Dementia and Aphasia—AD, FTD & aphasia

Shunichiro Shinagawa, Bruce L. Miller

Key words: Alzheimer’s disease, frontotemporal dementia, primary progressive aphasia

Alzheimer’s disease (AD) and frontotemporal dementia (FTD) are two different types of neurodegenerative dementia, which can cause aphasic symptoms. Problems in memory, visuospatial are the predominant symptoms in AD, while behavioral and language manifestations are core features in FTD. There have been many changes in the concept and history of primary progressive aphasia (PPA), recent studies have divided the syndromes into three subtypes based on type of aphasia, distribution of atrophy, and underlying histopathology: (i) nonfluent variant PPA; (ii) semantic variant PPA; and (iii) the logopenic variant of PPA. Relationship between neurodegenerative dementia and PPA provides us a unique window into brain–behavior relations.

(1) Alzheimer’s disease and frontotemporal dementia

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by accumulation of amyloid plaques, neurofibrillary tangles, and neuronal loss especially in posterior brain regions. AD is the most common causes of dementia in adults over 65 years old; problems in memory, visuospatial navigation, reading and writing are the predominant symptoms. In contrast, frontotemporal dementia (FTD) is one of the most common forms of dementia in adults younger than 65 years, with frontal and anterior temporal lobe predominant neurodegeneration due to several pathologies. Unique behavioral and language manifestations are core features of FTD, which can be divided into several clinical subtypes based on the early and predominant symptoms. Patients have relatively preserved memory, which is different from AD.

(2) History of classification for aphasic syndrome due to neurodegenerative disease

Arnold Pick first described the relationship between aphasia and dementia in clinical and anatomical paper more than 100 years ago. He described the presentation of focal language deterioration as a sign of a dementia and helped to introduce the concept of a neurodegenerative disease beginning focally: “Simple progressive brain atrophy can lead to symptoms of local disturbance through local accentuation of the diffuse process.” Sadly, these conditions did not attract much researcher interest until recently. The revival of interest in these syndromes was indicated by a series of seminal papers by Brun and Gustafson, and Mesulam’s description of slowly progressive aphasia in 1982; the syndrome with progressive aphasias without dementia in their early stage. The term
subsequently renamed as Primary progressive aphasia (PPA) in 1987. PPA is an impairment of language comprehension and expression without peripheral sensory and motor deficits. The language impairment must be insidiously progressive in nature to rule out non–neurodegenerative causes such as stroke or head trauma. The language disorder must be the primary deficit for about 2 years or more.

On the other hand, the selective degeneration of the frontal and temporal regions, which can be related with behavioral and aphasic symptoms, gives rise to the term FTD. First, FTD divided into three subtypes by Neary et al. based on the early and predominant symptoms in 1998: behavioral variant FTD (bvFTD); semantic dementia (SD), and progressive nonfluent aphasia (PNFA). Patients with bvFTD present with marked changes in personality and behavior such as disinhibition, apathy, loss of empathy, compulsive behaviors, hyperorality. SD is characterized by a fluent anomic aphasia and behavioral changes. Patients with PNFA present slow, effortful speech, impaired production and comprehension of grammar.

For almost 2 decades, cases of PPA were generally categorized as SD or PNFA within FTD spectrum. However, recent clinico–pathological researches revealed that there are many clinical subtypes in pathological proven AD cases, and FTD has many heterogeneous pathological backgrounds such as tau pathology, TDP–43 (TAR DNA–binding protein 43) pathology, and FUS pathology. Moreover, there are some patients with progressive language impairment who do not fit into the SD and PNFA of FTD spectrum: a third, more recently defined subtype of primary progressive aphasia called as logopenic progressive aphasia (LPA). Patients with LPA have impaired word–finding with hesitant speech and impaired repetition.

Consequently, recent studies of PPA have divided the syndromes into three subtypes: (i) nonfluent variant PPA (nfvPPA), used to known as PNFA; (ii) semantic variant PPA (svPPA), a used to known as SD; and (iii) the logopenic variant of PPA (LvPPA) used to known as LPA.

(3) Three subtypes of PPA

These three subtypes are associated with different localizations of cortical atrophy and with differences in pathological background. Figure 1 shows Characteristic patterns of atrophy in the three variants of PPA. Voxel–based morphometry was used to identify regions where each variant showed volume loss relative to controls (p < 0.05, corrected for multiple comparisons). Table 1 shows clinical features, region of cortical atrophy, and most common underlying pathology of three variant of PPA.

(3-1) non–fluent variant Primary Progressive Aphasia

nfvPPA is a progressive disorder of language expression and motor speech. Anatomically, it is associated with atrophy, hypometabolism and hypoperfusion of the left perisylvian area: frontal operculum, premotor and supplementary motor areas and anterior insula. Patients present with slow, effortful speech, impaired production and comprehension of grammar, and motor speech deficits. Apraxia of speech, defined as difficulty initiating speech, a slow rate of speech or incorrect sequencing or omission of phonemes, is highly characteristic of nfvPPA, while dysarthria is more variably present. Comprehension is spared for single words and for all except the complex syntactic structures. Reading is non–fluent and effortful, while writing is agrammatic and features phonemic paraphasias.

