Research advances in neuroimaging and genetic characteristics of the non-fluent/agrammatic variant of primary progressive aphasia

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Primary progressive aphasia (PPA), which typically refers to a neurodegenerative disease, such as frontotemporal lobar degeneration (FTLD) or Alzheimer disease (AD), is characterized by gradual loss of the brain systems that govern language, with relative sparing of other cognitive domains.[1] Based on specific speech and language features, clinical consensus criteria published in 2011 for the classification of the PPAs divided them into three subtypes: the semantic variant (svPPA), the non-fluent/agrammatic variant (naPPA), and the logopenic variant (lvPPA) [Supplementary Table 1; http://links.lww.com/CM9/A522]. The naPPA or "progressive non-fluent aphasia", as a form of progressive language disorder that is different from the other subtypes, was first described in 1996 by Grossman *et al*.[2] The major clinical characteristic of naPPA is effortful, non-fluent speech. Patients with naPPA present with agrammatism and/or apraxia of speech (AOS), resulting in articulatory errors and loss of prosody.[3]

According to the classification published in 2011 by a diverse International Consensus Group, significant progress has been made in the understanding of naPPA. This review brings together new improvements in neuroanatomical imaging and the genetic associations of naPPA and summarizes diagnoses and treatments based on them.

Although naPPA is defined by its clinical characteristics, morphometric assessment of cortical atrophy with structural imaging is currently necessary for *in vivo* localization of neurodegeneration in naPPA, which is the most commonly used method to establish clinicoanatomical correlations. Since most patients have left hemisphere language dominance, left posterior fronto-insular, and subcortical atrophy constitutes the unique anatomical pattern of neuronal loss in naPPA.[4] However, a few cases reports have noted that naPPA patients with right hemisphere language dominance were associated with asymmetrical right hemisphere degeneration.[5] Collectively, the anatomical patterns of atrophy observed in PPA encompass the language network of the brain. These neuroanatomical abnormalities are also associated with the speech and language features observed in naPPA subjects.

Several imaging techniques have been used to help specify the anatomic distribution in naPPA. Through structural magnetic resonance imaging (MRI), cortical atrophy in naPPA can be observed predominantly in the left frontal lobe hemisphere with an anterior perisylvian distribution, involving inferior, opercular, and insular regions.[4] As the disease progresses, atrophy extends from its initial locations to neighboring regions, including the left dorsolateral prefrontal cortex and left anterior temporal lobe, after which it extends medially to the orbital and anterior cingulate regions and spreads posteriorly along the Sylvian fissure into the parietal cortex.[6] In the early stages of PPA, cortical atrophy might be less prominent, and morphometric assessment might therefore be less sensitive at the individual level. Functional imaging could provide an alternative method for localizing dysfunction in such cases. Diffusion tensor imaging demonstrates reduced fractional anisotropy reflecting longitudinal patterns of white matter limited to the bilateral frontal lobes in naPPA. Research showed that semiquantitative analyses of

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) images could help to distinguish naPPA from other subtypes of PPA variants. FDG-PET statistical parametric mapping could also predict clinical progression of neurodegeneration in language networks even before the clinical appearance of key symptoms.[7] For example, hypometabolism in the parietal lobe and brainstem structures, which is evident in some naPPA cases, predicts conversion to corticobasal degeneration syndrome (CBD) and progressive supranuclear palsy (PSP).

An increasing amount of work has demonstrated that widespread neurodegeneration throughout regions of the language network, especially in the left hemisphere, contributed to the language deficit evident in naPPA.[4] The extent of reduced speech fluency is related to degeneration of frontal, parietal and superior temporal regions within the language network. Interruption of the ventral stream within this perisylvian language system might be associated with lexical processing deficits in naPPA. In addition, connectivity in the dorsal stream appears to play an important role in the complex syntactic disorders of naPPA.[3] The impaired grammatical comprehension in naPPA has been found to be associated with atrophy of the left inferior frontal cortex and anterior superior temporal regions. Word comprehension difficulties are associated with damage to the inferior temporal gyrus, the fusiform gyrus, and the white matter network, including the left temporal region and cingulate cortex.[8]

The clinical syndrome of naPPA is correlated with different neuropathologic diagnoses at autopsy. In naPPA, 50% to 70% of patients are pathologically diagnosed with FTLD with tau-positive pathology (FTLD-tau), consistent with CBD, PSP, or Pick disease.[9] Approximately 20% of naPPA cases stem from FTLD with 43-kDa TAR DNA-binding protein (TDP-43) pathology (FTLD-TDP), usually of type A, and 12% to 25% are due to AD. Very few cases exhibit dementia with Lewy bodies, dementia lacking a distinct pathology, or dementia with a mixed pathology.[1] Each of these genetic mutations is associated with a specific histopathological abnormality of naPPA. Inferior frontal and superior temporal atrophy was observed in naPPA with tau-positive disease.[7] Parietal cortical atrophy on MRI and reduced functioning in the parietal cortex upon FDG-PET were observed in naPPA patients with AD pathology.[10]

