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Primary Progressive Aphasia

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The existence of progressive aphasias has been known for more than 100 years. Pick, Sérieux, Dejerine, Franceschi, and Rosenfeld were among the first to report such patients.[1-5] The current resurgence of interest in this condition can be traced to a 1982 report of six patients and to the subsequent delineation of the primary progressive aphasia (PPA) syndrome.[6-8] The diagnosis of primary progressive aphasia (PPA) is made in any patient who displays an indolently progressive language disorder that remains relatively isolated in the initial stages of the disease. Hundreds of PPA cases have been reported and a sizable research literature on this topic has appeared.[9-16] However, the presence of ancillary aphasic features in many dementing diseases, and the existence of partially overlapping terms such as progressive nonfluent aphasia (PNFA) and semantic dementia (SD), have made the diagnosis appear more complicated than it needs to be.

Acquired language disorders are known as aphasias. Aphasias can be classified as being agrammatic, semantic, or anomic, depending on the specific aspect of language that is most severely affected. Progressive aphasias are not rare in neurological practice. Many patients with Alzheimer's disease (AD)* eventually develop an aphasia. Aphasia can also arise in the course of motor neuron disease (MND), corticobasal degenerations (CBD), frontotemporal dementia (FTD)**, and dementia associated with the posterior cortical atrophy (PCA) of Benson et al.[19] While all of these patients can be said to have progressive aphasias, the language impairment is not qualified as primary, either because it is of secondary importance in comparison to other more salient deficits or because it is a late manifestation of the disease.

In a unique group of patients, a slowly progressive aphasia arises in relative isolation, becomes the principal cause of restrictions in daily living activities, and remains the most salient aspect of the clinical picture for several years. This does not mean that all other cognitive and behavioral domains are intact, but that they are less severely impaired than language. Such patients are said to have a primary progressive aphasia or PPA. In contrast to the clinical syndrome of probable Alzheimer's disease (PRAD), which designates a memory-based (amnestic) dementia, or frontotemporal dementia (FTD), which designates a behavior-based (comportmental) dementia, PPA designates a language-based (aphasic) dementia.

* We will use the term AD to denote neuropathologically confirmed disease, and the term probable AD (PRAD) to denote the clinical diagnosis of neuropathologically unconfirmed AD during the lifetime of the patient.

** We will use the FTD designation according to the criteria of Neary et al. 17 to indicate a non-amnestic dementia characterized by behavioral and executive dysfunction whereas he term FTLD will be used to denote a neuropathological picture dominated by one or more of the following: focal neuronal loss with gliosis and superficial spongiosis, Pick bodies, neuronal and/or glial tau inclusions such as those seen in PSP and CBD, and tau-negative ubiquitin inclusions 18.

In a recently reported family, 3 of 4 siblings had a typical form of PPA, although none of the 12 members of the parental generation were affected.[20] Neuropathological examination in one of the affected siblings showed the findings of FTLD without concommitant AD neuropathology; while tau genotyping in another affected sibling showed none of the known mutations associated with autosomal dominant FTLD. This family supports the contention that PPA represents a coherent disease entity rather than the chance localization of a non-specific degenerative process within the language network. Such chance localization would be difficult to arise by coincidence in 3 of 4 siblings. However, this family also shows that the molecular relationship of PPA to other forms of FTLD may be more complex than heretofore surmised and that the role of environmental factors in pathogenesis cannot be excluded.

The designation of PPA makes no assumption about the presence of unitary neuropathology. It leaves open the possibility that the common denominator is not necessarily the nature of the molecular/cellular process but the a selective vulnerability of the language network. Such selective vulnerabilities may have genetic or developmental origins. For example, we reported that learning disabilities, including dyslexia, were overrepresented in patients with PPA and their first degree relatives when compared to controls and AD patients.[8] Upon questioning, other patients we have seen have reported prominent spelling problems during school years, but not necessarily at a level of severity that warranted a diagnosis of learning disability. Furthermore, two patients with PPA onset in their 60s were found to have left hemi-craniosynostosis, a mild developmental abnormality that interferes with the normal growth of the underlying cortex. In these two patients, the left hemisphere hypoplasia was functionally compensated throughout most adulthood but appears to have provided the neural background for the emergence of PPA in the 7th decade of life.[21] Such tardive manifestations of remote vulnerabilities are not unknown in neurology. One study, for example, showed that patients who had recovered from childhood hemiplegia reported the progressive emergence of hemiparkinsonism later in life on the side of the original weakness.[22]

Potential insights into possible molecular bases of regional susceptibilities come from a study showing that the MV polymorphism in codon 129 of the prion protein gene is more prevalent in PPA than in normals or AD 23. This does not imply that PPA is a prion disease, but that polymorphisms in the prion protein may influence the anatomical distribution of susceptibility to degeneration, as they do in fatal familial insomnia and familial Creutzfeld-Jacob disease.[24, 25] The possibility that the language network has a unique and identifiable molecular fingerprint that would make it the target of selective vulnerability in some genetic backgrounds but not in others is not as implausible as it may sound, especially in view of recent observations on the KE family where a speech and language disturbances are linked to a FOXP2 gene mutation.[26]

Collectively, these observations raise the possibility that PPA may reflect the tardive manifestation of a genetic or developmental vulnerability centered within the language network. This putative vulnerability seems to remain functionally compensated through most adulthood but eventually provides a locus of least resistance for the anatomical distribution of a degenerative disease that becomes identified as PPA. In other individuals with other vulnerabilities the same cellular pathology might lead to a different anatomical distribution of brain damage and therefore to a different clinical picture.

In conclusion, primary progressive aphasia needs to be considered in the differential diagnosis of dementia. The diagnosis is easily made on the basis of an initially isolated progressive aphasia. Other degenerative diseases can also eventually lead to language disturbances but the resultant aphasias are not "primary" because they are neither the most salient feature of the clinical picture nor early in onset. Primary progressive aphasia has a broad spectrum of clinical manifestations. Early in the course of the disease, agrammatic/dysfluent, semantic, logopenic/anomic variants can identified. The "progressive non-fluent aphasia" and "semantic dementia" designations of Neary et al 17 show partial overlap with the first two variants but do not encompass the third and most common subtype. Furthermore, the Neary et al. diagnoses make assumptions about the underlying neuropathology, whereas the PPA designation does not.
The manifestations of primary progressive aphasia are distinctly different from those of typical Alzheimer's disease. Different aspects of daily living activities are impaired and require different sorts of intervention. Some patients can learn sign language, others find it useful to carry laminated cards with specific messages, still others benefit from voice

synthesizers or laptops containing digitally stored words and phrases. An evaluation by a speech therapist is useful for exploring alternative communication strategies. In contrast to Alzheimer's disease where new information cannot be retained in memory, the recall and evaluation of recent events remains intact although the patient may not be able to express this knowledge verbally. Explaining this phenomenon to the family and offering an objective assessment of how the aphasia interferes with verbal expression and language comprehension tends to help the family cope with the patient's impairments.

The epidemiology and risk factors of PPA are largely unknown. There is currently no effective pharmacological treatment for this condition but clinical trials with potentially promising drugs are being initiated. In the meantime, PPA provides a unique syndrome for investigating the pathological mechanisms of focal degenerations, the molecular fingerprints of the language network, and the neuropsychological organization of aphasias.

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