in transcripts that she had recently dictated. These symptoms had progressed over time. More recently, her assistant had noticed that the patient had some comprehension difficulty as well. She did not seem to have significant difficulty with memory for recent events, and she had no problems with driving. She had no symptoms of elementary neurologic deficits, such as difficulty with strength or abnormal involuntary movements.

On examination, the patient was alert and fully oriented to person, place, and time. Her speech was fluent but at times circumlocutory. She used somewhat imprecise nouns in her speech but made no grammatical errors. She had significant confrontation naming difficulty (this was most notable for low-frequency words), and she substituted the names of more frequent words, such as calling a camel *horse* and a pelican *duck*. Repetition of phrases and sentences was intact. She had difficulty reading sight vocabulary words, pronouncing choir as *chore* and dough as *dog*. She appeared to make a similar error in a written sentence describing the weather outside (writing weather as *wether*). Grammatical comprehension and expression were preserved. She was able to demonstrate the use of familiar objects such as a hammer and a saw but did not know how to demonstrate the use of a scissors. While she had mild difficulty with verbal memory, her visual memory for recall of a complex visual geometric design after several minutes was intact. She had no difficulty with visuospatial tasks, such as copying a complex geometric design or judging whether two lines were parallel. Executive functioning was preserved, demonstrated by orally reciting a list of alternating letters and numbers. The remainder of the neurologic examination was unremarkable.

COMMENT

This patient had semantic variant primary progressive aphasia, characterized by progressive difficulty with confrontation naming and the classic substitution of high-frequency prototypes for lower-frequency targets during naming. She had some difficulty with object comprehension and surface dyslexia, pronouncing words during oral reading in a manner that made use of letter-sound correspondence rules. She showed no evidence of agrammatism or repetition difficulty.

concept of a camel might involve activation of associated color knowledge, activation of shape information associated with the humps of a camel, and activation of general world knowledge that a camel lives in a desert. The pattern of activation across these independent and distributed reservoirs of knowledge is then interpreted as *camel*. From this perspective, it is the coordinating hub, rather than representations of knowledge, that is compromised in semantic variant PPA.

However, mounting evidence exists against a universal semantic memory deficit in semantic variant PPA. This comes from experimental observations emphasizing that deficits in semantic variant PPA overwhelmingly involve object concepts and the associated visual feature knowledge.[28] Many patients with semantic variant PPA, in fact, show the phenomenon of *reversal of the concreteness effect*, in which patients have greater difficulty with concrete objects than with abstract concepts.[15,29–32] Relative deficits with concrete object concepts compared to abstract concepts have been found in large series of patients with semantic variant PPA, both in comprehension using word stimuli and in narrative expression.[24,33–35] For example, the vocabulary of patients with semantic variant PPA loses high-imageability words and consists of significantly more abstract words.[24,34,35] Patients with semantic variant PPA also appear to have relatively preserved appreciation of musical meaning,[36] although others have noted difficulty with musical knowledge in music-picture matching tasks.[37] Finally, patients with semantic variant PPA appear to have relatively preserved knowledge of number concepts[38–40] and the class of words that includes concepts such as *most*, *less than half*, and *few* (known as quantifiers),[41,42] although others have also noted difficulty with number knowledge in patients with semantic variant PPA who are very impaired.[43] In sum, it appears that patients with semantic variant PPA are disproportionately impaired in their ability to understand and name object concepts.

This pattern of impairment in semantic variant PPA differs in some notable ways from patients with the fluent stroke aphasia called *Wernicke aphasia*. Patients with Wernicke aphasia also have fluent speech with considerable confrontation naming difficulty. While this form of stroke aphasia is notable for difficulty with both comprehension and expression, the deficit seems to be largely restricted to words. Content words, such as nouns and verbs, are very difficult for these patients; thus, their speech contains many nonspecific words such as *this* and is often empty of content. Word comprehension in Wernicke aphasia can be approximate for all types of words, but unlike semantic variant PPA, there is little evidence that patients with Wernicke aphasia have relative difficulty understanding or expressing a particular category of knowledge, such as concrete object concepts. Thus, although they cannot access the name of the clear container used to hold water, patients with Wernicke aphasia rarely have difficulty knowing that a glass is a container from which one drinks water. Despite their approximate comprehension of single words, these patients tend to have relatively preserved comprehension of objects.

Second, patients with Wernicke aphasia typically have difficulty with repetition, whereas this is rarely evident in semantic variant PPA until the patient becomes quite impaired. This has been attributed to the fact that the bundle of fibers critical for repetition (known as the *arcuate fasciculus*) is compromised in Wernicke aphasia but not in semantic variant PPA.

KEY POINTS

- It appears that patients with semantic variant primary progressive aphasia are disproportionately impaired in their ability to understand and name object concepts.
- Despite their approximate comprehension of single words, patients with Wernicke aphasia tend to have relatively preserved comprehension of objects.
- Patients with Wernicke aphasia typically have difficulty with repetition, whereas this is rarely evident in semantic variant primary progressive aphasia until the patient becomes quite impaired.
- Patients with Wernicke aphasia have relatively preserved oral reading, whereas semantic variant primary progressive aphasia is associated with a specific disorder of reading known as *surface dyslexia*.