Approximately 40% of FTLD cases are caused by abnormal accumulation of the microtubule-binding protein tau (FTLD-tau). It is associated with a mutation of the microtubule-associated protein tau (MAPT) gene on chromosome 17.[9] Tau, localized to neuronal axons, regulates the stability of microtubules by promoting tubulin polymerization, and it is a major component of axonal transport.[11] The binding of tau to microtubules is regulated by the phosphorylation/dephosphorylation equilibrium of tau. In the human brain, alternative mRNA splicing of the microtubule-associated protein tau gene produces six tau isoforms, each of which exhibits either three or four repeat domains in the C-terminal part (3R and 4R tau).[11,12] Three microtubule repeats (3R) is associated with Pick disease, while the presence of four microtubule repeats (4R) is associated with PSP and CBD. 3R and 4R tauopathies are also strongly associated with naPPA. A recent study showed that, compared with healthy controls, naPPA-4R-tau patients exhibited gray matter atrophy in the left frontal lobe, precentral gyrus, supplementary motor area, insula, and putamen.[13] In addition, naPPA-4R-tau patients in this study also showed board frontal white matter atrophy, including the left superior longitudinal fasciculus, the callosum, and the bilateral anterior corona radiata.

More than 50% of FTLD cases are tau negative and characterized by abnormal accumulation of the TDP-43. The TAR DNA-binding protein is normally located in the nucleus and is functionally implicated in exon skipping and transcriptional regulation. There are four subtypes of TDP-43 pathology, known as types A, B, C, and D, and each of these subtypes correlates with different FTLD syndromes. Patients with progranulin (GRN) gene mutations exhibit type A, although both the behavioral variant of fronto-temporal dementia and naPPA can occur even without GRN mutations.[12] Most naPPA-3R-tau patients on neuroimaging analysis show gray matter atrophy found in the insula, frontal lobe, the precentral gyrus, and bilateral orbitofrontal cortex. White matter atrophy involves bilaterally the superior longitudinal fasciculus and anterior corona radiata, but with prevalence in the left hemisphere.[13] Neuroimaging data from a naPPA patient with FTLD-TDP-A pathology showed selective gray matter atrophy involving the left inferior frontal gyrus pars opercularis, precentral gyrus, insula, and inferior parietal lobule.[14]

The broad clinical and pathological overlap of naPPA with other disorders has been increasingly recognized. Through next-generation sequencing techniques and novel bioinformatics approaches, additional disease genes and risk genes are likely to be identified in the near future.

Based on the genetics of naPPA, an increasing number of studies are focusing on biological methods to improve clinical identification and to monitor etiology-specific treatments. Many studies have validated cerebrospinal fluid (CSF) neurofilament light chain (NfL) protein as a promising biomarker for disease severity and outcomes in patients with FTLD spectrum.[15] Higher blood NfL levels help to distinguish naPPA from lvPPA. Some research has supported that higher CSF and serum NfL levels are associated with TDP-43 pathology. Longitudinal analysis showed that, along with naPPA patients appearing to undergo a broad-based decline in clinical performance and progress of cortical atrophy, their serum NfL increased more over time as well.[16] Research into CSF biomarkers indicated that, in PPA patients with a non-AD pathology, two different clusters could be confirmed according to the phosphorylated tau (tauP)-181/total tau protein (tauT) ratio, possibly consistent with the tau and TDP-43 pathologies.[17] Another study showed that amyloid-beta42, tauT, and tauP in CSF could simply and reliably detect aphasia due to an underlying AD pathology.[18]

Currently, no medical treatments have been proved to improve or stabilize language deficits in naPPA. Advances in the understanding of the molecular pathology of naPPA

significantly impact new therapeutic interventions. The complex pathological mechanisms of naPPA render molecular research more difficult. Conversely, because of the low prevalence of naPPA, multicentric collaborations are essential, and large-scale screening techniques, such as genomics and proteomics, should be stimulated with the aim of discovering new biomarkers for precision medicine.

naPPA is a progressive dementia syndrome with slow and effortful speech, including agrammatism and motor speech deficits. Anatomically, degeneration of the language functions in naPPA is associated with atrophy and hypometabolism in regions of the language network and its connections to white matter tracts. Neuropathologically, naPPA is most commonly caused by a variant of FTLD, usually either FTLD-TDP or FTLD-tau, and an atypical form of AD. Based on advances in genetic research, the biomarkers NfL and tau are the most promising ones for the diagnosis of naPPA. Further studies of the neuropsychological characterization, imaging markers, and pathologic basis of naPPA are needed to improve understanding and facilitate the adequate diagnosis and treatment of this disease.

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Conflicts of interest

None.

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