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Primary Progressive Aphasia and Apraxia of Speech

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Abstract

Primary progressive aphasia is a neurodegenerative syndrome characterized by progressive language dysfunction. The majority of primary progressive aphasia cases can be classified into three subtypes: non-fluent/agrammatic, semantic, and logopenic variants of primary progressive aphasia. Each variant presents with unique clinical features, and is associated with distinctive underlying pathology and neuroimaging findings. Unlike primary progressive aphasia, apraxia of speech is a disorder that involves inaccurate production of sounds secondary to impaired planning or programming of speech movements. Primary progressive apraxia of speech is a neurodegenerative form of apraxia of speech, and it should be distinguished from primary progressive aphasia given its discrete clinicopathological presentation. Recently, there have been substantial advances in our understanding of these speech and language disorders. Here, we review clinical, neuroimaging, and histopathological features of primary progressive aphasia and apraxia of speech. The distinctions among these disorders will be crucial since accurate diagnosis will be important from a prognostic and therapeutic standpoint.

Keywords

Dementia; Primary progressive aphasia; Apraxia of speech

1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative condition that predominantly affects language. Pick introduced cases of focal language impairments that presented as the first signs of neurodegenerative illnesses over a century ago.[1] However, the term PPA was coined by Mesulam in 1982 when he described six patients with slowly progressing aphasia without other cognitive or behavioral dysfunction.[2] The language deficits in these patients included non-fluent halting speech and anomia with intact comprehension.[2] In an effort to more clearly define and classify PPA, consensus diagnostic criteria for the disorder were proposed in 2011.[3] For the diagnosis of PPA, language impairments need to be the primary deficits in the first two years or more, and the disease must be progressive.[4] Once the initial diagnosis of PPA is made, patients often can be divided into one of three subtypes: non-fluent/agrammatic variant PPA (naPPA), semantic variant PPA (svPPA), and logopenic variant PPA (lvPPA).[3]

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Unlike aphasia, apraxia of speech (AOS) is a motor speech disorder. It involves impaired planning or programming of movements that prevents accurate production of sounds and syllables across words or within multisyllabic words.[5] AOS most often results from left hemisphere stroke, which is associated with static or improving symptoms over time.[6] However, AOS can be a sign of an insidiously progressive illness. When AOS presents as the only or predominant symptom of a neurodegenerative condition, it is termed primary progressive AOS (PPAOS).[7]

Primary progressive aphasia variants and PPAOS have distinguishable clinical features, and are associated with distinctive cortical atrophy patterns and underlying pathology. As we advance our knowledge, careful differentiation among these disorders will be important since accurate diagnosis will likely guide appropriate medical and behavioral therapeutic measures in the future. In this review, we will provide an overview of clinical, neuroimaging, and histopathological findings associated with PPA and PPAOS.

2. Clinical Features of PPA and PPAOS

The clinical features of PPA and PPAOS are summarized in Table 1. The first variant of PPA, naPPA, is characterized by slow effortful speech, grammatic or syntactic errors, reduced sentence complexity, and sound errors.[3] Individuals with naPPA may simplify grammatical forms with short phrases and decreased use of passive sentences (e.g., a cat was chased by a dog). They may omit grammatical morphemes (e.g., the, a/an, -ed, un-, re-, and, of), use inappropriate inflections, or arrange words in a grammatically incorrect order. The average rate of speech produced by patients with naPPA is about 45 words per minute in comparison to 140 words per minute generated by healthy individuals.[8] The effortful speech observed in naPPA is thought to reflect effects of grammatical errors and apraxia of speech (AOS).[9–11]

Speech of individuals with AOS is characterized by slow speaking rate, distorted articulation, sound substitutions, articulatory groping, false starts and restarts, segmentation of syllables, and increased difficulty with increasing utterance length.[5] Progressive AOS is present in the majority of individuals with naPPA.[12, 13] In fact, the 2011 PPA consensus criteria define AOS as a core feature of naPPA.[3] However, recent studies suggest that progressive AOS may occur in the absence ofaphasia.[5, 13–15] When that is the case, AOS should be considered a primary neurodegenerative disorder (i.e., PPAOS), one distinct from naPPA.