Third, patients with Wernicke aphasia have relatively preserved oral reading, whereas semantic variant PPA is associated with a specific disorder of reading known as *surface dyslexia*.[21] In this condition, letter-sound correspondence rules are preserved but sight vocabulary is lost, resulting in mispronunciation of sight vocabulary words through the use of letter-sound correspondence rules. The word *choir* may be pronounced as *chore* and *dough* may be pronounced as *dog*. Nevertheless, patients with Wernicke aphasia may have difficulty understanding what they are reading.

Anatomic Features

Semantic variant PPA has a distinctive anatomic distribution of disease. Imaging studies associate semantic variant PPA with atrophy of left anterior and ventral gray matter regions of the temporal lobe as well as the anterior hippocampus and the amygdala.[44,45] Changes are also seen in the white matter projections from this area to other brain regions, including the middle longitudinal fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus.[46,47] Using a functional imaging technique known as arterial spin labeling, it appears that the disease progresses over time from areas of established disease in the anterior temporal lobe to adjacent regions.[48] Longitudinal imaging shows atrophy extending posteriorly and superiorly into the gray matter of the ipsilateral temporal lobe and dorsally into the insula and the ventral frontal lobe. While disease associated with semantic variant PPA may begin in the left hemisphere, pathology often spreads to involve the contralateral temporal lobe.[48,49] Some investigators emphasize the role of the left anterior temporal lobe in the semantic memory deficit of patients with semantic variant PPA,[50] but functional anatomy studies also implicate atrophic homologous regions of the right hemisphere.[51,52] Right anterior temporal lobe disease in FTLD is associated with behavioral abnormalities and the behavioral variant of frontotemporal dementia (bvFTD) syndrome.[53] The features most commonly seen are ritualistic and obsessive behaviors. Patients with semantic variant PPA very often develop additional right temporal and frontal disease along with a social disorder clinically consistent with bvFTD during the natural history of disease. Because these behavioral features are so common in semantic variant PPA, the authors do not view the presence of behavioral features as a criterion for excluding a patient from the diagnosis of semantic variant PPA.

Imaging studies have related difficulty with semantically mediated tasks directly to left anterior and ventral temporal gray matter disease in semantic variant PPA.[28,33,34,54–56] A critical feature of the semantic deficit in semantic variant PPA is difficulty with object concepts that depend on visual feature knowledge. Disease in ventral regions of the anterior temporal lobe encompasses the visual association cortex.[57,58] This structure has been linked with high-level aspects of visual perception,[59] mental imagery,[60] and high-level visual-object representation.[61] There is a functional anatomic gradient through the visual processing stream. Processing of elementary visual-perceptual features such as color and shape occurs in posterior regions of the temporal lobe, and the association of visual-perceptual features with semantic value occurs in more anterior portions of the visual stream, including the anterior fusiform and parahippocampal gyri. Difficulty with the meaning of words and pictures of objects that depend on visual feature knowledge is directly associated with

disease in the anterior fusiform gyrus[55] and the adjacent parahippocampal gyrus[28,33,34,56] in anterior portions of the ventral temporal lobe.

These findings are consistent, in part, with a sensorimotor approach to semantic memory, also known as *embodied cognition*, in which the neural representation of knowledge in semantic memory is linked to areas of the brain that are important for sensorimotor processing.[62,63] In semantic variant PPA, this is focused on the representation of visual feature knowledge that is crucial for representing the meaning of object concepts. Other examples of relating sensorimotor features to concepts include activation of the motor cortex for actions involving specific body parts,[64] the auditory association cortex for auditory feature knowledge,[65] the gustatory cortex for appetizing foods,[66] and the olfactory cortex for feature knowledge associated with smell.[67]

Patients with semantic variant PPA also have white matter disease. This includes reduced fractional anisotropy in white matter projections of the anterior temporal lobe.[46,47,49] Connectivity with other brain regions becomes compromised over time,[46,48,49] and this, too, may contribute to a semantic memory deficit in semantic variant PPA. These observations emphasize that the semantic memory deficit in semantic variant PPA is due, in part, to the disruption of a large-scale neural network involving multiple gray matter regions and white matter projections.[68]

Patients with semantic variant PPA frequently have pathology that is associated with the accumulation of transactive response DNA-binding protein 43 (TDP-43), an RNA-binding protein that functions normally in the nucleus to help regulate DNA and RNA processing.[20,69,70] Patients with semantic variant PPA with TDP-43 pathology often have additional right anterior temporal TDP-43 pathology along with a social disorder clinically consistent with bvFTD. Although up to 40% of all forms of FTLD have a family history and roughly 20% have a pathogenic mutation in the main genes associated with FTLD-TDP (ie, progranulin [*GRN*] or *C9orf72*) or FTLD-tau tauopathies (*MAPT*),[71] the form of FTLD-TDP found in association with semantic variant PPA is most often sporadic, without a strong family history or pathogenic mutation.[72] Less common neurodegenerative pathologies associated with semantic variant PPA include Pick disease and AD pathology.[12]

Other causes of a pattern of semantic memory difficulty resembling semantic variant PPA may also be encountered, such as herpes encephalitis,[50,73,74] but these are often subacute in onset and do not have the slow evolution of semantic variant PPA. Some forms of closed head trauma may resemble semantic variant PPA, but these are easily distinguished by their sudden onset and nonprogressive course.

