Primary Progressive Aphasia
A 25-year Retrospective

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Abstract: The diagnosis of primary progressive aphasia (PPA) is made in any patient in whom a language impairment (*aphasia*), caused by a neurodegenerative disease (*progressive*), constitutes the most salient aspect of the clinical picture (*primary*). The language impairment can be fluent or nonfluent and may or may not interfere with word comprehension. Memory for recent events is relatively preserved although memory scores obtained in verbally mediated tests may be abnormal. Lesser changes in behavior and object recognition may be present but are not the leading factors that bring the patient to medical attention. This selective clinical pattern is most conspicuous in the initial stages of the disease. Progressive nonfluent aphasia and some types of semantic dementia can be considered subtypes of PPA. Initially brought to the attention of contemporary literature 25 years ago, PPA has recently witnessed substantial progress related to its neurolinguistic features, neuroanatomy, imaging, neuropathology, genetics, and risk factors.

Key Words: dementia, language

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When Bruce Miller, the guest editor for this issue, invited me to contribute a paper on the history of primary progressive aphasia (PPA), I felt this would be a proper venue for a brief retrospective account of my experience with this syndrome.

The story can be traced back to 1975, when the Harvard Neurological Unit, chaired by Norman Geschwind, moved from Boston City Hospital to the Beth Israel Hospital. As I had just finished my residency at Boston City Hospital, Norman Geschwind asked me to move with him and establish a Behavioral Neurology Unit (BNU) at the new site.

The BNU attracted patients with disorders covering almost all aspects of behavioral neurology. We became particularly familiar with the progressive amnestic dementia of Alzheimer disease (AD) and the aphasic syndromes of focal strokes.

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THE PHENOTYPE

Not all cases we encountered fit these familiar patterns. I was particularly puzzled by a subset of aphasic patients who displayed atypical features. When asked about her chief complaint, one such patient said: "Syntax errors and no articles…Words in the my head and cut up…Writing syntax errors. Edit my work…computer." I must admit that my first impulse was to consider her an impostor sent to test the limits of my gullibility. Even for Broca aphasia, the agrammatism appeared overdone. If this was Broca aphasia, why was she not dysarthric or hemiparetic? Even more vexing was the absence of visible cerebrovascular lesions in Broca's area or anywhere in the left hemisphere. I was also intrigued by the history of gradual progression. We were familiar with indolent progressions of cognitive deficits, but such cases were usually attributed to AD and tended to be associated with memory loss, a feature that was definitely absent in this patient.

We soon gathered a handful of such patients: they had an isolated aphasia but no stroke; a progressive course but no amnesia. We were puzzled enough to proceed with a cortical biopsy in one of our patients. As the biopsy gave no indication of AD, it seemed that we had stumbled onto something that was neither in contemporary textbooks of neurology nor part of the clinical teaching at that time. Because those were the days when one was still rewarded for unearthing precedent, I spent the next several weeks at the basement of Countway Library at Harvard Medical School.

THE ARCHETYPE

I first focused on an 1892 report by Pick,[1] entitled "Ueber die Beziehungen der senilen Hirnatrophie zur Aphasie," in which he describes a patient he had first encountered on November 11, 1891. The history revealed a progressive aphasia. I first thought that this would be the archetypal case for the cluster of unusual patients I had seen. However, Pick also noted that the patient had "3 Jahren progressive Gedächtnisschwähe" (Progressive weakness of memory for 3 years) and that he "seine Frau mit dem Messer bedroht habe" (had threatened his wife with a knife). So I had to conclude that this patient could not be considered a perfect prototype for the relatively pure aphasias I had been seeing.

As I continued my library research, I found a paper by Paul Sérieux in which he describes a woman, brought to the hospital on March 11, 1891, who presented with a

progressive loss of word comprehension and in whom "la mémoire et l'intelligence de la malade étaient suffisamment conservées" (The patient's memory and intelligence were sufficiently preserved.). The patient died in 1897.[2] The brain, examined by Dejerine[3] at the Salpêtrière, showed bitemporal cortical atrophy and neuronal loss. There was obviously no way of knowing whether the patient had AD because Alzheimer would not be reporting the pathologic pattern that now bears his name for another 10 years, in 1906.[4]

I had a chance to discuss this case with Andre Roch Lecours at a time when we were serving as representatives of our respective countries, Canada for Andre and United States for me, at a meeting of the Human Frontiers for Research Organization in Strasbourg. I mentioned to Andre the uncertain neuropathologic status of the Dejerine/Sérieux case. A few months later, Andre visited Boston, bearing a totally unexpected gift. Through some stratagem known only to him, he had managed to "borrow" the Dejerine slides. As I did not have the heart to violate the sanctity of the material touched by Dejerine, I did not remove the coverslips for restaining with more up to date methods, but I did examine the cell and myelin preparations as carefully as I could. I found no evidence of either senile plaques or neurofibrillary tangles. I have since considered the Dejerine/Sérieux patient the closest prototypical example I have been able to find of the syndrome now known as PPA.