The hallmark of svPPA is progressive difficulty with naming and single word comprehension, especially for low-frequency words.[3] Impairments in lexical retrieval are thought to be attributable to increased use of closed class words (e.g., a/an, the, you, she, them, of, in) and high frequency nouns.[16] Individuals with svPPA may also develop surface dyslexia and/or dysgraphia for irregularly spelled words (e.g., yacht, comb, ache) with relatively spared ability to read and write non-real words. Unlike patients with naPPA, these individuals have fluent speech with normal rate and exhibit minimal speech or syntactic errors.[3] AOS is not a feature of svPPA.

lvPPA is the most recently described PPA subtype.[11] It is characterized by hesitant speech, sentence repetition deficits, and word-finding difficulty with preserved grammar and motor speech.[3] The rate of speech in lvPPA falls between naPPA and svPPA.[16] Phonological paraphasias are common.[17] Although both naPPA and lvPPA involve difficulty with repetition, the deficit in lvPPA is most often attributable to phonological short-term memory loss resulting in impaired storage of incoming verbal information or phonological planning deficits, rather than motor speech errors or agrammatism.[17] Impaired phonological memory also contributes to frequent word-finding pauses that result from errors in phonological retrieval. In comparison to svPPA, lexical retrieval deficits are less common in lvPPA.[16] Single word comprehension is relatively intact in individuals with lvPPA.

Because PPA predominantly presents as a language disorder, affected individuals often maintain their functional status relatively well. However, recent studies demonstrate that patients with PPA can develop impairments in other cognitive domains. Individuals with naPPA may develop working memory and executive control deficits.[9] lvPPA can be accompanied by relatively rapid global cognitive deterioration. Memory, attention, orientation, and visuospatial functions can be compromised in lvPPA.[18] In comparison to lvPPA, patients with svPPA show relatively preserved cognitive function with the exception of verbally mediated measures.[18] However, individuals with svPPA can exhibit early behavioral changes, such as compulsions and loss of empathy.[3, 19]

3. Pathological Features of PPA and PPAOS

Primary progressive aphasia and PPAOS display distinctive pathological associations with some overlapping features (Table 2). naPPA is predominantly associated with tau pathology when AOS is present.[14, 20, 21] Similarly, PPAOS is also related to tauopathy.[14, 22] Therefore, it is not surprising that naPPA and PPAOS sometimes share clinical features of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), which are tauopathies.[14, 23] However, tar-DNA binding protein 43 (TDP-43) or Alzheimer's disease pathology has been reported by some groups as the underlying histopathology in naPPA.[23–27] svPPA is predominantly associated with TDP-43, but some studies have reported that tau and AD related pathological changes can occur.[20, 24, 28,29] lvPPA is most commonly associated with Alzheimer's disease (AD) pathology.[21, 30,31] Recent studies demonstrate that cortical β-amyloid deposition, a key feature of AD, is also seen in lvPPA.[31–33] Amyloid deposition in lvPPA is similar to the pattern observed in AD.[33] In addition, a high CSF tau/Aβ ratio is seen in this subtype.[30] Interestingly, microhemorrhage that is typically observed in AD is also seen in lvPPA.[34] In addition, neurofibrillary tangles (NFT), an important pathological feature of AD, are also present in lvPPA. In comparison to AD, pathological samples of lvPPA display significantly increased NFT density in the left temporoparietal region, which is the area mostly affected in this subtype.[35] Despite the strong association with AD pathology, some cases of lvPPA have been reported with tau or TDP-43 pathology.[21, 27]

4. Neuroimaging Findings of PPA and PPAOS

Advanced imaging techniques have been useful for identifying the brain regions that are affected by PPA and PPAOS (Table 2). MRI of naPPA patients demonstrates atrophy in the

left inferior frontal regions, including the frontal operculum and the anterior insula.[11, 14, 36] The structural abnormalities may also extend to involve the left prefrontal and superior temporal lobes.[10, 37] Reduced fluency is associated with damage to regions dorsal to Broca's area, and grammatical errors are associated with damage to the inferior frontal and supramarginal gyri in naPPA.[16, 38] These associations are supported by FDG-PET findings that show hypometabolism in the posterior fronto-insular region as well as the superior temporal lobe (Figure 1).[15, 39]