Many of the language features that distinguish Wernicke aphasia from semantic variant PPA result because these two conditions affect different areas of the left hemisphere. In contrast to the anterior and ventral temporal anatomic distribution of disease in semantic variant PPA, more posterior and superior areas of the temporal lobe are compromised in Wernicke aphasia. This tends to be associated with the portion of the comprehension network important for lexical access, and disease in this area particularly compromises lexical comprehension and lexical retrieval.[75,76] Since the visual association network is relatively intact in Wernicke aphasia, object comprehension is correspondingly well preserved. The repetition deficit found in Wernicke aphasia (but not in semantic variant PPA) is also related to the anatomic distribution of disease.

KEY POINTS

- ***Surface dyslexia*** **refers to difficulty reading sight vocabulary words. Patients with surface dyslexia instead use their preserved letter-sound correspondence rules to sound out sight words, for example, reading *dough* as *dog*.**
- **Imaging studies associate semantic variant primary progressive aphasia with atrophy of left anterior and ventral gray matter regions of the temporal lobe as well as the anterior hippocampus and the amygdala.**
- **Right anterior temporal lobe disease in frontotemporal lobar degeneration is associated with behavioral abnormalities and the behavioral variant frontotemporal dementia syndrome, and patients with semantic variant primary progressive aphasia often develop additional right temporal (and frontal) disease along with a social disorder clinically consistent with behavioral variant frontotemporal dementia during the natural history of disease.**
- **Imaging studies have related difficulty with semantically mediated tasks directly to left anterior and ventral temporal gray matter disease in semantic variant primary progressive aphasia.**
- **Patients with semantic variant primary progressive aphasia frequently have pathology that is associated with the accumulation of transactive response DNA-binding protein 43, an RNA-binding protein that functions normally in the nucleus to help regulate DNA and RNA processing.**

KEY POINTS

- Semantic memory difficulty resembling semantic variant primary progressive aphasia due to other causes may be encountered, such as in herpes encephalitis, but these are often subacute in onset and do not have the slow evolution of semantic variant primary progressive aphasia. Some forms of closed head trauma may resemble semantic variant primary progressive aphasia, but these are easily distinguished by their sudden onset and nonprogressive course.
- In contrast to the anterior and ventral temporal anatomic distribution of disease in semantic variant primary progressive aphasia, more posterior and superior areas of the temporal lobe are compromised in Wernicke aphasia.
- The clinical hallmark of nonfluent/agrammatic primary progressive aphasia is slowed, effortful, nonfluent speech.
- One essential characteristic of speech in nonfluent/agrammatic primary progressive aphasia is its impoverished grammatical features.
- It is important to distinguish the nonfluent speech associated with the grammatical simplifications and errors seen in nonfluent/agrammatic primary progressive aphasia from the pattern of reduced speech output seen in fluent forms of aphasia, in which searching for words can slow speech output in the absence of grammatical deficits.

Thus, Wernicke aphasia (but not semantic variant PPA) includes insult to the arcuate fasciculus. This fiber tract is critical for repetition and projects between the posterior-superior temporal lobe and the inferior frontal lobe.

NONFLUENT APHASIAS

The nonfluent aphasias include nonfluent/agrammatic PPA and Broca aphasia. The major clinical feature shared by these aphasic syndromes is the characteristically effortful and slowed speech. However, these syndromes also differ in some subtle but important ways.

Clinical Features

The clinical hallmark of nonfluent/agrammatic PPA is slowed, effortful, nonfluent speech. The effortful nature of speech in PPA was first described by Mesulam[3] as slowly progressive aphasia. The linguistic characteristics of this disorder were described several years later with the designation *progressive nonfluent aphasia*.[77] While effortful speech has long been recognized clinically,[77,78] quantification of slowed speech rate has only been documented more recently.[79–81] Speech is produced by patients with nonfluent/agrammatic PPA at an average rate of about 45 words per minute. By comparison, the speech rate is about 140 words per minute in healthy age-matched adults and about 90 words per minute in other PPA syndromes. While patients with nonfluent/agrammatic PPA have many lengthy pauses in their effortful speech, speech remains significantly slowed even when pauses of more than 2 seconds in duration are taken into consideration.[82]

The rate of speech in these patients appears to be more acceptable when producing overlearned sequences, such as counting or reciting the alphabet. Careful analyses have allowed investigators to test several hypotheses about the basis for the slowed, effortful speech found in nonfluent/agrammatic PPA. One essential characteristic of nonfluent/agrammatic PPA speech is its impoverished grammatical features (CASE 4-2).[79–81] Grammatical deficits in speech are highly correlated with effortfulness and slowed words per minute. In semistructured speech samples that involve describing a single picture[26] or a lengthier, wordless picture story,[79,82] analyses reveal that the variety of grammatical forms is impoverished, and grammatical forms are simplified with fewer utterances containing features such as a subordinate clause or the passive voice. Grammatical simplifications also result in a shortened mean length of utterance (fewer words per statement). When syntactic features are produced, they are more likely to contain errors. Grammatical morphemes may be omitted, including inflections such as the past tense ending *-ed* and freestanding morphemes such as *was* and articles such as *a*. Inappropriate grammatical inflections may also be used. It is important to distinguish the nonfluent speech associated with the grammatical simplifications and errors seen in nonfluent/agrammatic PPA from the pattern of reduced speech output seen in fluent forms of aphasia in which searching for words can slow speech output in the absence of grammatical deficits.

