Left Hemicranial Hypoplasia in 2 Patients With Primary Progressive Aphasia

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Background: Primary progressive aphasia (PPA) leads to a gradual and relatively isolated dissolution of language function. The factors that determine the selectivity of the disease process remain unknown. We had speculated that PPA may occasionally arise as a tardive manifestation of genetic or acquired vulnerabilities involving the language network of the brain.

Objective: To explore predisposing factors for PPA.

Results: In 2 patients, PPA developed with a background of mild left hemicranial hypoplasia.

Conclusion: In keeping with other observations of PPA in patients with dyslexia and childhood injury to the left temporal lobe, these 2 patients support the contention that some cases of PPA may arise in settings where the language network has become a locus of least resistance.

Arch Neurol. 2004;61:265-268
cal examination displayed multiple word-finding hesitations. Naming by visual confrontation was impaired. Repetition of phrases was impaired. She was unable to obey complex commands. Reading and writing could not be appropriately assessed due to her low educational level. She had good memory for daily events. Results of routine laboratory studies were normal, and the apolipoprotein E genotype was 3/3. Left hemicranial hypoplasia, predominantly of the middle cranial fossa, and left perisylvian atrophy were noticed on neuroimaging studies (Figure 1). The cranial asymmetry was compatible with mild unilateral left coronal suture synostosis. Left hemisphere hypoperfusion with a perisylvian predominance was seen on SPECT (Figure 1). The aphasia slowly progressed, and at the age of 72 years, 9 years after onset, she could barely utter more than 2 to 3 words at a time, could not carry out simple commands, and needed help with most of her activities of daily living. By then, her right arm swing was slightly impaired when walking, there was a fixed facial expression, and both sucking and snout reflexes were elicited. Cerebral atrophy had progressed on magnetic resonance images, and hypoperfusion had become bilateral, but still with a left hemisphere predominance.

PATIENT 2

A 43-year-old right-handed man had 2 focal right-sided somatosensory epileptic events, followed a few days later by a grand mal seizure. Left temporal spikes were detected on an electroencephalogram. The epilepsy was controlled with carbamazepine. A computed tomographic scan obtained 5 years later (1980) noted cranial asymmetry based on a smaller left middle cranial fossa and a larger frontal ventricular horn on the left. No temporal or perisylvian cortical atrophy on the left was noted. Sixteen years later, at the age of 59 years, he complained of progressive word-finding difficulties as well as additional problems in writing and calculations. Electroencephalographic findings at that time were normal. He retired from his office job at age 63 years because of his language problems. At an examination at that time, 4 years after symptom onset, he was fully oriented, remembered daily events, and carried out all customary daily activities, including shopping and banking. He had a nonfluent aphasia. Conversational speech was effortful, with a slight stammering quality, mild dysarthria, loss of prosody, and circumlocutions. He also had acalculia, left-right disorientation, and ideomotor apraxia, although the
aphasia was by far the most dominant finding and the chief cause of his limitations at work. Routine laboratory tests were unrevealing. Apolipoprotein E genotype was 3/3. Cranial computed tomographic scan and magnetic resonance imaging at that time (1996) showed the left hemicranial hypoplasia that had been seen before and additional left frontotemporal cerebral atrophy with perisylvian predominance (Figure 2). Left hemisphere hypoperfusion was reported on SPECT. At age 69 years, 10 years after the onset of aphasic problems, he was still able to choose his clothes, shave, dress, and travel without getting lost, even though he could barely speak. At that time, the cerebral atrophy had increased on magnetic resonance imaging and the SPECT hypoperfusion became more generalized, but still with a left perisylvian predominance.

**COMMENT**

The patients in this report had 2 features in common. First, they had progressive neurologic impairment that initially exhibited a relatively isolated aphasic disturbance consistent with the diagnosis of typical PPA without any known history of childhood stuttering or learning disability. Second, they had radiologic evidence for a hypoplastic left hemisphere, predominantly within the middle cranial fossa, where the major components of the language network are located. The cranial asymmetry in these patients reflects a remote process that originated at the stage of craniocerebral development, decades before the emergence of the aphasia. At least in case 2, the cortical atrophy in the left hemisphere appears to represent a more recent event, perhaps temporally related to the onset of the progressive aphasia. The absence of a language deficit prior to the onset of the PPA indicates that the putative cognitive effect of this hypoplasia had been compensated. However, the focal seizures in patient 2 also indicate that the left hemisphere process was not entirely silent.

We had previously described a patient with a history of abscess removal from the left temporoparietal area at the age of 11 years. Although the surgery during childhood left no aphasic sequelae, he experienced a focal dissolution of language function almost 60 years later. There is also preliminary evidence that patients with PPA and their first-degree relatives have a greater incidence of de-
velopmental learning disabilities, especially dyslexia, when compared with patients with AD or normal controls. These relationships, together with the 2 cases reported here, support the possibility that PPA, at least in some patients, may reflect the tardive manifestation of a preexisting genetic or acquired vulnerability centered around the left hemisphere language network.

Premorbid dyslexic deficits in such patients could conceivably reflect the mild manifestations of a genetically determined left hemisphere dysfunction that eventually leads to PPA, perhaps in response to the additional biological stress of aging. An analogous phenomenon was identified in families with chromosome 17 mutations known to cause frontotemporal dementia. Carriers of such mutations displayed mild neuropsychologic evidence of frontal lobe dysfunction decades prior to the expected onset of the dementia.

There are several settings in which acquired lesions provide a locus of least resistance for the clinical expression of subsequent disease processes. Women who recover from Sydenham chorea in childhood, for example, can experience chorea gravidarum during pregnancy in response to alterations of the hormonal milieu; patients who have recovered from poliomyelitis can develop, decades later, a progressive motor neuron disease in the previously affected muscles; and patients who have recovered from childhood hemiplegia can develop a progressive hemiparkinsonism on the side of the recovered weakness later in life.

The relationship between PPA and left hemicranial hypoplasia in the 2 patients described here may be coincidental. However, it is also possible that there is a causal link between the 2 events, supporting the contention that PPA may occasionally arise on a background of focal vulnerabilities affecting the language network of the brain. In some patients, this vulnerability may be visible in the form of hypoplasia. In others, it may elude detection by currently available imaging approaches. The clinical picture in such patients, and perhaps in many other local degenerations, would thus reflect an interaction between the molecular aspects of the disease and host-specific regional vulnerabilities. According to this formulation, the incidence of hemicranial hypoplasia need not be elevated in PPA and, conversely, the incidence of PPA need not be elevated in hemicranial hypoplasia. The implication of the present report is that early injuries or developmental perturbations such as hemicranial hypoplasia may delineate the area of greatest involvement in some patients who later develop a disease that promotes cortical degeneration. It would be important to determine the frequency of this phenomenon in a larger sample of patients and to explore its biological mechanisms.

Accepted for publication August 12, 2003.

Author contributions: Study concept and design (Drs Alberca, Gil-Néciga, and Mesulam); acquisition of data (Drs Alberca and Montes); analysis and interpretation of data (Drs Russell and Mesulam); drafting of the manuscript (Drs Alberca, Montes, and Mesulam); critical revision of the manuscript for important intellectual content (Drs Alberca, Russell, Gil-Néciga, and Mesulam); administrative, technical, and material support (Drs Alberca, Montes, and Russell); study supervision (Drs Alberca and Mesulam).

This study was supported by grant AG13854 from the National Institute on Aging, Bethesda, Md (Alzheimer’s Disease Center, Northwestern University, Chicago, Ill).

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