Interestingly, PPAOS displays unique cortical involvement that is different from the areas affected by naPPA with damage in the superior lateral premotor and supplementary motor areas in the left hemisphere (Figure 1).[7, 14] In a recent FDG-PET study, Whitwell and colleagues demonstrated that hypometabolism in the left lateral superior premotor cortex was strongly associated with AOS rating scale performance in patients with PPAOS.[40] However, Western Aphasia Battery (WAB)[41], a global measure of aphasia severity, and Token Test [42], a measure of grammatic/syntactic comprehension, were correlated with hypometabolism in the areas that were previously shown to be affected by naPPA, such as the left inferior triangularis, pars opercularis, middle frontal gyrus, superior temporal gyrus and inferior parietal lobe. The unique regions of FDG hypometabolism in PPAOS may enable anatomic differentiation of PPAOS from naPPA.

In svPPA, the most prominent MRI and PET abnormalities are seen in the bilateral temporal lobes, although there is evidence of asymmetric involvement favoring the left (Figure 1).[11, 31, 43] Disruptions in semantic processing in svPPA are correlated with the anterior temporal pole atrophy, whereas lexical retrieval errors are associated with the anterior and inferior temporal atrophy.[16] As the disease progresses, the damage extends along the middle and inferior temporal gyri without involving Wernicke's area.[43]

Structural and functional abnormalities in lvPPA are concentrated in the left temporoparietal junction involving the posterior superior temporal, medial temporal, and inferior parietal regions as well as the posterior cingulate (Figure 1).[44–46] Impaired phonological memory in lvPPA is linked to the left posterior temporoparietal atrophy.[17, 38] lvPPA shows increased atrophy and decreased hypometabolism in the left inferior, middle, and superior lateral temporal regions in comparison to AD, which is consistent with the asymmetrical pathologic involvement observed in a previous study.[35, 44]

As PPA advances, the clinical features that differentiate one PPA subtype from another become less distinct. Despite the presence of asymmetrical involvement of the brain, anatomical progression resulting in wider areas of cortical atrophy becomes noticeable in advanced stages of the disease. Furthermore, the progressing patterns of atrophy become more closely related to specific language functions, rather than the individual PPA subtypes. A recent study by Rogalski and colleagues demonstrates significant clinical and pathological progression in PPA patients over a 2-year period.[47] In these subjects, unique clinico-anatomical features of each subtype became less distinctive with disease progression. Cortical involvement extended beyond the initial areas of atrophy to include all major language networks, such as the inferior frontal, temporoparietal, and lateral temporal regions. Impairments in naming and single-word comprehension were noted in individuals

with lvPPA because of the new involvement of the lateral and anterior frontotemporal lobe as well as worsening of the preexisting atrophy in the left temporoparietal region. Similarly, the spread of cortical atrophy to the inferior frontal gyrus lead to the development of impaired grammatical processing in svPPA.[47]

5. Genetics of PPA and PPAOS

Although most cases of PPA and PPAOS are sporadic, familial forms of the disorders exist. The degree of heritability varies among the PPA subtypes. About 35% of naPPA cases are hereditary, and 7% of them are inherited in an autosomal dominant fashion.[48] On the other hand, 17% of svPPA cases are familial with 2% being autosomal dominant.[48] PPAOS has not been reported to be familial.[7, 13] Several genetic mutations have been linked to familial cases of PPA. Microtubule associated protein tau (MAPT) on chromosome 17q21.32 is associated with tau pathology.[49] Progranulin (PGRN) on chromosome 17q21.31 and chromosome 9 open reading frame 72 (C9ORF72) on chromosome 9p21.2 are associated with TDP-43 pathology.[24, 50–53] APOE ε4 haplotype, which is linked to AD pathology, is also associated with these disorders.[11] In familial cases, language and speech deficits may lack specific characteristics of PPA subtypes.[50] Heterogeneity in phenotypes may exist within the same family, as well.[54]

6. Management

The management of PPA and PPAOS is primarily symptomatic at this time, and typically provided by speech-language pathologists. It is generally accepted that established behavioral strategies for managing aphasia and AOS due to stroke are applicable to neurodegenerative etiologies when general criteria are met for recommending therapy,[55] and there are an accumulating number of single case reports suggesting that focused treatment may maintain or improve word retrieval and speech production or improve communication using alternative strategies (e.g., text-to-speech device) in well-selected individuals with PPA or progressive AOS [56–58]. Counseling about the nature of the communication difficulties and their likely course, the capacity to work and work accommodations, and the need for and possible benefits to be derived from formal therapy are essential. Management efforts that focus on compensatory strategies, including augmentative and alternative communication, are often best staged with periodic reassessment and updated recommendations about methods to facilitate communication during everyday activities. Support groups and dedicated web sites (www.ppaconnection.org; www.aphasia.org) that serve as a registry and/or information resources can be very beneficial.