Some patients with nonfluent/agrammatic PPA appear to have a motor disorder that may contribute to their effortful speech. Patients with an extrapyramidal disorder, such as progressive supranuclear palsy or corticobasal syndrome, have poor control of the motor apparatus, and this can affect their speech just as it affects the use of their hands for motor tasks and compromises their gait.[83] This is known as apraxia of speech. The combination of these

linguistic and speech characteristics has led to clinical research consensus criteria for the syndrome known as nonfluent/agrammatic PPA,[17] which has reliable and widely accepted recognition.[5,18,19]

Apraxia of speech involves impaired coordination and planning of the motor articulators. Clinical characteristics of apraxia of speech include the production of incorrect speech sounds and sequences of sounds that do not occur in the speaker's native language, groping for the correct sound although not necessarily producing the intended target after several attempts, and oddly placed pauses in the speech stream. These speech disorders occur independently of oral apraxia or the demonstration of nonlinguistic oral gestures such as blowing out a match. However, the association between apraxia of speech and oral apraxia is inconsistent. While these clinical features of nonfluent/agrammatic PPA have

CASE 4-2

A 62-year-old right-handed man reported progressive difficulty with his speech. He was a smartphone salesman and was experiencing increasing difficulty expressing himself during sales to clients. His speech had become progressively slowed, although he typically used the correct words. At times, he sounded like an old-fashioned telegram. Comprehension otherwise was preserved. Recently, he had begun to experience falls when walking, and these did not appear to be associated with tripping or weakness. He also reported occasional double vision.

On examination, he was alert and fully oriented. His speech was slowed and effortful. He made no speech sound errors, including no speech sounds not heard in English, and had no unusual locations of pauses in his speech. He omitted small grammatical morphemes, such as *was* and *the*, and did not inflect verbs for past tense. His writing and oral reading similarly omitted small grammatical morphemes, but the content otherwise seemed preserved. He was able to repeat phrases and sentences. His comprehension of single words, objects, and grammatically simple sentences seemed good. However, he had some difficulty when required to demonstrate understanding of sentences that depended on grammatical information (eg, "Point to the window after you point to the door"). Memory and visuospatial processing seemed preserved. He was slow at performing measures of executive functioning. The remainder of the neurologic examination was significant for difficulty with the fast phase of ocular movements in an assessment of opticokinetic nystagmus and some mild neck rigidity.

COMMENT

This patient had nonfluent/agrammatic primary progressive aphasia. He had agrammatic speech and comparable changes in writing and oral reading. Comprehension of single words and grammatically simple sentences was preserved, but he had difficulty with grammatical comprehension. Repetition was also preserved. He had mild difficulty with executive functioning, although he did well in other aspects of cognitive functioning. He had experienced falls and had mild difficulty with saccades in the vertical axis, raising a question of progressive supranuclear palsy.

been incorporated into diagnostic criteria for progressive supranuclear palsy and corticobasal syndrome,[84–86] apraxia of speech can occur without any other observable motor disorder.[10,87]

It is crucial to quantify apractic speech disorders objectively so that these observations can be reproduced reliably in other laboratories. In one attempt to quantify speech errors consistent with apraxia of speech in nonfluent/agrammatic PPA, phonetic errors involving misarticulated speech sounds that are not part of the English speech sound system were used as markers of misplaced articulators related to an impaired motor coordination system.[88] Patients with nonfluent/agrammatic PPA were found to produce significantly more speech errors than controls, consistent with other observations.[84,87] However, only 21% of speech errors in nonfluent/agrammatic PPA could be attributed to a motor speech planning disorder because they were distortions that are not part of the English speech sound system. In another study, duration of syllable production was lengthened and stress of initial versus subsequent syllable was disordered in apraxia of speech compared to controls and other PPA patient groups.[89] Two classes of speech sound errors have been identified by some authors: one consists of speech sound errors, distortions, and substitutions and the second consists of syllabically segmented prosodic speech patterns. The former type of error was said to be seen more commonly in nonfluent/agrammatic PPA, while the latter was found in individuals with isolated apraxia of speech.[90]

Patients with nonfluent/agrammatic PPA also are impaired in their oral grammatical comprehension.[5,77] Likewise, they exhibit grammatical errors in their reading comprehension of written material and their writing. This provides additional evidence that the effortful speech in nonfluent/agrammatic PPA is not determined entirely by an apractic motor disorder. In a sentence such as "Boys that girls hug are friendly," for example, patients with nonfluent/agrammatic PPA often err when asked "Who did the hugging?"[91] These patients also have difficulty pointing to one of two pictures based on a sentence in which selecting the correct picture depends on appreciating the sentence's grammatical structure.[25,92] Another study used an anagram task (ordering of cards with printed words into a sentence) to show that patients with nonfluent/agrammatic aphasia have difficulty ordering words printed on cards into a grammatically complex question about a picture.[93] Grammatical difficulties such as these may help distinguish nonfluent/agrammatic PPA from other PPA variants.[5,25,91] However, care must be taken since comprehension of center-embedded subordinate clause constructions and complex anagram tasks are impaired across all PPA variants: Sentences such as "The dog with white fur that the cat chased is friendly" are lengthy and involve multiple propositions, and anagram tasks involve planning and organizing. Thus, difficulty with these tasks may be sensitive for nonfluent/agrammatic PPA, but they appear to be less specific. This may be, in part, because they are vulnerable to processing resource limitations. One example is limited working memory that may be needed to temporarily retain a lengthy, complex sentence until its message can be interpreted by manipulating many propositions. Likewise, substantial executive resources underlying planning and organizing are needed for an anagram task. Patients with nonfluent/agrammatic PPA have some working memory and executive deficits on nonlinguistic measures, such as reverse digit span and category naming fluency.[94,95] Thus, deficits in working memory and executive functioning may confound the ability to detect a grammatical impairment.