In addition to the aphasia, neuropsychological tests
may show mild deficits in executive function, with relatively spared episodic memory and visuospatial function. Behavioral disturbances are less frequent and severe than in bvFTD and svPPA, reflecting less damage in the orbitofrontal areas and the right hemisphere in general. Pathologically, nfvPPA is usually associated with a tauopathy but occasionally other pathologies.

(3-2) semantic variant Primary Progressive Aphasia

svPPA is characterized by a fluent, anomic aphasia and behavioral changes with remarkable, often asymmetric degeneration of the anterior temporal lobes. Patients with primarily left-sided predominant atrophy present initially with progressive loss of word knowledge and meaning about words, objects and concepts; so called ‘semantic’ knowledge. This is obvious as a fluent aphasia with poor speech content and semantic paraphasic errors, but intact syntax, prosody and motor speech, which may not be meaningful. When the disease disproportionately involves the right temporal lobe, deficits in knowledge of facial emotion, diminished recognition of familiar faces and deficits in empathy for others predominant the clinical syndrome.

Anomia is the most common symptom. The inability to name an object is matched by the patient’s inability to give a detailed description of the object. In addition, patients with svPPA have a multimodal agnosia and are unable to recognize word meanings via written, auditory, olfactory and visual modalities. Patients with svPPA present a surface dyslexia while

| Table 1. Clinical features, distribution of atrophy and underlying pathology of three variant of primary progressive aphasia |
| clinical features | region of cortical atrophy | most common underlying pathology |
| semantic variant PPA | Poor confrontation naming Impaired single-word comprehension | Anterior and ventral temporal lobe | FTLD-TDP |
| non-fluent variant PPA | Effortful speech with speech sound errors Grammatical errors in language production | Left inferior frontal and insula | FTLD-tau |
| logopenic variant PPA | Impaired single-word retrieval Impaired repetition of phrases and sentences | Left posterior temporal and inferior parietal | AD |

PPA: primary progressive aphasia
AD: Alzheimer’s disease
FTLD-tau: frontotemporal lobar degeneration with tau-positive pathology
FTLD-TDP: frontotemporal lobar degeneration with TDP43-positive pathology
reading; a condition in which the patient has difficulty reading words with irregular pronunciations, for example, yacht is pronounced “ya-ch”. These language symptoms are known more generally as “Gogi (word–meaning) aphasia” in Japan. Two systems of letters were used in writing Japanese, Kana (phonogram) and Kanji (phonogram). svPPA patients is not impaired at reading of Kana because of its invariant relationship between orthography and phonology. By contrast, reading of Kanji is impaired in a graded fashion depending on the consistency characteristics of the Kanji target words, with worst performance on words whose component characters take atypical pronunciations, especially if the words are of lower frequency.\(^\text{[4]}\)

Conversely, episodic memory (particularly visual memory), and visuospatial abilities are relatively preserved in general. Most patients with svPPA have non–tau pathology, most of these cases have TDP–43 pathology.

(3-3) logopenic variant Primary Progressive Aphasia

Word retrieval in spontaneous speech and sentence repetition deficits are the core features of the lvPPA. Spontaneous speech is characterized by slow rate, with frequent pauses due to significant word–finding problems. Other diagnostic features include phonologic paraphasias in spontaneous speech and naming. However, there is no apraxia of speech or agrammatism. Speech production deficits are therefore distinct from those of patients with the nfvPPA. Also, a useful differentiating feature between these 2 variants is also the relative sparing of single–word comprehension in logopenic patients. Consistent with the hypothesis that a phonologic short–term memory deficit is a key cognitive mechanism underlying most language deficits in the logopenic variant, sentence and phrase repetition is characteristically impaired, while reproduction of short, single words can be spared. This same mechanism can cause impairment in sentence comprehension, which is influenced more by length and probability of a sentence than by its grammatical complexity.

Imaging abnormalities in the left temporoparietal junction area, left posterior superior temporal, posterior temporal, supramarginal, and angular gyri, are necessary to make a diagnosis of imaging–supported logopenic variant. Recent evidence shows that AD might be the most common underlying pathology of lvPPA groups, therefore lvPPA was thought to be a clinical subtypes of AD.

(4) Conclusion

Recent detailed study of PPA has resulted in more complex correlations with underlying pathology of these syndromes. Only detailed information about present history and attentive examination of the neurobehavioral, cognitive and language features, supported by patterns of regional atrophy on structural imaging can lead us to the correct syndromic diagnosis. We need further researches on pathology, biomarkers, genetic mutation analysis, and amyloid ligand PET studies in order to understand the biological background of aphasic syndrome. These techniques may provide earlier diagnosis and biological therapy of these patients. Relationship between neurodegenerative dementia and PPA provides us a unique window into brain–behavior relations.

References

3) Pick A. (1892) Über die Beziehungen der senilen Hirnatrophie zur Aphasie. Prager Med Wochenschr 10,