7. Conclusion and Future Directions

Primary progressive aphasia and PPAOS are neurodegenerative disorders that have predominant effects on language and speech. Recently, significant advances have been made in our understanding of these illnesses, permitting identification of their unique clinical, histopathological, and neuroimaging characteristics. Recognizing these features is an essential first step towards early detection and diagnosis as well as therapeutic interventions. Further refinement of the clinical diagnostic criteria may help minimize diagnostic uncertainty. Longitudinal studies that include molecular and pathological approaches will be

also be informative for identifying biomarkers that may be targeted by disease-modifying agents in the future.

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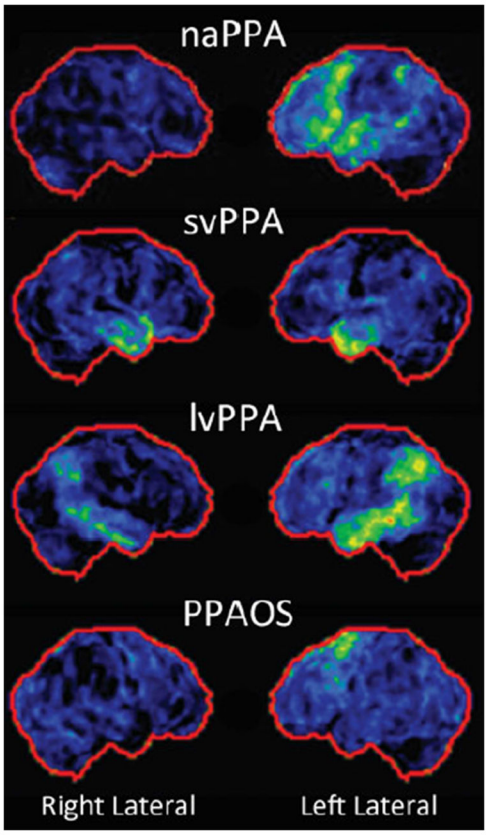

Figure 1.

Fluorodeoxyglucose positron emission tomography demonstrates hypometabolism in the left posterior frontoinsular region in the nonfluent/agrammatic variant of primary progressive aphasia, bilateral anterior temporal regions in the semantic variant of primary progressive aphasia, left temporoparietal region in the logopenic variant of primary progressive aphasia, and premotor/supplementary motor areas in primary progressive apraxia of speech.

Table 1

Clinical characteristics of PPA and PPAOS

		naPPA	svPPA	lvPPA	PPAOS
Clinical features	Agrammatism	+	−	−	−
	Apraxia of speech	+	−	−	+
	Impaired comprehension	+ (syntactically complex sentences)	+ (single words)	+/−	−
	Impaired naming	−	+	+/−	−
	Impaired object knowledge	−	+	−	−
	Paraphasia	+	+/−	+	−
	Speech rate	Significantly reduced	Normal	Moderately reduced	Significantly reduced
	Impaired repetition	+ (single words)	−	+ (sentences and phrases)	+ (single words)
	Other		Surface dyslexia or dysgraphia		

Abbreviations: naPPA=non-fluent/agrammatic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; lvPPA = logopenic variant of primary progressive aphasia; PPAOS = primary progressive apraxia of speech

Table 2

Pathological and anatomical correlations of PPA and PPAOS

	naPPA	svPPA	lvPPA	PPAOS
Pathology	Tau (52%) AD (25%) TDP-43 (19%)	TDP-43 (69%) AD (25%) Tau (6%)	AD (50%) TDP-43 (38%) Tau (12%)	Tau (100%)
Cortical atrophy or hypometabolism	Left posterior fronto-insular	Anterior temporal	Left temporo-parietal	Superior premotor, supplementary motor

Abbreviations: naPPA=non-fluent/agrammatic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; lvPPA = logopenic variant of primary progressive aphasia; PPAOS = primary progressive apraxia of speech; AD = Alzheimer's disease; TDP-43 =tar-DNA binding protein 43