Cleft grammatical sentences, such as "It was the eagle that the hawk chased," are more likely to be selectively impaired in nonfluent/agrammatic PPA and are not significantly impaired in other patient groups because they contain only two propositions and are not too lengthy.[25] It does not appear that nonspecific cognitive difficulty contributes substantially to comprehension impairments, as a correlation between nonspecific measures of dementia such as the Mini-Mental State Examination (MMSE) and comprehension performance is typically not found in nonfluent/agrammatic PPA. Finally, it should be emphasized that nonfluent/agrammatic PPA is a progressive disorder of language, and several studies have shown progressive decline of grammatical comprehension.[96,97]

Patients with Broca aphasia due to stroke have been shown to have slowed, effortful speech.[98] A disorder of grammatical expression and grammatical comprehension is seen, although the precise basis for this deficit remains to be discovered.[99] A disorder of prosody is also seen, with distortion or absence of the typical declination of pitch found in statements and distortion or absence of the terminal rise in pitch for a yes/no question. Thus, considerable overlap exists in the language and speech characteristics of patients with Broca aphasia and patients with nonfluent/agrammatic PPA.

However, some features appear to distinguish Broca aphasia from nonfluent/agrammatic PPA. For example, nonfluent/agrammatic PPA may include apraxia of speech, while this appears to occur much less often in Broca aphasia. An impairment of repetition is less common in nonfluent/agrammatic PPA, while Broca aphasia is often associated with impaired repetition. Indeed, a qualitative analysis of the repetition deficit in Broca aphasia often reveals grammatical errors. Patients with nonfluent/agrammatic PPA also appear to be more vulnerable to anagram tasks and the executive resource demands of sentences with many propositions.

Anatomic Features

Extensive imaging evidence suggests that a clinical marker for nonfluent/agrammatic PPA is focal disease centered in the left frontal lobe. Structural MRI studies emphasize gray matter atrophy in the inferior frontal region of the left hemisphere.[45,77,91,100] This typically extends beyond the pars opercularis and pars triangularis (regions in the inferior frontal lobe colloquially known as the Broca area) to involve the frontal operculum and anterior insula, left prefrontal regions that are more dorsal and anterior, and superior portions of the left anterior temporal lobe.[79,81] Functional imaging techniques such as PET confirm structural imaging observations. PET also shows deficits in the left inferior frontal lobe, including the frontal operculum and the anterior insula, as well as the anterior-superior temporal lobe.[77,101] Gray matter atrophy and reduced PET glucose metabolism is said to be centered in the superior lateral premotor cortex and supplementary motor area. Associated white matter disease involves premotor components of the superior longitudinal fasciculus and extends into the body of the corpus callosum.[85]

Regression analyses have been used to link the slowed effortful characteristic of speech in nonfluent/agrammatic PPA directly to these left frontal regions.[79–81] Grammatical simplifications observed in semistructured speech samples have been related to gray matter atrophy in inferior frontal and anterior-superior temporal regions of the left hemisphere.[79–81] Motor speech abnormalities in

KEY POINTS

- Apraxia of speech involves impaired coordination and planning of the motor articulators. Clinical characteristics of apraxia of speech include the production of incorrect speech sounds and sequences of sounds that do not occur in the speaker's native language, groping for the correct sound although not necessarily producing the intended target after several attempts, and oddly placed pauses in the speech stream.
- Patients with nonfluent/agrammatic primary progressive aphasia are impaired in their oral grammatical comprehension.
- Patients with nonfluent/agrammatic primary progressive aphasia have some working memory and executive deficits on nonlinguistic measures, such as reverse digit span and category naming fluency.
- Patients with Broca aphasia have slowed, effortful speech.
- Nonfluent/agrammatic primary progressive aphasia may include apraxia of speech, while this appears to occur much less often in Broca aphasia. An impairment of repetition is less common in nonfluent/agrammatic primary progressive aphasia, while Broca aphasia is often associated with impaired repetition.

patients with movement disorders such as progressive supranuclear palsy are associated with atrophy of deep gray matter structures, such as the striatum and supplementary motor areas involved in motor planning.[86]

Sentence comprehension appears to be related to regional gray matter atrophy in nonfluent/agrammatic PPA as well. In a study of simple, dichotomous (yes/no) probes of simpler and more complex sentences, impaired grammatical comprehension was associated with the posterior-inferior frontal and anterior-superior temporal regions of the left hemisphere.[91] In a two-alternative, forced-choice, sentence-picture matching task, comprehension of grammatically complex sentences in nonfluent/agrammatic PPA was related to left inferior frontal and anterior-superior temporal gray matter atrophy.[25] Grammatical comprehension was related to left inferior frontal atrophy in a heterogeneous group of patients with progressive aphasias that included individuals with nonfluent/agrammatic PPA.[92]