THE SLOWLY PROGRESSIVE APHASIA STAGE AND "LOGOPENIA"

Armed with the authority of a precedent and faced with additional patients, I felt comfortable reporting an initial set of 6 cases in 1982 under the rubric of "Slowly Progressive Aphasia Without Generalized Dementia." The term "progressive" was used to differentiate the patients from stroke-caused aphasia and the word "slowly" was added to differentiate them from the progressive but relatively faster course of neoplasm.[5] The phrase "without generalized dementia" was included to highlight the difference from typical forms of AD.

The language disorders were heterogeneous. Some patients were fluent others not, some had word comprehension impairments but not others. Furthermore, the aphasias rarely fit the canonical patterns established in stroke. Dysarthria, an almost invariable component of agrammatic dysfluent aphasias due to stroke, was rarely present. Comprehension deficits were generally confined to single words and rarely displayed the severity seen in typical Wernicke aphasia. In contrast to patients with stroke-induced loss of fluency, many of our patients were intermittently dysfluent. They produced fluent speech when allowed to engage in small talk and circumlocutions, but became nonfluent because of word-finding hesitations when forced to be precise. I coined the neologism "logopenia" to describe this state of fluctuating fluency in patients without the frank agrammatism of classic nonfluent aphasias.[5] The intermittent interruption of fluency also showed that the fluent-nonfluent distinction, a gold standard for the classification of stroke-based aphasias, would be of more limited usefulness in the classification of these patients.

THE PPA DESIGNATION

Following the 1982 paper, dozens of patients were reported in clinics around the world and I soon realized that the terminology needed modification. First, the phrase "slowly progressive" seemed redundant. Second, the qualification of "without generalized dementia" seemed to be a bit of an overkill because it was becoming quite clear that memory loss is not the only or even necessary criterion for dementia. A patient with a progressive aphasia could be said to have a language-based dementia, just as patients with typical AD are said to have a memory-based dementia.

In 1987, in an *Annals of Neurology* editorial Art Asbury had asked me to write as a companion piece to the pioneering neuropathologic study on progressive aphasia by Kirschner and colleagues,[6] I proposed a change of terminology to PPA.[7]

As PPA is caused by a progressive neurodegeneration that goes on to invade most of the cerebral cortex, patients eventually displayed many additional deficits. To capture the pivotal nature of the language impairment, Sandra Weintraub[8,9] and I introduced the 2-year diagnostic criterion according to which the aphasia had to be the most salient deficit and the major cause of impaired daily living activities for approximately 2 years. This "rule" allowed us to weed out patients with Creutzfeldt-Jacob disease with an aphasic onset but rapid deterioration and also typical amnestic AD patients who might eventually develop a language disorder. Exact timing of onset in progressive disease is notoriously difficult, and we stressed that the "2 year" rule was meant to be interpreted with considerable latitude.[9]

These criteria were eventually codified and the PPA diagnosis can now be made in any patient who has a fluent or nonfluent language disorder (*aphasia*) that is due to a neurodegenerative disease (*progressive*) and in whom the aphasia is initially the most salient feature of the clinical picture (*primary*).[10,11] The *aphasia* can interfere with word-finding, object naming, syntax, phonology, morphology, spelling or word comprehension. The *progression* occurs in the course of years rather than months, and the *primary* nature of the aphasia is demonstrated by showing that memory for recent events, the recognition of familiar faces and objects, reasoning, and basic aspects of comportment are relatively preserved at the initial stages.[12] The fact that the language disorder in PPA could be fluent or nonfluent and that it could be associated with normal or impaired word comprehension was emphasized in the initial description and subsequent reviews.[5,8] These features are now incorporated in the Uniform Data Set used by the Alzheimer's Disease Centers of the United States.[13]

CONGENERS, VARIANTS, BOUNDARIES

Terms such as progressive nonfluent aphasia (PNFA), semantic dementia (SD), aphasic variant of frontotemporal dementia (FTD), temporal variant of frontotemporal lobar degeneration (FTLD), Gogi aphasia, and progressive aphasia have been used, mostly implicitly, to denote variants of PPA.[14,15] We prefer the PPA term as a root diagnosis for 2 reasons: not all progressive aphasias fulfill the PPA criteria and not all PPA cases are caused by FTLD pathology.

The PNFA criteria of Neary et al[15] fit the PPA criteria perfectly and this syndrome can be considered a PPA subtype. The roots of the SD syndrome can be traced to a 1975 report by Warrington.[17] If the original Neary et al criteria for SD (ie, the requirement to have both poor word comprehension and also an associative agnosia) are interpreted literally, SD does not seem to fit the PPA criteria. However, the Cambridge group seems to have redefined SD as a language disorder accompanied by lesser and variable agnosic deficits, mostly for unfamiliar objects.[16] This latter definition of SD makes it a subtype of PPA.