It is important to point out that neurodegenerative disease, such as that found in nonfluent/agrammatic PPA, interrupts large-scale neural networks; this is emphasized by the white matter disease that is also found in nonfluent/agrammatic PPA. This disease implicates pathways containing reciprocal projections involving the left inferior frontal lobe. Interrupted pathways important for language and speech include the anterior corpus callosum, which integrates left and right inferior frontal regions; the arcuate/superior longitudinal fasciculus complex, which constitutes the so-called dorsal stream projecting between frontal and posterior-superior temporal regions; and the inferior frontooccipital fasciculus and the inferior longitudinal fasciculus, which are part of the so-called ventral stream between frontal and posterior temporal regions.[102–105] White matter disease in nonfluent/agrammatic PPA also appears to involve the uncinate fasciculus, which contains projections between the inferior frontal lobe and the anterior temporal lobe. This is consistent with observations of patients with autopsy-confirmed nonfluent/agrammatic PPA, who have imaging evidence of white matter disease in the superior longitudinal fasciculus, inferior frontooccipital fasciculus, and uncinate fasciculus.[103,106]

Regression analyses have linked large-scale networks of disturbed anatomy directly to language deficits in nonfluent/agrammatic PPA. Three gray matter-white matter networks for language expression have been identified.[106] In the first network, disease in the left inferior frontal cortex and white matter disease in the anterior corpus callosum projections to the right inferior frontal lobe appear to be related to slowed, effortful speech rate. Speech errors may also be related to this network. In a second network, the left frontal lobe and tracts in the arcuate/superior longitudinal fasciculus project to posterior perisylvian cortical regions (the so-called dorsal stream), and this is disrupted by white matter disease in nonfluent/agrammatic PPA. The dorsal stream is thought to mediate, in part, long-distance syntactic dependencies in sentences,[107] and disease in this network may contribute to deficits in sentence-level grammatical expression and comprehension in nonfluent/agrammatic PPA. The third large-scale neural network that is disrupted in nonfluent/agrammatic PPA includes the left inferior frontal lobe and the inferior frontooccipital fasciculus projecting through the external capsule to posterior-superior temporal regions. This is the so-called ventral stream, which may support lexical representations important for grammatical processing, such as the major grammatical category of words.[108] Interruption of this network by

white matter disease in the left inferior frontal lobe and the left inferior frontooccipital fasciculus is associated with difficulty in understanding grammatically complex sentences.[25]

Functional MRI (fMRI) has also been used to assess the neuroanatomic basis for grammatical processing in nonfluent/agrammatic PPA. In one study, patients with nonfluent/agrammatic PPA did not appear to recruit the left inferior frontal cortex during comprehension of grammatically complex sentences, although they recruited dorsal portions of the left frontal lobe associated with working memory and left posterior-superior temporal regions associated with comprehension of nongrammatical language material.[109] Another fMRI study showed greater left inferior frontal activation during grammatically complex sentences compared to simple sentences in controls, while patients with nonfluent/agrammatic PPA did not show a difference in left inferior frontal activation between these two types of sentences.[92] In a 2016 study, activation of an extensive left hemisphere language network was disrupted in patients with grammatical comprehension difficulty due to nonfluent/agrammatic PPA.[110] Thus, language deficits in nonfluent/agrammatic PPA appear to be attributable, in part, to interruption of large-scale neural networks centered in left perisylvian regions that support language processing.

Nonfluent/agrammatic PPA is most often associated with forms of FTLD involving the accumulation of the microtubule-associated protein tau (FTLD-tau), as seen at autopsy.[10,12–14] Less commonly, AD pathology or FTLD-TDP can present with language features consistent with nonfluent/agrammatic PPA.[12] Nonfluent/agrammatic PPA with TDP-43 pathology may be associated with *GRN* mutations,[111–113] while *C9orf72* mutations are rarely associated with any form of PPA.[114]

Broca aphasia due to stroke is often associated with ischemia centered in the left inferior frontal lobe.[115,116] The ischemic area typically extends into more dorsal regions of the frontal lobe as well as the anterior superior temporal lobe and into the white matter deep in the frontal lobe. In addition to effortful, agrammatic speech, this type of lesion is also associated with impairment of grammatical comprehension.[117] Thus, considerable overlap exists between the progressive and stroke forms of nonfluent aphasia associated with left anterior perisylvian disease. The impairment of repetition found in Broca aphasia more often than nonfluent/agrammatic PPA has been attributed to ischemia that also involves the arcuate fasciculus. Smaller ischemic lesions restricted to the frontal operculum tend to manifest clinically as aphemia. This is a disorder of slowed speech expression but without the sound distortions found in apraxia of speech, and aphemia is associated with minimal comprehension difficulty.[116]

KEY POINTS

- Structural MRI studies emphasize gray matter atrophy in the inferior frontal region of the left hemisphere in nonfluent/agrammatic primary progressive aphasia.
- Sentence comprehension appears to be related to regional gray matter atrophy in left inferior and dorsolateral prefrontal regions in nonfluent/agrammatic primary progressive aphasia.
- Neurodegenerative disease, such as that found in nonfluent/agrammatic primary progressive aphasia, interrupts large-scale neural networks; this is emphasized by the disease found in white matter projections between the gray matter areas of the language network in nonfluent/agrammatic primary progressive aphasia.
- Nonfluent/agrammatic primary progressive aphasia is most often associated with forms of frontotemporal lobar degeneration involving the accumulation of the microtubule-associated protein tau, as seen at autopsy.
- Broca aphasia due to stroke is often associated with ischemia centered in the left inferior frontal lobe.

APHASIAS WITH MIXED FLUENCY

Aphasias with mixed fluency include logopenic variant PPA and conduction aphasia. These syndromes hold in common variable rates of speech fluency because speech rate depends on the content of speech.

Clinical Features

With the increased clinical recognition of PPA, it has become clear that many patients have a language disturbance that does not clearly fit into the category of either nonfluent/agrammatic PPA or semantic variant PPA. Patients with periods of slowed, hesitant speech due to prominent lexical retrieval difficulties in

conversational speech (ie, "logopenia") and phonologic loop disturbance were first described by Gorno-Tempini and colleagues.[45,118] Lexical retrieval difficulty is ubiquitous to some extent in all variants of PPA. However, the distinguishing feature of the logopenic variant of PPA appears to be the disturbance of the phonologic loop. The phonologic loop is a component of auditory-verbal short-term memory that contributes to the processing of verbally coded information, such as a lengthy sentence.[119] Thus, the hallmark of logopenic variant PPA is impaired repetition. The current clinical criteria for logopenic variant PPA include core elements of lexical retrieval difficulties in spontaneous speech and impaired repetition, with supportive features of phonologic paraphasic errors or speech-sound substitutions and the absence of motor speech and single-word/object comprehension difficulties.[17]

Some refer to logopenic variant PPA as "mixed," because many of these patients have some language features that can resemble both nonfluent/agrammatic PPA and semantic variant PPA.[120] Patients with logopenic variant PPA resemble patients with nonfluent/agrammatic PPA in that they may also have at times slowed, hesitant speech because of circumlocutions and lexical retrieval difficulties. However, the average quantitative rate of speech production is about 90 words per minute, or about twice the rate of nonfluent/agrammatic PPA.[26] Grammatical expression and comprehension can be limited for lengthy sentences because of the short-term memory deficit, although these patients tend to have better comprehension for shorter sentences and written material that does not depend on short-term memory.[25,118] Moreover, a relative absence of motor speech difficulties is seen in logopenic variant PPA as compared to nonfluent/agrammatic PPA.

Patients with logopenic variant PPA may also superficially resemble patients with semantic variant PPA because of some overlapping characteristics. The often-severe word-finding difficulty with circumlocutory speech in logopenic variant PPA may be difficult to distinguish from the single-word expression difficulties found in semantic variant PPA. Patients with logopenic variant PPA may also demonstrate some word comprehension difficulty similar to what is seen in semantic variant PPA. However, successful responses following prompts (eg, "it is used for cutting; it's a wood…") or gestures demonstrated by the patient with logopenic variant PPA during confrontation naming (eg, demonstrating a cutting motion for the use of a saw despite the inability to retrieve the word saw) distinguish these patients from patients with semantic variant PPA. Likewise, patients with logopenic variant PPA have preserved knowledge of objects.

Patients with conduction aphasia following stroke resemble those with logopenic variant PPA. The key feature of conduction aphasia is a profound repetition deficit.[121,122] Qualitative analysis of repetition errors reveals that some patients have grammatical errors in their repetition, while others may have limited repetition based solely on length. Patients with conduction aphasia may also have some word-finding difficulty, occasionally display circumlocutory speech, and have mild comprehension limitations for lengthy sentences. Patients with conduction aphasia also often display some ideomotor apraxia.

Anatomic Features

The phonologic loop, the component of auditory-verbal short-term memory responsible for the processing of verbally coded information, is often associated

with inferior parietal and superior temporal regions.[119] MRI studies show that patients with logopenic variant PPA have atrophy in the inferior parietal and superior temporal lobes.[45,123] Studies using in vivo PET imaging of amyloid pathology find a high rate of AD pathology in these patients.[124,125]

Since being introduced into modern clinical criteria for PPA, the diagnostic criteria for logopenic variant PPA have been examined in autopsy cohorts.[113,126] Published logopenic variant PPA diagnostic criteria are relatively specific for underlying AD pathology but are less sensitive since many patients with PPA with AD pathology do not meet criteria for logopenic variant PPA because of either the absence of the core clinical criterion of difficulty in repetition or the presence of additional motor speech or semantic features. Indeed, the current criteria for logopenic variant PPA are largely unreliable,[5,18,19] as lexical retrieval difficulty is common for all forms of PPA and other supporting features of logopenic variant PPA are largely based on the absence of core features of nonfluent/agrammatic PPA and semantic variant PPA rather than the presence of specific features of language. Furthermore, it has been challenging to implement an operational definition of impaired repetition using traditional measures. Phonologic loop impairment results in length-dependent repetition difficulty in which increasing difficulty is encountered with multisyllabic words or increased length of phrases.[118] Data from the authors' autopsy series associated AD pathology with reduced performance on a quantitative measure of phonologic loop functioning (forward digit span [ie, repeating a short list of numbers]), and this impairment was related to pathology in superior temporal and inferior parietal regions that are more commonly diseased in AD than in forms of FTLD.[111] Finally, some patients with PPA without prominent phonologic loop dysfunction instead display mixed features of single-word and object comprehension difficulties and expressive speech disturbance that are not classifiable.[113] The underlying neuropathology of these patients with mixed PPA is varied and includes AD, FTLD-tau, and FTLD-TDP.