The PNFA and SD subtypes do not account for all of PPA. The logopenia term of the 1982 paper described a clinical state intermediate between nonfluent and fluent aphasia.[5] The most comprehensive recent development to take this "third" form of PPA into account is the work of Gorno-Tempini and colleagues[18] who codified a "logopenic" variant of PPA. The defining criteria for these 3 PPA variants were reviewed by an international group of investigators who met just after the September 2006 International Frontotemporal Dementia conference in San Francisco.

On the basis of the initial proceedings of this meeting, convened by Gorno-Tempini, Grossman, and Hillis, we are now subdividing our cases into 3 variants: *agrammatic/dysfluent*, *semantic*, and *logopenic*. In our clinical practice, the agrammatic/dysfluent variant (also known as PNFA) is characterized by impairments of syntax and fluency but preserved word comprehension; the semantic variant is characterized by poor word comprehension but preserved syntax and fluency; and the logopenic variant is characterized by interruptions of fluency due to frequent word-finding pauses but relatively intact syntax and word comprehension. Anomia is present in all variants but may become the principal feature of the logopenic subtype.

As the disease progresses, PPA patients may develop memory disorders, associative agnosias, personality changes (reminiscent of the behavioral variant FTD), motor neuron disease, or asymmetric extrapyramidal deficits (of the type seen in corticobasal degeneration), underlining the lack of rigid boundaries in neurodegenerative syndromes.[19] When such additional findings emerge, we use the designation "PPA-plus."

CURRENT STATE OF RESEARCH

Since the introduction of PPA to the modern literature 25 years ago, more than 700 papers on this subject have been published. Neurolinguistic investigations have revealed the rich spectrum of language impairments in the areas of syntax, category-specific naming deficits, and language comprehension.[20–22] The imaging has generally shown asymmetric atrophy and hypometabolism, more prominent in the language-dominant (usually left) hemisphere.[23–25] The atrophy tends to be mostly in the perisylvian region in the agrammatic/dysfluent and logopenic variants but extends into anterior and medial temporal cortex in the semantic variant.[18,26,27] The neuropathology shows subtypes of FTLD in 60% to 70% of cases and the plaques and tangles of AD in the others. The FTLD pathology may include focal neuronal loss, gliosis, tauopathy, ubiquinopathy with TDP-43 proteinopathy (a pattern known as FTLD-U), and superficial vacuolation.[28,29] A major conundrum in this area is to figure out how AD pathology, which is known to cause the greatest initial neuronal loss in entorhinal and hippocampal areas, can account for the "aphasia without amnesia" pattern that identifies the initial stages of PPA.

In nonfamilial cases, the agrammatic/dysfluent variant (PNFA) seems more closely associated with tauopathy whereas the semantic variant may be more closely associated with FTLD-U.[30] Although most PPA is sporadic, familial cases have also been described and linked to FTLD-U pathology and mutations in the progranulin gene.[31–33] In contrast to the sporadic cases, the familial cases display an association of FTLD-U pathology with the agrammatic/dysfluent rather than the semantic variant of PPA.[34]

In some of these progranulin mutation families, affected members display phenotypical homogeneity for PPA,[33] whereas in others some members have PPA and others the behavioral variant of FTD.[34] The cellular mechanisms that make the same mutation lead to the behavioral variant of FTD in some family members and to the PPA phenotype in others remains mysterious. The frequency of learning disabilities, especially of the dyslexic type, is higher in PPA families than in controls or typical AD, raising the possibility that the selective vulnerability of the language network may also be genetically determined, at least in some of the patients.[35] A critical review of these recent developments in the imaging, neuropathology, and genetics of PPA is beyond the scope of this paper. They are mentioned to highlight the vigor and productivity of research in this area.

THE FUTURE

The single most pressing challenge is to discover effective treatments. The record thus far is not very encouraging. A small but controlled trial with bromocriptine has been negative[36]; a memantine versus placebo trial is reaching completion; our uncontrolled clinical experience with cholinesterase inhibitors has been disappointing. Some patients with PPA benefit from speech therapy, others learn to use communication enhancement devices, and others acquire rudiments of sign

language. But these are temporary measures. We find that psychosocial interventions, support groups and targeted educational programs are necessary components of a comprehensive approach to patients and families.[37]

While we await the appearance of effective therapies, PPA offers a unique experiment of nature for exploring the molecular fingerprints that make the language network a primary disease target and for probing the cognitive architecture of human language as it undergoes a slow but relentless dissolution. Considering the progress achieved during the past 25 years, it is safe to predict that future work on PPA will yield pivotal insights into human language, the mechanisms of neurodegeneration, and the molecular underpinnings of system-based selective vulnerabilities.

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