Conduction aphasia following stroke, from the classic connectionist perspective, is associated with damage to the arcuate fasciculus, the white matter that carries projections between the inferior parietal and superior temporal region known as the Wernicke area and the inferior frontal region known as the Broca area.[122,127,128] This fiber bundle is thought to be crucial in the lateralization of language since it is much thicker in the left hemisphere than the right hemisphere.[129] However, others have argued instead that repetition deficits are due in part to a limitation in auditory-verbal short-term memory,[119,130] and this difficulty is associated with disease in the inferior parietal lobule.[131]

INTERVENTIONS

Traditional speech therapies are often recommended; these are symptomatic interventions. Some interventions involve attempts to improve the underlying speech and language difficulty. While few large-scale well-designed (ie, placebo-controlled) trials have been conducted, interventions involving traditional speech therapies do not appear to be very successful. Some smaller experimental studies targeting specific aspects of comprehension or expression have shown some success, but larger cohorts are needed to demonstrate reliable efficacy.

Another class of speech therapy involves training in alternate modes of communication. These focus on the underlying purpose (communicating a message to others) and are less concerned with oral speech production or aural

KEY POINTS

- The current clinical criteria for logopenic variant primary progressive aphasia include core elements of lexical retrieval difficulties in spontaneous speech and impaired repetition, with supportive features of phonologic paraphasic errors or speech-sound substitutions and the absence of motor speech difficulties and single-word/object comprehension difficulties.
- Patients with logopenic variant primary progressive aphasia resemble patients with nonfluent/agrammatic primary progressive aphasia in that they may also have slowed, hesitant speech because of circumlocutions and lexical retrieval difficulties that can superficially resemble nonfluent/agrammatic primary progressive aphasia. However, the quantitative rate of speech production is about 90 words per minute, or about twice the rate of nonfluent/agrammatic primary progressive aphasia.
- The often-severe word-finding difficulty with circumlocutory speech in logopenic variant primary progressive aphasia may be difficult to distinguish from the single-word expression difficulties found in semantic variant primary progressive aphasia.
- Patients with logopenic variant primary progressive aphasia have preserved knowledge of objects.
- The key feature of conduction aphasia is a profound repetition deficit.

KEY POINTS

- Patients with logopenic variant primary progressive aphasia have atrophy in the inferior parietal and posterior temporal lobes.
- Studies using in vivo positron emission tomography imaging of amyloid pathology find a high rate of Alzheimer disease pathology in patients with logopenic variant primary progressive aphasia.
- Logopenic variant primary progressive aphasia diagnostic criteria are relatively specific for underlying Alzheimer disease pathology but are less sensitive since many patients with primary progressive aphasia with Alzheimer disease pathology do not meet criteria for logopenic variant primary progressive aphasia because of either the absence of core clinical criteria of difficulty in repetition or the presence of additional motor speech or semantic features.
- Conduction aphasia following stroke, from the classic connectionist perspective, is associated with damage to the arcuate fasciculus, the white matter that carries projections between the inferior parietal and superior temporal region known as the Wernicke area and the inferior frontal region known as the Broca area.
- Distinctions between progressive and stroke forms of aphasia may be due, in part, to the anatomic locus of disease.

comprehension.[132] Examples of alternative communication modalities include the use of picture dictionaries and gestures instead of word use. Recently, speech therapies have been augmented by the use of transcranial direct current stimulation. While this remains highly experimental, some success has been achieved in single-blind, crossover trials.[133–138]

CONCLUSION

Progressive aphasia and stroke aphasia result in relatively discrete disorders of language. Both fluent and nonfluent forms of aphasia exist that are progressive or associated with an acute stroke. Semantic variant PPA is a fluent form of PPA that interferes with word meaning and object knowledge and thus also interferes with lexical retrieval. Wernicke aphasia, while a fluent form of aphasia, is largely limited to difficulty with comprehension and expression of content words; object knowledge is relatively preserved. Distinctions between progressive and stroke forms of fluent aphasia may be due, in part, to the anatomic locus of disease. The aphasia syndrome associated with semantic variant PPA is centered in anterior and ventral portions of the left temporal lobe, while Wernicke aphasia follows stroke to the posterior perisylvian regions of the left hemisphere.

The nonfluent forms of progressive and stroke aphasia tend to have more overlap in the locus of disease, and thus the syndromes associated with these nonfluent aphasias tend to be more similar. Nonfluent/agrammatic PPA compromises the ability to understand and express the grammatical characteristics of language. These are needed to link together the words composing a sentence. Without these structural features of a sentence, speech tends to be slow and effortful, and comprehension and expression of grammatically complex sentences is compromised. Apraxia of speech is more common in nonfluent/agrammatic PPA than in Broca aphasia.

Logopenic variant PPA is a syndrome of impaired phonologic loop functioning due to disease in the inferior parietal and posterior temporal lobes that accounts for some, but not all, patients with PPA who do not meet clinical criteria for semantic variant PPA or nonfluent/agrammatic PPA. Future work in prospectively assessed patients with antemortem biomarkers for molecular pathology and postmortem autopsy confirmation will improve diagnostic criteria for PPA to predict specific proteinopathies.

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